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Comorbidity within mental disorders: a comprehensive analysis based on 145 990 survey respondents from 27 countries

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Abstract

Aims. Epidemiological studies indicate that individuals with one type of mental disorder have an increased risk of subsequently developing other types of mental disorders. This study aimed to undertake a comprehensive analysis of pair-wise lifetime comorbidity across a range of common mental disorders based on a diverse range of population-based surveys.

Original Article

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Methods. The WHO World Mental Health (WMH) surveys assessed 145 990 adult respondents from 27 countries. Based on retrospectively-reported age-of-onset for 24 DSM-IV mental disorders, associations were examined between all 548 logically possible temporally-ordered disorder pairs. Overall and time-dependent hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. Absolute risks were estimated using the product-limit method. Estimates were generated separately for men and women.

Results. Each prior lifetime mental disorder was associated with an increased risk of subsequent first onset of each other disorder. The median HR was 12.1 (mean = 14.4; range 5.2–110.8, interquartile range = 6.0–19.4). The HRs were most prominent between closely-related mental disorder types and in the first 1–2 years after the onset of the prior disorder. Although HRs declined with time since prior disorder, significantly elevated risk of subsequent comorbidity persisted for at least 15 years. Appreciable absolute risks of secondary disorders were found over time for many pairs.

Conclusions. Survey data from a range of sites confirms that comorbidity between mental disorders is common. Understanding the risks of temporally secondary disorders may help design practical programs for primary prevention of secondary disorders.

Introduction

Comorbidity within mental disorder is common – individuals with one type of mental disorder often develop other types of mental disorders across their lifespan (Pincus *et al.*, 2004; Maj, 2005; Kessler *et al.*, 2011, 2012). Understanding patterns of comorbidity within mental disorders is essential if we wish to understand the influence of mental disorders on premature mortality (Plana-Ripoll *et al.*, 2019*a*) and the contribution of mental disorders to the global burden of disease (Weye *et al.*, 2020). Recently, we published a comprehensive study of pair-wise comorbidity within mental disorders based on Danish health registers (Plana-Ripoll *et al.*, 2019*b*). That study found that receiving a diagnosis of a wide range of mental disorders were associated with significantly elevated risks of a subsequent diagnosis of a wide range of other types of mental disorder. In other words, lifetime comorbidity among mental disorders was pervasive. That study also presented age- and sex-specific hazard ratios (HRs) and cumulative incidence proportions (CIPs) for all disorder pairs studied. However, the study had several important limitations, including that it only examined broad ICD-10 F subchapter headings (e.g. mood disorders) rather than specific types of disorders (e.g. Major Depressive Episode, Bipolar Affective Disorder etc.) and was based on registers limited to cases diagnoses in hospital and outpatient settings (i.e. those who received treatment only from their general practitioners were not included). In addition, as Denmark is a wealthy country, estimates may not be generalisable to a wider range of sites.

We had the opportunity to address these gaps by examining data from the WHO World Mental Health (WMH) Surveys (Kessler *et al.*, 2009), a series of community epidemiological surveys that assessed lifetime prevalence of a wide range of both untreated and treated mental disorders in a representative household sample across a range of nations. The study aimed to examine pair-wise temporally-ordered lifetime comorbidity between all logically possible pairs of DSM-IV disorders (24 types) assessed in the WMH surveys and to generate age- and sex-specific HRs and CIPs for each of these pairs. Our study is observational, and thus we do not make any claim that prior mental disorders cause later mental disorders. Our guiding hypothesis is that comorbidity within mental disorders is pervasive. The data are available in an interactive data visualisation webpage (https://holtzy.github.io/Como-in-World-Heath-Survey/index.html).

Methods

Samples and procedures

Data came from 29 coordinated WMH Surveys conducted in 27 countries. Spain and Colombia have separate national and regional surveys. A total of 19 of these surveys were nationally representative, and several focused on selected urban or metropolitan areas within the country. These surveys included six lower-middle-income countries, seven upper-middle-income countries, and 16 high-income countries, according to the World Bank classification at the time the survey was conducted. In most countries, internal subsampling was used to reduce respondent burden and average interview time by dividing the interview into two parts (see Supplement for additional details).

Measures

All surveys used the WHO Composite International Diagnostic Interview (CIDI 3·0) (Kessler *et al.*, 2005), a validated, fully structured lay administered interview. Mental disorders were diagnosed using DSM-IV criteria. A total of 24 mental disorders were assessed, including lifetime mood disorders (Major Depressive Episode [MDE], Bipolar Disorder, Dysthymia), lifetime anxiety disorders (Panic Disorder, Generalised Anxiety Disorder [GAD], Social Phobia, Specific Phobia, Agoraphobia without Panic Disorder, Post-Traumatic Stress Disorder [PTSD], Obsessive-Compulsive Disorder [OCD], Child and Adult Separation Anxiety Disorder), lifetime impulse-control disorder (Intermittent Explosive Disorder, Conduct Disorder, Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Anorexia Nervosa, Bulimia Nervosa, Binge Eating Disorder), lifetime substance-use disorder (Alcohol abuse and dependence, Drug abuse and dependence, Nicotine Dependence). CIDI organic exclusion rules were applied when making a diagnosis but hierarchy rules were not applied in this study.

The CIDI was developed as an interview to be conducted by trained laypersons. The questions and answers are standardised to a high level in order to reduce the interpretation by interviewers to a maximum extent. In the WMH surveys, all survey interviewers went through a two-week certification training course for CIDI 3.0 instrument prior to starting fieldwork. All

interviewers have received the same training and adhere to the same protocol regarding contacts and interview administration. The trainers of the interviewers also attended a one-week training course carried out by WHO-certified trainers. Blinded clinical reappraisal interviews using SCID with CIDI found good concordance between diagnoses (Haro *et al.*, 2006).

Statistical analysis

We estimated the associations between all logically possible pair-wise DSM-IV disorders accounting for the temporality of these disorders. As the surveys were cross-sectional, temporality was established using retrospectively reported of age-of-onset for each disorder. We estimated the risk of reporting later disorder in those who were exposed to a disorder of interest (henceforth referred to as 'prior disorder'). All prior disorders were treated as time-varying exposures when assessing the risk of a later disorder. Cox proportional hazards models with the age of onset of the prior disorder as a time-dependent covariate were used to calculate the HR of the first onset of later disorder associated with the prior disorder. We examined models that (i) adjusted for country, age-cohort (i.e. age-at-interview) and sex ('Model A'), and (ii) adjusted for country, age-cohort, sex, type and number of mental disorders with onset preceding the prior disorder ('Model B'). For overall HRs and the CIPs, we repeated the analysis to obtain sex-specific estimates. We further investigated if the associations between prior and later disorders differed by time since the onset of the prior disorder by estimating time-dependent HRs. For this analysis, we repeated models A and B using six dummy variables representing time since the exposure of prior disorder: 0–1, 1–2, 2–5, 5–10, 10–15, 15 years or more (in order to be comparable to the analysis by Plana-Ripoll *et al.* (2019*b*)). All parameter estimates (beta) were exponentiated to obtain HRs. The cumulative incidence or cumulative failure probability curves were generated using the product limit approach (Kaplan and Meier, 1958) by restricting the analysis to the subset of those with a prior disorder. These were stratified by sex and age of onset of the prior disorder (<20, 20–40, >40 years; consistent with the analysis by Plana-Ripoll *et al.* (2019*b*)). Respondents were followed until they developed later disorder or until the time at an interview (censored). This allowed us to estimate the absolute risk of later disorder after developing the prior disorder. All analyses were performed using SAS 9.4. The Supplementary Material, and all the data management and analysis codes can be found on https://github.com/clim072/NB-COMO. An interactive webpage was also created to display all the results from this study https://holtzy.github.io/Como-in-World-Heath-Survey/index.html.

Results

Pair-wise associations between mental disorders

The characteristics of the sample are presented in Table 1. The estimates for the pair-wise comorbidity between mental disorders are presented in online Supplementary Fig. 1. A selection of the four panels is shown in Fig. 1. In the basic model adjusting for age-cohort, sex and country (model A; purple circles in the plots), all prior disorders were associated with an elevated risk of the onset of later disorders (a vertical line at HR = 1 representing 'null effect' is also plotted in each panel). For model B (orange triangles in the plots), the effect sizes attenuated substantially and the confidence intervals (CIs) included one for some disorder pairs (e.g. when alcohol or drug dependence was the prior disorder). However, in general, the overall pattern of the findings remained comparable between the two models. The sex-specific associations with adjustment for comorbidity (model B) are shown in online Supplementary Fig. 2. The median HR was 12.1 (mean = 14.4; range 5.2–110.8, interquartile range = 6.0–19.4). Some of the highest HRs were found between closely-related types of mental disorders. For example, prior MDE and later dysthymia (HR = 45.9, 95% CI = 40.5–51.9) and prior Bulimia Nervosa and later Binge Eating Disorder (HR = 62.3, 95% CI = 48.5–80.2).

Time-dependent associations between mental disorders

Online Supplementary Fig. 3 shows the time-dependent HRs for all disorder pairs. Figure 2 shows the HR of later disorder depending on a previous onset of the prior disorder and the time since the onset of the prior disorder after adjusting for the type and number of comorbid disorders (model B) for selected pairs. Generally, respondents had the highest HRs in the first 2 years after the onset of the prior disorder. The risk of developing later disorder then fell slowly over time or plateaued out after 10 years. For example, after adjusting for comorbidity, the risk of developing GAD is 55 times greater in the initial year after developing major depression compared to those without (HR = 55.1, 95% CI = 51.0–59.6). Between 2 and 5 years after, the risk decreased by half (HR = 27.4, 95% CI = 25.3–29.7) and by 15 years, the risk was about one-eight in those with major depression compared to those without (HR = 6.6, 95% = 5.7–7.7).

Absolute risks

The absolute risks for all disorder pairs can be found in online Supplementary Fig. 4. Figure 3 shows the overall absolute risk of developing later disorder among respondents with a prior mental disorder for selected pairs. Each panel shows the overall absolute risks (solid orange line) and 95% CI (shaded area in grey – however often the line size masks the precise CIs). For many disorder pairs, the absolute risk of a subsequent disorder increased linearly and continued to increase over the period of observation (e.g. prior PTSD, and later MDE). Other disorder pairs have a small linear increase over the first few years, which then plateaued out over time (e.g. prior PTSD and later alcohol abuse) (see Fig. 3). The absolute risk of developing a subsequent disorder varies by sex in keeping with the sex ratio of the consistent mental disorders within the pairs (see online Supplementary Fig. 5). Interestingly, we found that the absolute risk of a subsequent disorder is generally higher among those who developed a prior disorder before 20 years of age (compared to those who have their onset 20 years or later, but who are followed up for a similar period) (see online Supplementary Fig. 6). Using Major Depressive Episode–Nicotine Dependence pair as an example, ~2% of the respondents developed nicotine dependence within 1 year of the onset of MDE. This risk increases to 22.7% 20 years after the initial onset of MDE and is higher for men (30.3%, 95% CI = 29.8–30.8) than for women (19.3%, 95% CI = 19.0–19.5%). The absolute risk of developing nicotine dependence 20 years after the initial onset of MDE is the highest in those with an early onset of MDE (onset of MDE aged <20 years = 32.7%, 95% CI = 32.3–33.1%). In those who have the onset of MDE between ages 20 and 40 years, the risk of nicotine dependence is 17·1% (95% CI = 16.8–17.4%). Finally, in those with the onset

Table 1. WMH sample characteristics by World Bank income categories[a]

Country	Survey	Sample characteristics[b]	Field dates	Age range	Sample size			Response rate[d]
					Part I	Part II	Part II and age <44[c]	
Low and lower-middle-income countries								
Colombia	NSMH	All urban areas of the country (about 73% of the total national population).	2003	18–65	4426	2381	1731	87.7
Iraq	IMHS	Nationally representative.	2006–7	18–96	4332	4332	–	95.2
Nigeria	NSMHW	21 of the 36 states in the country, representing 57% of the national population.	2002–3	18–100	6752	2143	1203	79.3
PRC[e] – Shenzhen[f]	Shenzhen	Shenzhen metropolitan area. Included temporary residents as well as household residents.	2006–7	18–88	7132	2475	–	80.0
Peru	EMSMP	Five urban areas of the country (~38% of the total national population).	2004–5	18–65	3930	1801	1287	90.2
Ukraine[f]	CMDPSD	Nationally representative.	2002	18–91	4725	1720	540	78.3
Total					31 297	14 852	4761	83.6
Upper-middle-income countries								
Brazil – São Paulo	São Paulo Megacity	São Paulo metropolitan area.	2005–7	18–93	5037	2942	–	81.3
Bulgaria	NSHS	Nationally representative.	2003–7	18–98	5318	2233	741	72.0
Lebanon	LEBANON	Nationally representative.	2002–3	18–94	2857	1031	595	70.0
Mexico	M-NCS	All urban areas of the country (about 75% of the total national population).	2001–2	18–65	5782	2362	1736	76.6
Colombia – Medellin[g]	MMHHS	Medellin metropolitan area	2011–12	18–65	3261	1673	–	97.2
Romania	RMHS	Nationally representative.	2005–6	18–96	2357	2357	–	70.9
South Africa[f]	SASH	Nationally representative.	2003–4	18–92	4315	4315	–	87.1
Total					28 927	16 913	3072	78.5
High-income countries								
Argentina	AMHES	8 largest urban areas of the country (about 50% of the total national population).	2015	18–98	3927	2116	–	77.3
Australia[f]	NSMHWB	Nationally representative.	2007	18–85	8463	8463	–	60.0
Belgium	ESEMeD	Nationally representative.	2001–2	18–95	2419	1043	486	50.6
France	ESEMeD	Nationally representative.	2001–2	18–97	2894	1436	727	45.9
Germany	ESEMeD	Nationally representative.	2002–3	18–95	3555	1323	621	57.8
Israel	NHS	Nationally representative.	2002–4	21–98	4859	4859	–	72.6
Italy	ESEMeD	Nationally representative.	2001–2	18–100	4712	1779	853	71.3
Japan	WMHJ 2002–2006	11 metropolitan areas.	2002–6	20–98	4129	1682	–	55.1
The Netherlands	ESEMeD	Nationally representative.	2002–3	18–95	2372	1094	516	56.4
New Zealand[f]	NZMHS	Nationally representative.	2003–4	18–98	12 790	7312	–	73.3
N. Ireland	NISHS	Nationally representative.	2004–7	18–97	4340	1986	–	68.4
Poland	EZOP	Nationally representative	2010–11	18–64	10 081	4000	2276	50.4
Portugal	NMHS	Nationally representative.	2008–9	18–81	3849	2060	1070	57.3
Spain	ESEMeD	Nationally representative.	2001–2	18–98	5473	2121	960	78.6

(*Continued*)

Table 1. (*Continued.*)

Country	Survey	Sample characteristics[b]	Field dates	Age range	Sample size			Response rate[d]
					Part I	Part II	Part II and age <44[c]	
Spain- Murcia	PEGASUS-Murcia	Murcia region	2010–12	18+	2621	1459		67.4
United States	NCS-R	Nationally representative.	2002–3	18–99	9282	5692	3197	70.9
Total					85 766	48 425	10 706	63.1
Overall sample					145 990	80 190	18 539	69.5

[a]The World Bank (2012) Data. Accessed 12 May 2012, at http://data.worldbank.org/country. Some of the WMH countries have moved into new income categories since the surveys were conducted. The income groupings above reflect the status of each country at the time of data collection. The current income category of each country is available at the preceding URL.
[b]Most WMH surveys are based on stratified multistage clustered area probability household samples in which samples of areas equivalent to counties or municipalities in the US were selected in the first stage followed by one or more subsequent stages of geographic sampling (e.g. towns within counties, blocks within towns, households within blocks) to arrive at a sample of households, in each of which a listing of household members was created and one or two people were selected from this listing to be interviewed. No substitution was allowed when the originally sampled household resident could not be interviewed. These household samples were selected using area probability design in all countries other than France (where telephone directories were used to select households) and the Netherlands (where postal registries were used to select households). Several WMH surveys (Belgium, Germany, Italy) used municipal resident registries to select respondents without listing households. The Japanese sample is the only totally un-clustered sample, with households randomly selected in each of the 11 metropolitan areas and one random respondent selected in each sample household. 21 of the 30 surveys are based on nationally representative household samples.
[c]Argentina, Australia, Brazil, Colombia-Medellin, Iraq, Israel, Japan, New Zealand, Northern Ireland, PRC – Shenzhen, Romania, South Africa and Spain-Murcia did not have an age restricted Part 2 sample. All other countries, with the exception of Nigeria, PRC (B-WMH; S-WMH), and Ukraine (which were age restricted to ⩽39) were age restricted to ⩽44.
[d]The response rate is calculated as the ratio of the number of households in which an interview was completed to the number of households originally sampled, excluding from the denominator households known not to be eligible either because of being vacant at the time of initial contact or because the residents were unable to speak the designated languages of the survey. The weighted average response rate is 69.5%.
[e]People's Republic of China.
[f]For the purposes of cross-national comparisons we limit the sample to those 18+.
[g]Colombia moved from the 'lower and lower-middle-income' to the 'upper-middle-income' category between 2003 (when the Colombian National Study of Mental Health was conducted) and 2010 (when the Medellin Mental Health Household Study was conducted), hence Colombia's appearance in both income categories. For more information, please see footnote *a*.

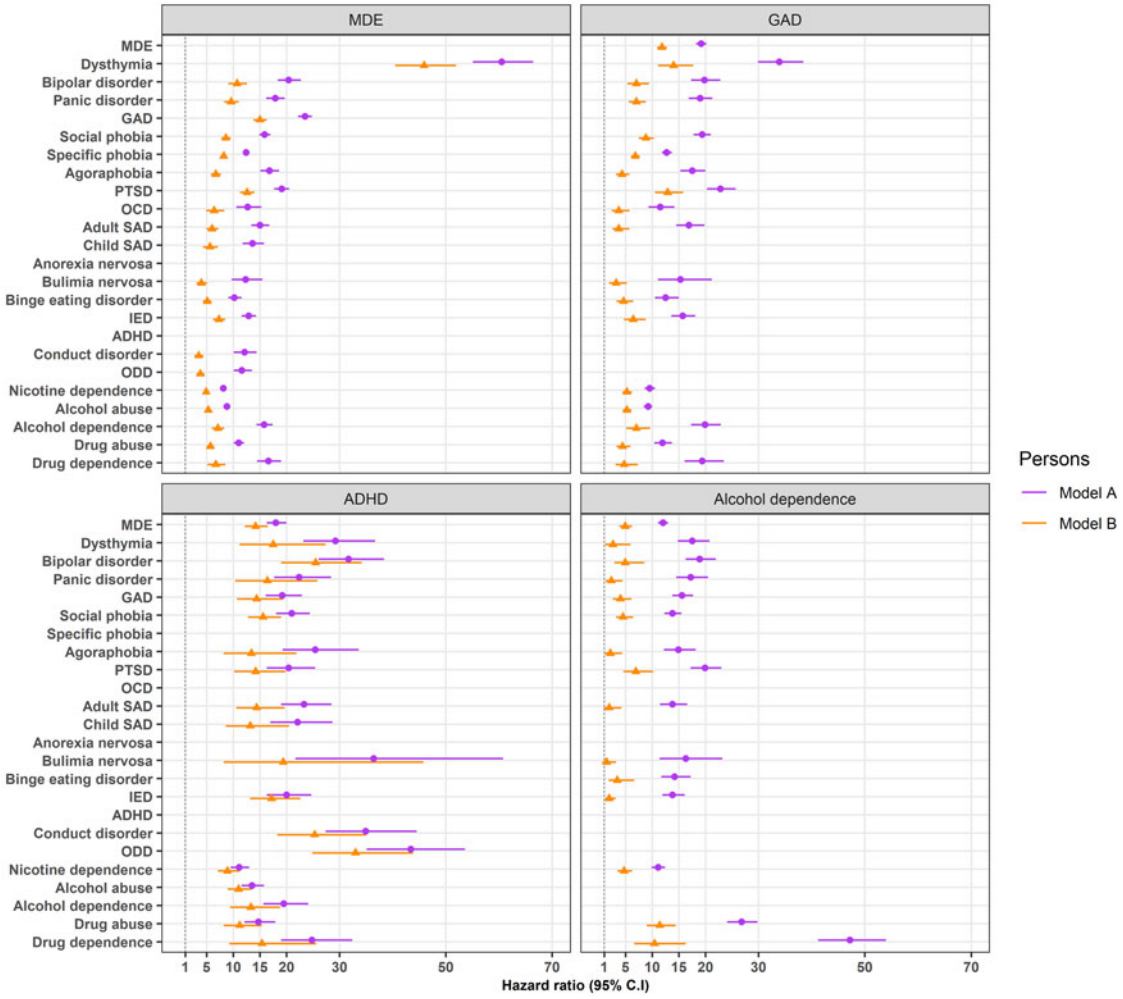

Fig. 1. Visualisation of several of the pair-wise associations between mental disorders

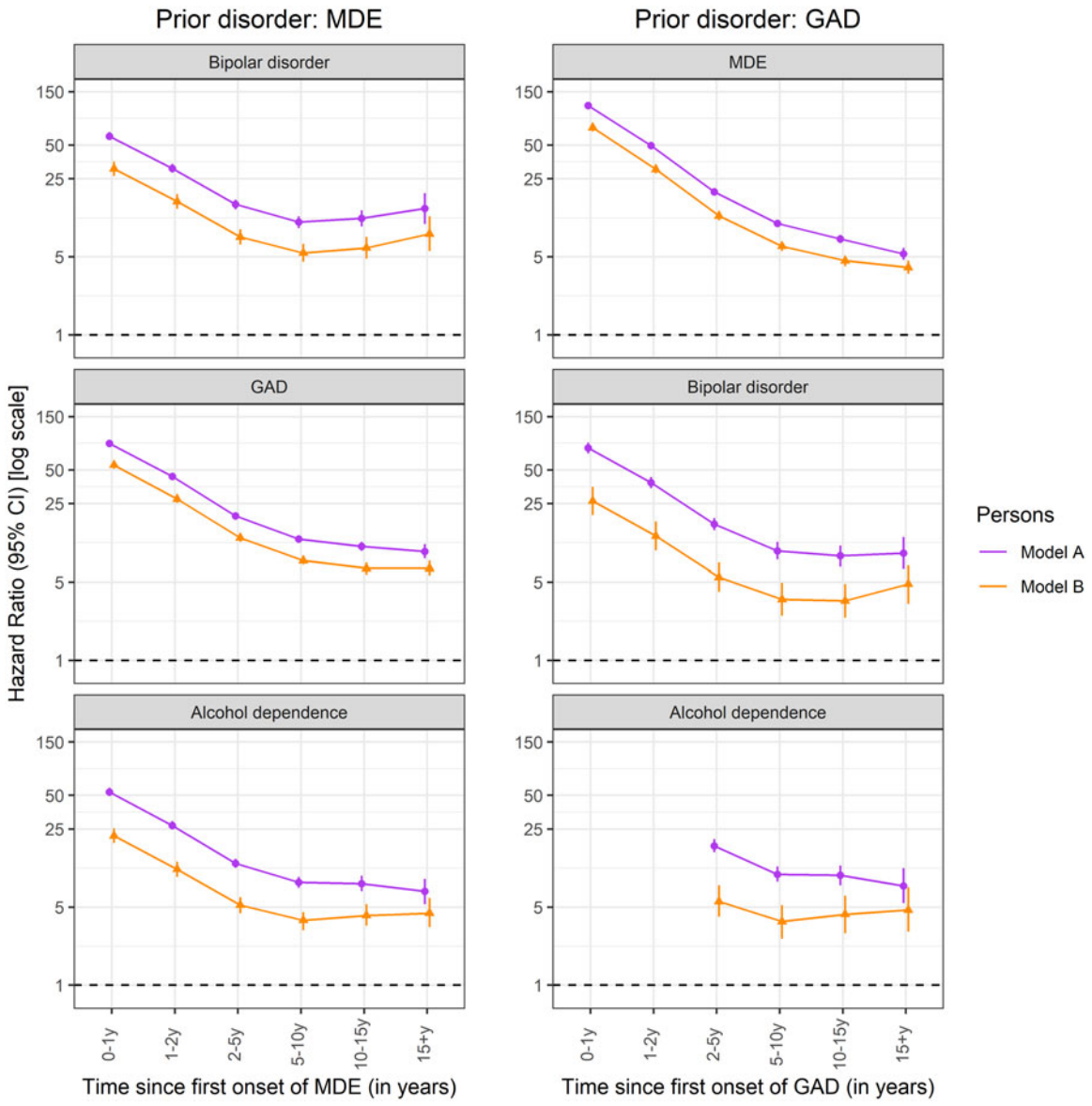

Fig. 2. Time-dependent (lagged) associations between prior disorders and subsequent later disorders.

of MDE aged 40 years or older, the risk of nicotine dependence is only 7.0% (95% CI = 6.6–7.3%). (Note – these groups have each been followed for 20 years).

Discussion

Based on survey data from many nations, we have provided a comprehensive map of pair-wise comorbidity within mental disorders. We confirm that the pair-wise comorbidity estimates from our cross-national study demonstrate the pervasive nature of comorbidity within mental disorders – the estimates were broadly consistent with those found in Danish registers (Plana-Ripoll *et al.*, 2019*b*). The current study addresses several important gaps in the literature. First, in the current study, we provide estimates based on specific types of mental disorders as classified by DSM-IV criteria (our previous study was based on broad ICD-10 subchapters). Second, we demonstrate the very high risk of developing comorbidity between closely-related types of mental disorders. Third, the time-dependent HRs for the onset of each type of later-disorder show persistence over several decades. Finally, we confirm that some types of prior mental disorders were associated with appreciable absolute risks for later disorder over the following 30–40 years.

In keeping with prior studies based on the WMH Surveys, the increased risk of comorbidity was *pervasive* across all types of disorder pairs (Kessler *et al.*, 2005, 2012, 2018). Despite the substantial methodological differences between the current study and the prior studies (e.g. international *v.* single nation; DSM-IV specific disorders *v.* ICD-10 broad subchapters; register-based diagnoses *v.* population-based survey), the overall pattern of findings was striking – each type of prior mental disorder was associated with an increased risk of most other types of mental disorders. In particular, we confirm very high risks for individuals with pairs of closely-related disorders (e.g. bulimia nervosa and subsequent binge eating disorder) (Kotov *et al.*, 2018). Closely-related disorders often share symptoms; thus, it is feasible that

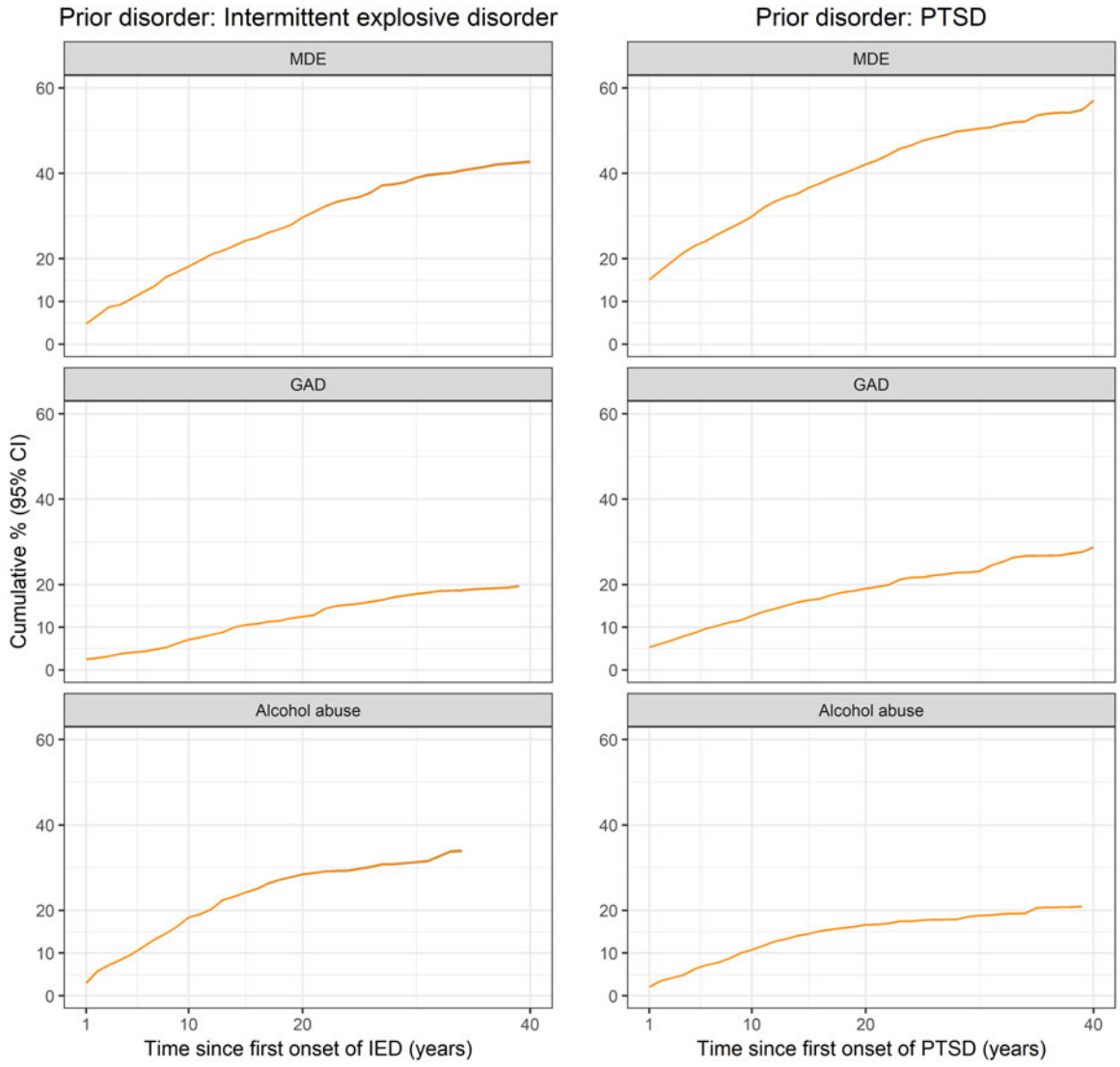

Fig. 3. Absolute risk of a subsequent disorder after developing a prior disorder.

respondents may have an imperfect recall for the precise sequence of such disorders. Previous studies based on the WMH surveys have identified that people with one type of prior disorder (e.g. an internalising disorder) were more likely to develop subsequent additional internalising disorders (in contrast to subsequent externalising disorders) (Kessler *et al.*, 2011).

In keeping with our prior register-based study (Plana-Ripoll *et al.*, 2019*b*), the time-dependent HRs between mental disorder pairs confirmed that the risk of later-disorder was substantially higher within the first 1–2 years after the onset of the prior-disorder (compared to longer intervals). The Danish study identified very large HRs within the first 6 months of the prior disorder, perhaps reflecting Berkson's bias (Snoep *et al.*, 2014). The current estimates within the first 6–12 months were more conservative and plausible. Mindful that the surveys were cross-sectional, and the recollection of lifetime psychiatric history may be imperfectly recalled (especially for long passed events), the two studies provide convergent evidence for the persistent nature of the increased risk of comorbidity. In general, regardless of the source of the data (longitudinal registers or cross-sectional recall), the risk of subsequent mental disorders remained persistently elevated over the entire period of observation (at least 15 years). These findings lend weight to the hypothesis that a wide spectrum of mental disorders has a shared risk factor background (which includes genetic and non-genetic factors) (Caspi and Moffitt, 2018; Hyman, 2019).

The study provides important new insights into the absolute risk of developing later disorders over several decades. For example, in those with prior MDE, the risk of subsequently developing GAD was appreciable, with absolute risks (and 95% CIs) at 5, 10 and 15 years of 8.9%, (8.8–9.0%), 11.4% (11.3–11.4%) and 13.6% (13.6–13.7%), respectively. Conversely, in those with prior GAD, the risk of subsequent MDE was even more pronounced with absolute risks (95% CIs) at 5, 10, 15 years of 28.2% (28.0–28.4%), 37.7% (37.5–38.0%) and 46.9% (46.6–47.1%). Finally, we note that people with early-onset mental disorders (<20 years) are more likely to develop other types of mental disorders within a set time frame, compared to those who have their first mental disorder at older ages. These findings are salient in light of recent increased investments in youth mental health services and clinical staging models (Iorfino *et al.*, 2019), and highlight the need to invest in programs that

may reduce the burden of additional comorbidity in this vulnerable group (Kessler and Price, 1993).

Our study has several important strengths. Surveys allow for the detection of both treated and untreated mental disorders (in contrast, the Danish register-based study was unable to identify mental disorders treated exclusively by primary practitioners, or those who did not seek treatment). Furthermore, the WMH surveys were based on the CIDI, which is designed to assess mental disorders against established diagnostic criteria, with quality control mechanisms related to training and interviewer fidelity. We know that the lifetime prevalence of mental disorders can vary between countries (Kessler *et al.*, 2007) and broad socioeconomic and cultural factors impact on the profiles of some types of mental disorders (e.g. substance use disorders are less common in some countries). The current study included surveys from 27 nations, and analyses were adjusted by the site in order to focus on cross-national findings. We believe that the estimates from the current study are more generalisable across sites.

We wish to draw attention to several limitations. Despite the relatively large sample, for many disorder pairs we lacked sufficient power to generate reliable estimates, and (in contrast to the Danish study) were not able to generate age- and sex-specific estimates for many of the disorder pairs. Survey data relies on the respondent's memory and recall bias may result in a systematic bias against the recall of temporally distant events. Respondents interviewed as adults may conflate the age of onset of two or more disorders (especially if the disorders shared symptoms). In our study, this bias could inflate the number of ties (where respondents report the onset of two or more disorders during the year). While we used a conservative strategy to break ties, this bias cannot influence HRs estimates when the lag is 2 or more years. In addition, while we have the age of onset of each type of disorder, detailed information about the course of each disorder was not available. The surveys included in our analyses were conducted from 2001 to 2015, and it is feasible that the prevalence of the underlying disorders and related patterns of comorbidity may have changed over time. Finally, this study only concentrated on pairs of disorders (with and without adjustment for additional prior disorders). We plan to explore more complex permutations of comorbidity within mental disorders in future studies.

To the best of our knowledge, this is the first study to provide a comprehensive set of age- and sex-specific estimates of absolute risks of comorbidity within DSM-IV mental disorders. We have also provided an interactive data visualisation tool that may assist clinicians in planning management protocols and monitoring potential emergent comorbidity over time. These estimates may have clinical utility – they can remind the clinician to remain vigilant for the emergence of additional types of mental disorders. We hope that our findings will guide future hypothesis-driven research related to the mechanisms underlying the patterns of comorbidity within mental disorders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796020000633.

Data. Due to data-sharing restrictions contained in some individual country agreements with the World Mental Health Surveys Initiative, sharing of the cross-national dataset is not possible.

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