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The regional distribution of anxiety disorders: implications for the Global Burden of Disease Study, 2010

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Key words
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Abstract

Anxiety disorders are increasingly acknowledged as a global health issue however an accurate picture of prevalence across populations is lacking. Empirical data are incomplete and inconsistent so alternate means of estimating prevalence are required to inform estimates for the new Global Burden of Disease Study 2010. We used a Bayesian meta-regression approach which included empirical epidemiological data, expert prior information, study covariates and population characteristics. Reported are global and regional point prevalence for anxiety disorders in 2010. Point prevalence of anxiety disorders differed by up to three-fold across world regions, ranging between 2.1% (1.8–2.5%) in East Asia and 6.1% (5.1–7.4%) in North Africa/Middle East. Anxiety was more common in Latin America; high income regions; and regions with a history of recent conflict. There was considerable uncertainty around estimates, particularly for regions where no data were available. Future research is required to examine whether variations in regional distributions of anxiety disorders are substantive differences or an artefact of cultural or methodological differences. This is a particular imperative where anxiety is consistently reported to be less common, and where it appears to be elevated, but uncertainty prevents the reporting of conclusive estimates. *Copyright © 2014 John Wiley & Sons, Ltd.*

Introduction

Measures of disease epidemiology are essential for monitoring global population health. Epidemiologically-based summary measures such as the disability-adjusted life year (DALY) permit comparison of health-loss across disease and injuries and between populations. This is relevant to identifying shifts in population health and providing an evidence-based tool for decision-making in public health.

Initial Global Burden of Disease (GBD) estimates, released in the 1990s, identified mental disorders as important causes of disease burden. Obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and panic disorder were the only anxiety disorders included. Subsequent national burden (Begg *et al.*, 2007) and epidemiological studies (Kessler *et al.*, 2007; McEvoy *et al.*, 2011; Phillips *et al.*, 2009) found these, and other anxiety disorders, were highly prevalent and costly in terms of health care expenditure, life-course outcomes and personal suffering.

While anxiety disorders are increasingly acknowledged as an important health issue, their global distribution remains poorly understood. Prevalence data for these disorders are inconsistent and incomplete as studies use different approaches to measurement that can significantly impact on reported estimates and obscure true differences in prevalence across populations (Baxter *et al.*, 2013a).

Current literature suggests that prevalence of anxiety disorders differs across countries (Kessler *et al.*, 2009b) and cultures (Baxter *et al.*, 2013a) however the degree to which this difference is substantive or an artefact of measurement remains unclear. It has been postulated that population characteristics such as collectivistic cultural values may be linked with increased resilience to anxiety disorders (Chiao and Blizinsky, 2010). However, it is also possible that the relative insensitivity of current diagnostic criteria to non-Western expressions of anxiety disorders (Phillips *et al.*, 2009; Steel *et al.*, 2009b) underestimates prevalence.

There are substantial gaps in the global data for anxiety disorders. Our previous review found nationally-comparable studies were available for less than one out of five countries (Baxter *et al.*, 2013a). Information on anxiety disorders is particularly scarce for low- and middle-income countries (LMIC) (Baxter *et al.*, 2013b) and extrapolating estimates from culturally and demographically different populations (e.g. Western Europe and North America) may misrepresent true health loss in those regions. In view of the difficulties with compiling comparable prevalence data, additional methods are needed to assess epidemiological data to arrive at a consistent global profile of anxiety disorders.

Disease modelling has previously been used to impute missing data through exploiting principles of interrelatedness between epidemiological measures that describe new cases, existing cases, recovered cases and cause-specific mortality of disease (Kruijshaar *et al.*, 2002; Barendregt *et al.*, 2003; Saha *et al.*, 2008). A similar generic model of disease process was applied to estimate disease distributions in the new Global Burden of Disease Study 2010 (GBD 2010). By taking a Bayesian approach to these analyses, existing information such as clinical knowledge could be incorporated in addition to the empirical epidemiological data. This paper describes that process, and the inputs used, in modelling the prevalence distributions for anxiety disorders used to calculate disease burden estimates for GBD 2010.

The aim of this study was to estimate point prevalence of anxiety disorders, by age and sex, for 21 world regions. These estimates were used to explore regional variation in the distribution of anxiety disorders. In addition to informing new burden of disease estimates, these methods and findings also demonstrate how heterogeneous data sources can be used to impute local patterns of anxiety prevalence and build on the existing knowledge of the epidemiology of anxiety disorders.

Methods

For the purposes of GBD2010, countries were grouped into 21 regions based on geographic proximity and levels of child and adult mortality (Murray *et al.*, 2012). These were further grouped into seven super-regions (based on cause of death patterns) to help predict estimates for regions with sparse data. Appendix B provides more information on the GBD 2010 hierarchical grouping of regions and super-regions.

Primary input for the analyses included (1) epidemiological data, referred to here as "empirical data", and (2) estimates of levels or ranges of individual parameters derived from sources such as expert clinical knowledge. We refer to the range of probability settings to account for prior clinical knowledge of disease patterns as "expert priors".

Defining anxiety disorders

We aimed to capture all cases of anxiety disorders reaching diagnostic threshold, including generalized anxiety disorder (ICD-10 code F41.1); panic disorder (F41.0); agoraphobia (F40.0); social phobia (F40.1); specific phobia (F402); OCD (F42.9); PTSD (F43.1); separation anxiety disorder (F93.0); and anxiety disorders not otherwise specified (NOS) (F41.9). To avoid "double-counting" individuals with multiple disorders, a case was defined as meeting clinical threshold for *any* of the specific anxiety conditions.

Data sources

Our systematic review was conducted according to the PRISMA guidelines (Moher *et al.*, 2009). This process has been described in detail elsewhere (Baxter *et al.*, 2013a, 2013b). Briefly, estimates of prevalence, incidence, remission and all-cause excess mortality were sought for composite measures of "any" anxiety disorder. Our review included electronic searches of Medline, Embase and PsycINFO databases; manual searches of reference lists in review articles, editorials and resource books; and data requests from international collaborative research projects such as the World Mental Health Survey (WMHS) Collaboration (http://www.hcp.med.harvard.edu/wmh/). Expert consultation was an ongoing process involving critical review of the shortlisted studies and requests for additional sources of published or unpublished data.

Studies were included that reported prevalence or incidence with a maximum recall period of one year for any anxiety disorder in a representative sample of a country's population. The exception to this rule was the inclusion of prevalence estimates for PTSD-only in populations that had been exposed to conflict and would not otherwise be represented in the data. Due to the paucity of population-representative remission and mortality data for anxiety, inclusion criteria were broadened to include studies of specific anxiety disorders and treatment-seeking samples with naturalistic follow-up (minimum of two-year follow-up period). Remission studies were accepted where remission was defined as no longer meeting diagnostic threshold for "caseness" and excess mortality was estimated using standardized mortality ratios (SMRs) or relative risk of death (RR).

As GBD 2010 aimed to systematically quantify uncertainty around all estimates, we included information on within-study uncertainty, that is, standard errors (SEs) or confidence intervals (CIs). Where authors did not report uncertainty we calculated SE as $\sqrt{2.1 \times (P \times (1 - P))/N}$ where P is prevalence, 2.1 is the average design effect and N the denominator. The average design effect compensated for any increase in uncertainty due to study design and methods and was calculated based on a sample of design effects ($n = 110$) from datasets for anxiety and depressive disorders. Remission estimates were standardized for the varying period of follow-up by calculating remission rates (Saha *et al.*, 2008; Mathers *et al.*, 2001) as shown in Appendix C.

Data availability

Ninety-one prevalence studies met our inclusion criteria, providing at least some coverage for 17 of the 21 GBD world regions. More detail on these studies can be found in our previous review paper (Baxter *et al.*, 2013a). Whilst global coverage of prevalence data coverage was reasonably good, the data were inequitably distributed with much more information available from high-income countries (HIC) compared to LMIC. A number of national mental health surveys provided data for adults while data for children more often came from smaller community studies.

Information on other epidemiologic parameters was scarce and largely represented populations from North America, Western Europe and Australasia. Our review found only three studies reporting incidence for "any" anxiety disorder in a community-representative sample (Grant *et al.*, 2009; Bijl *et al.*, 2002; Daradkeh *et al.*, 2000). Five studies were found for remission (Reddy *et al.*, 2003; Wewetzer *et al.*, 2001; Perkonigg *et al.*, 2005; Cantwell and Baker, 1989; Schuurmans *et al.*, 2005) and two for excess all-cause mortality in community cases of anxiety (Van Hout *et al.*, 2004; Bruce *et al.*, 1994).

Expert prior settings

Current diagnostic criteria do not specify a minimum age for onset of anxiety disorders. Separation anxiety disorder may be present as early as six months but is difficult to diagnose as childhood anxieties are often transient and communication skills are still developing (Beesdo *et al.*, 2009). In the absence of other evidence, incidence and prevalence values were set to zero before the age of two as this was the minimum age for any of our epidemiological data. Some studies suggest that anxiety disorders tend to decrease in older age groups (McEvoy *et al.*, 2011; Jorm, 2000; Wells *et al.*, 2006). Data for the oldest ages were scarce and compositional bias in age group heterogeneity meant there was insufficient power to arrive at a consistent pattern at oldest ages. We therefore included a prior that suggested prevalence was non-increasing as a function of age after age 75.

We set limits on remission rates allowing values between zero and 0.25 based on preliminary analyses that showed pooled weighted remission rate of 0.14 with 95% uncertainty of 0.02–0.25 (see Appendix C for included studies and remission rate calculations).

The evidence for excess mortality in anxiety disorders was inconsistent. Of the two studies that met our criteria one reported higher mortality in older males but not in females (Van Hout *et al.*, 2004) while the other found mortality was not significantly higher in individuals with panic disorder, phobia or OCD (Bruce *et al.*, 1994). We decided to assume there is no excess mortality.

Int. J. Methods Psychiatr. Res. 23(4): 422–438 (2014). DOI: 10.1002/mpr

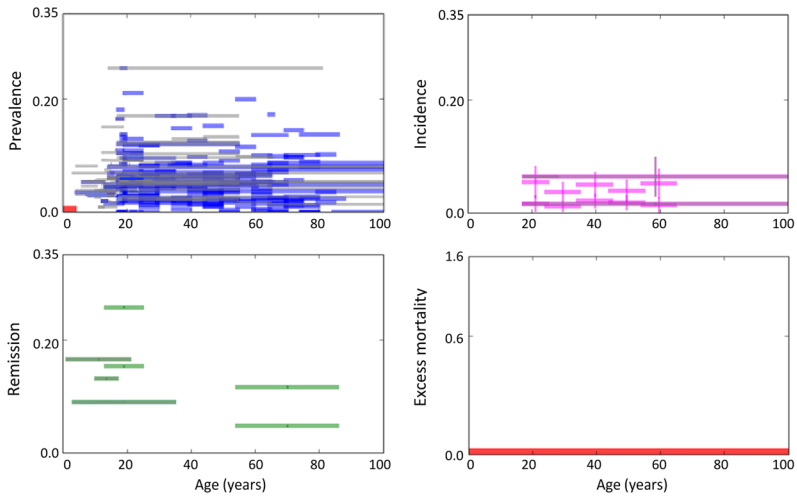
Statistical analysis

Analyses were conducted using DisMod-MR, a Bayesian meta-regression tool which pools data for multiple epidemiological parameters, whilst accommodating known methodological and substantive determinants (Vos *et al.*, 2012). It generated an internally consistent series of epidemiological parameters based on a generalized negative-binomial model using both fixed and random effects, with imputed estimates and uncertainty for parameters and populations with missing values (Vos *et al.*, 2012). Expert prior knowledge was implemented by setting informative prior settings on minimum age of onset and age knots, that is, the points at which primary estimates in the Bayesian model are made (0,2,10,20,30,45,60,75,85,100). An additional age prior was calculated within DisMod-MR using the fixed effects method and applied where only "person" empirical data estimates were available (Figure 1).

An initial consistency check at the global level showed that the few high incidence data points could not be reconciled with the more abundantly available prevalence data. As the incidence data were comparatively sparse in comparison to prevalence (12 age-specific estimates compared with 1196 estimates, respectively), we decided to exclude incidence data and allowed prevalence and remission to inform subsequent models.

To account for data heterogeneity, Dismod-MR permits the inclusion of covariates in the model to adjust data

Geographical representation of all empirical data points and prior settings



Key: Each horizontal bar represents a single data point extracted in systematic review. The left and right endpoints indicate the start and end ages of the age interval for a data point and vertical lines represent 95% uncertainty. The level of prevalence is represented by the distance of the bar above the y-axis. Blue lines are prevalence data points, pink lines are incidence data points and green horizontal lines are remission. Solid red lines along the horizontal axes indicate parameter-specific prior settings.

Final model input

Empirical data used in final model	Parameter	Number of studies	Number of data points	Countries with data	Regions with data
	Prevalence	91	1196	48	17
	Remission	5	7	4	3
Prior settings	Parameter	Setting			
	Prevalence	Prevalence commencing after 2 years of age with decreasing trend after age 75 years			
	Incidence	Incidence commencing after 2 years of age			
	Remission	Remission rate between zero and 0.25			
	Mortality	Relative risk of mortality=1			

Figure 1. Summary of anxiety prevalence model input including epidemiological data and prior settings.

points from sub-optimal study designs. Dichotomous study-level covariates were created for *prevalence type* where current prevalence was the reference category and past-year estimates were adjusted downward. *Diagnostic criteria* was coded and alternately tested as: (a) DSM versus ICD and (b) more recent versions of criteria (i.e. DSM-IV and ICD-10) versus earlier versions; and *case identification* dichotomoised as clinical versus survey instrument. A final study-level covariate was created for comprehensiveness, whereby studies were considered *comprehensive* if seven or more of the specific conditions were captured in the overall prevalence estimate and less comprehensive if fewer (six or less) disorders were included.

Regional distributions were calculated using nested random effects on super-region, region, and country to capture unexplained systematic variation besides the measurement error and study-level unexplained variation. Fixed effects were applied as country covariates previously identified as explaining variance in anxiety disorders. Past and current exposure to war and conflict have been associated with elevated prevalence of anxiety disorders (Baxter *et al.*, 2013a; Steel *et al.*, 2009a) so we included these as country predictors to inform calculations for missing country data. The natural log of the mortality rate from war or conflict in any given year in a country as estimated for GBD 2010 (Lozano *et al.*, 2012) determined the country-level *conflict* covariate. The *post-conflict* covariate was a lagged variable of the natural log of mortality rates from war or conflict in the previous 10 years. Regional estimates were then age-standardized using direct methods with the World Health Organization (WHO) global standard population for 2010 as reference.

Error estimates were carried forward from empirical data inputs, estimated age patterns, prior settings, regional and country patterns and study and country covariates to inform the final model. Uncertainty was calculated through fitting with a randomized Markov-Chain Monte–Carlo (MCMC) algorithm (Vos *et al.*, 2012). Uncertainty is reported throughout as 95% uncertainty intervals (UI).

Results

The final model included two covariates, namely prevalence type and comprehensiveness of anxiety disorder inclusions. Once data were pooled and adjusted for the above factors, diagnostic criteria and the case finding instrument were not associated with reported prevalence and therefore not included in the final analyses. Table 1 presents the range of data inputs from systematic review and the estimated prevalence by GBD world region. Broad confidence intervals around the estimates indicate the degree of uncertainty carried forward from empirical data sources and covariate effects.

Figure 2 demonstrates the overall effect of study-level and country-level covariates on the empirical data, summarizing the (A) unadjusted and (B) adjusted prevalence data points for Australasian females (horizontal lines indicating the age range with a vertical line aproportionate in size to the 95% UI for the data point). The highest values for unadjusted data reflect past-year estimates from Australia, which were adjusted downward toward the reference category – point prevalence. As none of the Australasian countries were classified post-conflict the country-level covariate had no effect on these estimates. The regional mean prevalence is indicated by the solid line with grey shaded region showing 95% uncertainty.

Prevalence distributions

In 2010, 272.2 million individuals worldwide had a diagnosable anxiety disorder at any point in time. Age-weighted point prevalence was 2.8% (95% UI 2.6–3.0%) for males and 5.2% (95% UI 4.8–5.7%) for females. Prevalence rose sharply between 10 and 19 years of age and peaked between the ages of 20 and 34 years with a steady decline thereafter (Figure 3). Point prevalence for both sexes combined across broad age groups was approximately 2.4% in children/adolescents (0–19 years), 5.0% in working age adults (20–64 years) and 3.7% in older adults (65+ years).

Overall, sex differences were consistent across the lifespan with a male to female ratio of 0.46 (95% UI 0.43–0.49). However there are five regions (Oceania, Asia Central, Andean Latin America, Central Sub-Saharan Africa and the Caribbean) where the sex ratio is less pronounced (approximately two males to every three females) and the first four of these were regions without empirical data. Figure 3 shows age-weighted point prevalence for males and females by region.

Regional differences

Regional estimates for point prevalence differed by up to three-fold, ranging between 2.1% (95% UI 1.8–2.5%) in East Asia up to 6.1% (95% UI 5.1–7.4%) in North Africa/Middle East (Figures 4 and 5). Figure 4 demonstrates that anxiety disorders are more common in regions with post-conflict countries (North Africa/Middle East and Sub-Saharan Africa Central); high income Westernized countries (North America and Australasia); and Latin American countries (Andean and Southern Latin America). Figure 5 shows a substantial degree of overlap between regional uncertainty, with particularly broad uncertainty ranges for the four regions without empirical data.

Int. J. Methods Psychiatr. Res. 23(4): 422–438 (2014). DOI: 10.1002/mpr

Table 1. Comparison of empirical prevalence (input data) ranges and adjusted point prevalence (model output) for anxiety disorders by GDB world regions in 2010

GBD region	Empirical prevalence data					**Estimated prevalence**		
	Number of studies*	Study ages	Sex	Prevalence types	Prevalence range,	Sex	Point prevalence (95% UI)	
High Income regions								
Asia Pacific, High Income	2 [a,b]	18–64	M	Point & 12-months	2.1–3.0%	M	2.4%	(2.0–2.8%)
			F		3.0–9.4%	F	4.3%	(3.6–5.0%)
Australasia	6 [b–i]	15, 16–85	M	Point, 6- & 12-months	4.7–11.7%	M	3.7%	(3.3–4.1%)
			F		10.9–22.3%	F	7.1%	(6.4–7.9%)
Europe, Western	30 [b,j–ae]	5+	M	Point, 3-,	0.9–11.1%	M	3.2%	(2.9–3.5%)
			F	6- & 12-months	1.7–24.1%	F	6.5%	(5.9–7.2%)
Latin America, Southern	1 [s,w]	15+	M	Point & 12-months	2.2–3.7%	M	3.8%	(2.0–7.6%)
			F		11.0–16.5%	F	7.1%	(3.8–13.4%)
North America, High Income	10 [b,ah–ao]	6+	M	Point, 3-,	1.5–11.8%	M	4.0%	(3.5–4.5%)
			F	6- & 12-months	2.9–22.6%	F	7.5%	(6.6–8.6%)
Eastern Europe/Central Asia								
Asia, Central	0	—	—	—	—	M	3.9%	(2.3–6.0%)
						F	6.1%	(3.6–10.0%)
Europe, Central	4 [b,ac,ag]	16+	M	Point & 12-months	1.8–19.0%	M	3.6%	(2.6–5.5%)
			F		4.7–27.3%	F	7.0%	(4.8–11.1%)
Europe, Eastern	1 [b]	18+	M	Point & 12-months	1.8–2.8%	M	2.2%	(1.1–4.4%)
			F		3.6–5.9%	F	4.1%	(2.0–7.9%)
Sub-Saharan Africa								
Sub-Saharan Africa, Central	0	—	—	—	—	M	4.5%	(2.2–8.8%)
						F	6.7%	(3.2–13.9%)
Sub-Saharan Africa, East	4 [ar–au]	14+	M	Point	3.1–19.6%	M	3.8%	(2.9–5.1%)
			F		4.3–29.7%	F	7.0%	(5.4–9.2%)
Sub-Saharan Africa, Southern	3 [b,l,ag]	14+	M	Point & 12-months	2.2–24.0%	M	2.9%	(2.4–3.6%)
			F		3.5–21%	F	5.3%	(4.3–6.4%)
Sub-Saharan Africa, West	2 [b,al]	13+	M	Point & 12-months	1.9–11.4%	M	2.8%	(2.3–3.4%)
			F		2.8–19.6%	F	5.2%	(4.3–6.4%)
North Africa/Middle East								
North Africa/Middle East	8 [b,ad,ax–bb]	15+	M	Point & 12-months	2.9–28.3%	M	4.1%	(3.2–5.4%)
			F		7.0–20.6%	F	8.1%	(6.5–10.6%)
South Asia								
Asia, South	7 [b,bc–bi]	5+	M	Point & 12-months	0.7–6.4%	M	2.8%	(2.3–3.6%)

(*Continues*)

Int. J. Methods Psychiatr. Res. 23(4): 422–438 (2014). DOI: 10.1002/mpr

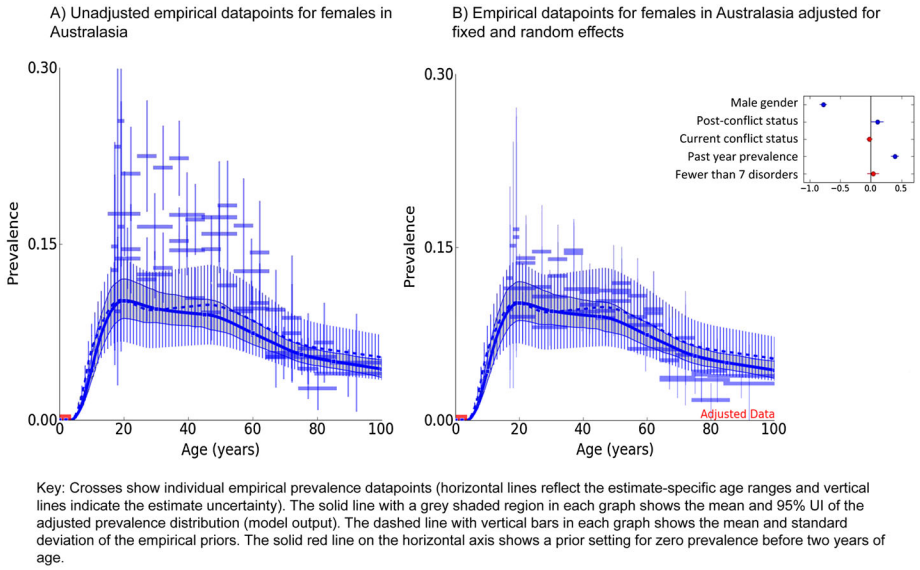
Table 1. (Continued)

GBD region	Empirical prevalence data					Estimated prevalence		
	Number of studies*	Study ages	Sex	Prevalence types	Prevalence range,	Sex	Point prevalence (95% UI)	
Asia, Southeast	2 [aj,as]	10+	F	12-months	2.9–11.6%	F	5.2%	(4.2–6.4%)
			M		0.5–2.4%	M	2.5%	(1.5–4.0%)
			F		1.1–5.3%	F	4.7%	(2.9–7.8%)
			P**	Point	5.5%			
East Asia and Pacific								
Asia, East	5 [b, bl–bn]	10+	M	Point & 12-months	0.9–5.0%	M	1.5%	(1.2–1.8%)
			F		1.4–8.7%	F	2.7%	(2.2–3.4%)
Oceania	0	—	—	—	—	M	3.4%	(1.5–6.9%)
						F	5.3%	(2.3–11.6%)
Non-OECD Latin America/Caribbean								
Caribbean	1 [bo]	4–17	P**	12-months	6.90%	M	4.1%	(2.3–7.0%)
						F	6.4%	(3.6–11.1%)
Latin America, Andean	0	—	—	—	—	M	4.6%	(2.2–9.0%)
						F	6.9%	(3.3–13.3%)
Latin America, Central	3 [b, ah]	18+	M	Point & 12-months	1.9–9.9%	M	2.9%	(2.4–3.7%)
			F		5.9–14.4%	F	5.5%	(4.5–7.0%)
Latin America, Tropical	2 [bp, bq]	7–14, 18+	M	Point & 12-months	3.5–10.3%	M	3.4%	(3.1–3.8%)
			F		6.1–20.9%	F	6.3%	(5.7–7.0%)

*Some studies provided data for multiple regions so the sum of studies add to fewer than the total of 91.

**Specific studies only provided overall person estimates.

[a]Cho *et al.*, 2007. [b]WMHS Consortium, 2008. [e]McEvoy *et al.*, 2011. [c]Australian Bureau of Statistics, 1998. [c]Australian Bureau of Statistics, 2008. [f]Fergusson *et al.*, 1993. [g]Fergusson and Horwood, 2001. [h]Anderson *et al.*, 1987. [i]Oakley-Browne *et al.*, 1989. [j]Aalto-Setala *et al.*, 2001. [k]Almqvist *et al.*, 1999. [l]Beekman *et al.*, 1998. [m]Bijl *et al.*, 1998. [n]Canals *et al.*, 1997. [o]Carta *et al.*, 1991. [p]Faravelli *et al.*, 2004. [y]Faravelli *et al.*, 1989. [r]Ford *et al.*, 2003. [s]Gigantesco *et al.*, 2006. [t]Green *et al.*, 2005. [u]Jacobi *et al.*, 2004. [v]Lynch *et al.*, 2006. [w]Mathet *et al.*, 2003. [x]McConnell *et al.*, 2002. [y]Meyer *et al.*, 2001. [z]Pirkola *et al.*, 2005. [aa]Ritchie *et al.*, 2004. [ab]Sandanger *et al.*, 1999. [ac]Verhulst *et al.*, 1997. [ad]West *et al.*, 2003. [ae]Wittchen *et al.*, 1998. [af]Vicente *et al.*, 2004. [ag]Vicente *et al.*, 2006. [ah]Andrade *et al.*, 2000. [ai]Angold *et al.*, 2002. [aj]Costello *et al.*, 2003. [ak]Kessler *et al.*, 1994. [al]Lewinsohn *et al.*, 1993. [am]Narrow *et al.*, 2002. [an]Nguyen *et al.*, 2005. [ao]Regier *et al.*, 1990. [ap]Eytan *et al.*, 2004. [aq]Szadoczky *et al.*, 2004. [ar]Awas *et al.*, 1999. [as]Seedat *et al.*, 2004. [at]Pham *et al.*, 2004. [au]Orley and Wing, 1979. [av]Abas and Broadhead, 1997. [aw]Adewuya *et al.*, 2007. [ax]Ventevogel *et al.*, 2007. [ay]Ghanem *et al.*, 2009. [az]Ghubash *et al.*, 1992. [ba]Yasan *et al.*, 2009. [bb]Kadri *et al.*, 2007. [bc]Reddy *et al.*, 2003. [bd]Hosain *et al.*, 2007. [be]Islam *et al.*, 2003. [bf]Mullick and Goodman, 2005. [bg]Pillai *et al.*, 2008. [bh]Premarajan *et al.*, 1993. [bi]Joshi *et al.*, 2003. [bj]Krishnaswamy *et al.*, 2012. [bk]Nguyen *et al.*, 2011. [bl]Phillips *et al.*, 2009. [bm]Leung *et al.*, 2008. [bn]Gau *et al.*, 2005. [bo]Canino *et al.*, 2004. [bp]Andrade *et al.*, 2002. [bq]Fleitlich-Bilyk and Goodman, 2004.



Key: Crosses show individual empirical prevalence datapoints (horizontal lines reflect the estimate-specific age ranges and vertical lines indicate the estimate uncertainty). The solid line with a grey shaded region in each graph shows the mean and 95% UI of the adjusted prevalence distribution (model output). The dashed line with vertical bars in each graph shows the mean and standard deviation of the empirical priors. The solid red line on the horizontal axis shows a prior setting for zero prevalence before two years of age.

Figure 2. Unadjusted and adjusted empirical prevalence values for Australasia in 2010, showing relative association of the fixed and random effects.

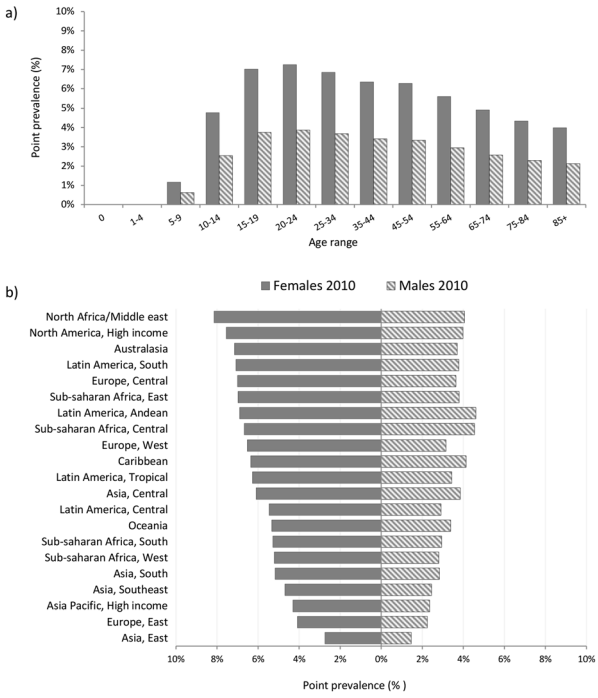


Figure 3. Estimated point prevalence for anxiety disorders for males and females in 2010 by (a) age group and (b) GBD world region.

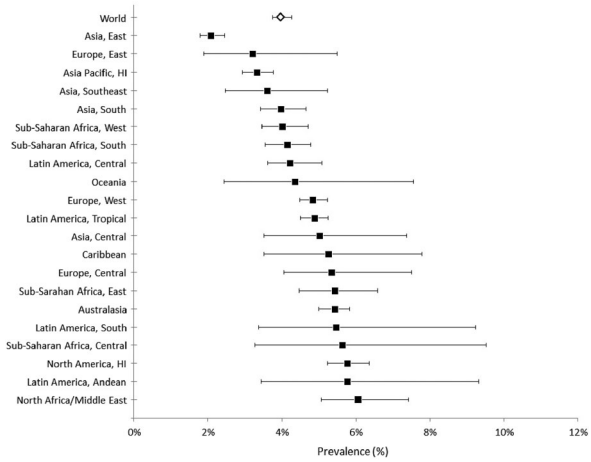


Figure 4. Age-weighted adjusted prevalence of anxiety disorders in 2010 with error bars showing 95% uncertainty.

Discussion

Anxiety disorders are prevalent in every population but incomplete and inconsistent data have obscured the distribution of clinical cases across regions. The Bayesian approach to hierarchical modeling allowed us to use all relevant information, including different epidemiologic parameters and prevalence estimates from studies with variable methods, resulting in a more empirically-driven prevalence model than was previously possible.

Estimated prevalence

Consistent with our previous findings, anxiety disorders were more common in females compared with males and in adolescents and young- to mid-aged adults compared

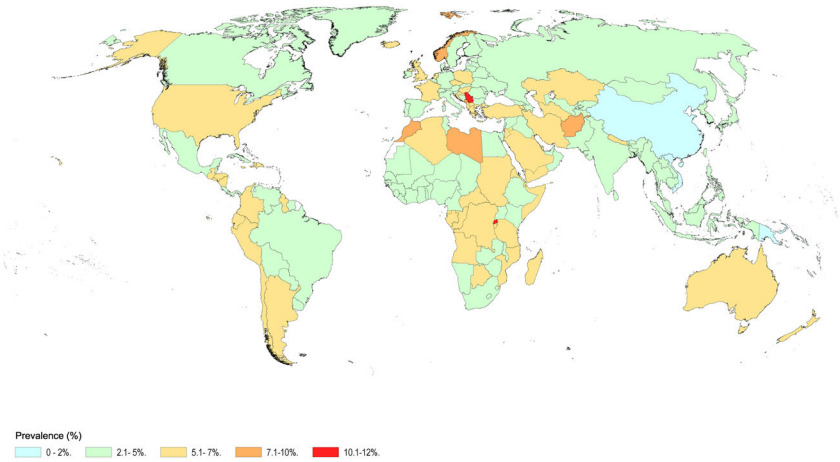


Figure 5. Age-standardized prevalence of anxiety disorders in 2010.

with older adults (Baxter *et al.*, 2013a). Recent evidence from the WMHS suggests that decreasing trends for depression in older ages may only be present in higher income countries (Kessler *et al.*, 2010). The same may apply for anxiety disorders but it is not yet clear from the available data.

The adjusted point prevalence, ranging between 2.1% and 6.1%, was lower than that predicted in our previous meta-regression which varied between 5.3% in Indo/Asian and African cultures and 10.4% in Euro/Anglo cultures (Baxter *et al.*, 2013b). This likely demonstrates the effect of using different covariates in a model, for instance culture (included in the meta-regression to explore sources of population variance) and variable definitions of covariates (e.g. conflict covariates in earlier analyses were based on "reported" conflict rather than number of deaths). Another factor that may contribute to this difference is the age-and sex-standardization of these new estimates. Published studies frequently use either broad or non-standardized age groups and previous analyses, including our meta-regression, were unable to establish an age pattern due to lack of statistical power. Using a Bayesian approach we were able to derive an age-pattern from the data which, when applied to the model as a prior, produced prevalence distributions across 20 age groups spanning the life-course. Pooling of these estimates, standardized by age and sex, provides us with the first estimate made for a population prevalence (ages zero to 100 years) rather than for adults alone as has been previously reported (Baxter *et al.*, 2013b).

An important factor in comparing models is the use of differently categorized covariates. This model has attempted to address some of the causes of heterogeneity in the data, however it essentially includes only dichotomous study-level covariates which may obscure the effects of multiple categories. For example meta-regression results show that prevalence was higher when more anxiety conditions were captured: compared with studies that captured 8–9 conditions, those with 6–7 conditions reported 30% lower prevalence and those with five or fewer conditions reported 40% lower prevalence (Baxter *et al.*, 2013b). The current model found little association for a dichotomized covariate as studies reporting six or fewer conditions achieved an odds ratio (OR) of 1.0 (95% UI 0.9–1.1) compared with studies reporting seven or more conditions, resulting in minimal adjustment for non-comprehensive estimates.

Regional differences

Prevalence differed by up to three-fold across GBD world regions, however there was substantial uncertainty around the adjusted estimates acknowledging the limitations in compiling a comprehensive global model based on incomplete and heterogeneous data. Uncertainty was particularly broad around the regions without empirical data.

Consistent with previous findings, anxiety tended to be less prevalent in Asian populations (Baxter *et al.*, 2013b; Somers *et al.*, 2006; Kessler *et al.*, 2009a) compared with other populations. Yet, population genetics demonstrate that a polymorphic expression of the serotonin transporter gene, most prevalent in East Asia populations, is significantly associated with anxiety-related personality traits such as neuroticism (Sen *et al.*, 2004) and fear conditioning (Lonsdorf *et al.*, 2009). Novel gene-by-environment research findings hypothesize that protective cultural values such as collectivism have evolved which buffer

genetically susceptible populations from increased prevalence of anxiety disorders (Chiao and Blizinsky, 2010). It is possible therefore that cultural characteristics such as collectivism, generally found outside the high-income and Westernized cultures, may be a protective factor against developing anxiety disorders.

It should be noted, however, that this hypothesis is predicated on a negative association between specific cultural characteristics and current prevalence estimates. Yet the accuracy of that data is still being debated. Cross-national comparisons thus far (including this analysis) are based on Westernized diagnostic criteria (DSM and ICD) and survey tools. There is potential for cultural bias in the diagnostic criteria and this is relevant to identifying true regional differentials as culturally-distinctive presentation may reduce identification of cases (Phillips *et al.*, 2009; Lewis-Fernández *et al.*, 2010). The potential risk for under-estimating anxiety in such populous countries, in terms of developing a global disease model, is that regional differentials may be misrepresented.

Prevalence was highest in regions with populations previously exposed to conflict and those comprising high income countries, consistent with previous findings (Baxter *et al.*, 2013a; Kessler *et al.*, 2009a). Given the overlapping uncertainty limits however these results can only be considered indicative, The sole data for some populations exposed to conflict (for instance those in Kenya, Rwanda, Serbia and Kosovo) were for PTSD only. Whilst we assumed that PTSD would be the predominant anxiety disorder, cases of other specific disorders could also have been present in the community. Therefore lack of data on the full spectrum of anxiety disorders across regions likely resulted in an under-estimate of total anxiety disorders in conflict and post-conflict populations. Our current lack of understanding of the relative importance of specific anxiety disorders in different populations suggests this is an area where further research needs to be undertaken.

Limitations

Anxiety disorders share core features and often co-occur, however specific anxiety disorders can vary considerably in terms of onset and persistence. It is important to acknowledge, therefore, that both the prior settings and final prevalence estimates reported here can only be considered a broad generalization of the anxiety disorder category of illnesses.

Further, a dearth of information was found for remission and mortality in community cases of anxiety disorders. Our analyses did not consider increased relative risk of mortality. Most findings of increased mortality in anxiety disorders have been based on clinical samples, particularly in terms of higher suicide rates, and samples with later age at ascertainment, possibly due to associated diseases in older age such as circulatory disease (Grasbeck *et al.*, 1996). However there was insufficient data available to inform these calculations.

Other substantive population characteristics were likely not captured. Regional prevalence estimates were informed by the GBD 2010 super-region which potentially obscured cultural differences. For instance Asia Pacific High Income was grouped with Western Europe, North America, Australasia and Southern Latin America in the "High income" super-region. In addition to cultural variability other population-specific factors may have been obscured. For instance, exposure to trauma other than conflict, such as natural disaster, is strongly correlated with higher prevalence and increased persistence of anxiety disorders. However these often (but not always) affect sub-populations within a country so it is difficult to quantify effects at the population level. Consideration of these factors is important for quantifying country-level health loss and response priorities, highlighting the need for additional national and sub-national burden of disease studies.

A potential limitation in the Bayesian approach is the use of "priors". Whilst incorporation of prior information can be a strength where empirical data are limited, its value is limited by the accuracy of the information chosen to inform priors. However, where the amount of empirical data increases, prior distributions tend to become less influential. The goal in improving a disease model should therefore be improving the coverage and accuracy of epidemiological data.

Whilst our analyses were conducted using a Bayesian approach, other approaches such as multiple bias modelling can be valuable when working with sparse and noisy data. Comparison of alternate approaches for modelling systematic error in descriptive epidemiological data would be a constructive area for future research.

Conclusion

Epidemiological input forms the core of non-fatal estimates of disease burden and while inconsistencies and gaps characterize the available data modelling techniques will be necessary to ensure burden is accounted for in non-represented populations. An important area of future research is improving the evidence for substantive difference in prevalence of anxiety disorders, particularly in Asia East where anxiety is reported to be less common, and those regions

where anxiety appeared elevated in our estimates, but uncertainty prevented the reporting of conclusive estimates.

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Appendix A. Specific conditions included in the definition of "any" anxiety disorder

Specific anxiety disorders included under the GBD2010 definition for "any" anxiety disorder
• separation anxiety disorder [DSM-IV: 309.21, ICD10: F93.0]
• panic disorder [DSM-IV: 300.01,300.21, ICD10: F41.0]
• agoraphobia [DSM-IV: 300.22, ICD10: F40.00]
• specific phobia [DSM-IV: 300.29, ICD10: F40.2]
• social phobia [DSM-IV: 300.23, ICD10: F40.1]
• obsessive-compulsive disorder (OCD) [DSM-IV: 300.3, ICD10: F42.9]
• post-traumatic stress disorder (PTSD) [DSM-IV: 309.81, ICD10: F43.1]
• generalized anxiety disorder (GAD) [DSM-IV: 300.02, ICD10: F41.1]
• anxiety disorder not otherwise specified (NOS) [DSM-IV: 300.00, ICD10: F41.9]

Appendix B. World regions and super-regions used in modelling disease parameters in GBD2010

GBD Super Region	GBD Region	Country
High income regions	Asia Pacific, High Income	Brunei Darussalam, Japan, Republic of Korea (South Korea), Singapore
	Australasia	Australia, New Zealand
	Europe, Western	Akrotiri and Dhekelia, Aland Islands, Andorra, Austria, Belgium, Channel Islands, Cyprus, Denmark, Faeroe Islands, Finland, France, Germany, Gibraltar, Greece, Greenland, Holy See, Iceland, Ireland, Isle of Man, Israel, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, United Kingdom
	Latin America, Southern	Argentina, Chile, Falkland Islands (Malvinas), Uruguay
	North America, High Income	Canada, Saint Pierre et Miquelon, United States of America

(*Continues*)

Appendix B. (Continued)

GBD Super Region	GBD Region	Country
	Asia, Central	Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan
Eastern Europe/ Central Asia	Europe, Central	Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Kosovo, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, The Former Yugoslav Republic of Macedonia
	Europe, Eastern	Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
	Sub-Saharan Africa, Central	Angola, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon
	Sub-Saharan Africa, East	Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mayotte, Mozambique, Rwanda, Somalia, Sudan, Uganda, United Republic of Tanzania, Zambia
	Sub-Saharan Africa, Southern	Botswana, Lesotho, Namibia, South Africa, Swaziland, Zimbabwe
	Sub-Saharan Africa, West	Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Cote d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria,
Sub-Saharan Africa		Saint Helena, Sao Tome and Principe, Senegal, Sierra Leone, Togo
		Algeria, Afghanistan, Bahrain, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Occupied
North Africa/ Middle East	North Africa/ Middle East	Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, Western Sahara, Yemen
	Asia, South	Bangladesh, Bhutan, India, Nepal, Pakistan
South Asia	Asia, Southeast	Cambodia, Christmas Island, Cocos Islands, Indonesia, Lao People's Democratic Republic, Malaysia, Maldives, Mauritius, Myanmar, Philippines, Réunion, Seychelles, Sri Lanka, Thailand, Timor-Leste, Viet Nam
	Asia, East	China, Democratic People's Republic of Korea (North Korea), Hong Kong, Taiwan
East Asia and Pacific	Oceania	American Samoa, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, New Caledonia, Niue, Norfolk Island, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna Islands
	Caribbean	Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican Republic, French Guiana, Grenada, Guadaloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, Netherlands Antilles, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos Islands, US Virgin Islands
Non-OECD Latin America/Caribbean	Latin America, Andean	Bolivia, Ecuador, Peru
	Latin America, Central	Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela
	Latin America, Tropical	Brazil, Paraguay

Source: The Global Burden of Diseases, Injuries and Risk Factors Study Operations Manual. Final draft: 20 January, 2009. Produced by the Harvard Initiative for Global Health, Institute for Health Metrics and Evaluation at the University of Washington, Johns Hopkins University, University of Queensland, and the World Health Organization.
Note: OECD, Organization for Economic Cooperation and Development.

Int. J. Methods Psychiatr. Res. 23(4): 422–438 (2014). DOI: 10.1002/mpr

Appendix C. Model inputs

(A) Minimal input required for DisMod-MR

For DisMod and other analysis purposes, we needed certain minimal information about the parameter of interest (e.g. incidence, remission, case fatality, etc.) or proportion (e.g. prevalence). These were: GBD Cause, GBD Cause Code, Sequela, Case Definition, Region, Parameter, Sex, Country, Urbanicity, Coverage, Age Start, Age End, Age Units, Estimate Year Start, Estimate Year End, Parameter Value, Standard Error, Units, Type of Confidence Limit, Sampling Strategy, Total Study Size *N*, Study Information, and Citation.

Source: http://winthrop.ihme.washington.edu/public/file_formats.html [accessed 20 June 2012].

(B) Defining epidemiological parameters required as input for DisMOD-MR

- Prevalence: A "case" was defined as meeting criteria as per the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the World Health Organization (WHO) Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines (ICD).
- Incidence hazard rates: Incidence where person years of follow-up were used as the denominator.
- Remission: remission was defined as no longer meeting the clinical threshold according to DSM or ICD diagnostic criteria.

Source: The Global Burden of Diseases, Injuries and Risk Factors Study Operations Manual. Final draft: 20 January, 2009. Produced by the Harvard Initiative for Global Health, Institute for Health Metrics and Evaluation at the University of Washington, Johns Hopkins University, University of Queensland, and the World Health Organization.

(C) Additional information on remission and mortality studies which provided input for the final model

- Remission

Of the five remission studies that reported sufficient information to meet our selection criteria, one focussed on children with OCD (Reddy *et al.*, 2003); three on youths and young adults diagnosed with OCD (Wewetzer *et al.*, 2001), PTSD (Perkonigg *et al.*, 2005) and "any" anxiety disorder (Cantwell and Baker, 1989); and the finally, on older adults with 'any' anxiety disorder (Schuurmans *et al.*, 2005).

Calculations of remission rates

Source	Sample	Remission proportion	Followup (years)	proportion remitted
Schuurmans, 2005	14	0.50	6.0	0.12
	48	0.25	6.0	0.05
Perkonigg, 2005	47	0.65	4.1	0.26
Perkonigg, 2005	78	0.47	4.1	0.15
Cantwell, 1989	31	0.48	4.0	0.17
Wewetzer, 2001	55	0.64	11.2	0.09
Reddy, 2003	58	0.48	5.0	0.13
Total weighted remission rate				0.14

$$\text{Weighted remission rate} = \sum \frac{a\left(\frac{-\ln((1-b))}{c}\right)}{\sum a}$$

Where: a = sample size, b = remission proportion, and c = follow-up (years)

- Mortality

(*Continues*)

Appendix C. (Continued)

Community-representative studies looking at excess all-cause mortality in anxiety disorders were scarce. The table below shows those that met our inclusion criteria. Insufficient information was available to stratify by gender or age.

Source	Study design	Follow-up (years)	Outcome measured	Mortality estimate
Longitudinal Aging Study Amsterdam (LASA). Van Hout *et al.*, 2004	Longitudinal community-based study. Older adults (aged 55–85 yrs)	7.5	DSM-III anxiety disorder	Males: SMR 1.78 (95% CI 1.01–3.13) Females: 0.89 (95% CI 0.51–1.56)
New Haven ECA Study. County Bruce *et al.*, 1994	Longitudinal community-based study. Adults (aged 40 years +)	9	DSM-III anxiety disorders	Panic disorder: RR 1.05 ($p = 0.95$) Phobia: RR 1.19 ($p = 0.25$) OCD: 1.22 ($p = 0.42$)

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