Onset and temporal sequencing of lifetime anxiety, mood and substance use disorders in the general population

T. Slade^{1*}, P. M. McEvoy², C. Chapman¹, R. Grove¹ and M. Teesson¹

¹ National Drug and Alcohol Research Centre University of New South Wales, Sydney, Australia

² Centre for Clinical Interventions, School of Psychology, University of Western Australia, Perth, Australia

Aims. To date, very few studies have examined the bi-directional associations between mood disorders (MDs), anxiety disorders (ADs) and substance use disorders (SUDs), simultaneously. The aims of the current study were to determine the rates and patterns of comorbidity of the common MDs, ADs and SUDs and describe the onset and temporal sequencing of these classes of disorder, by sex.

Methods. Data came from the 2007 Australian National Survey of Mental Health and Wellbeing, a nationally representative household survey with 8841 (60% response rate) community residents aged 16–85.

Results. Pre-existing mental disorders increase the risk of subsequent mental disorders in males and females regardless of the class of disorder. Pre-existing SUDs increase the risk of subsequent MDs and ADs differentially for males and females. Pre-existing MDs increase the risk of subsequent ADs differentially for males and females.

Conclusions. Comorbidity remains a significant public health issue and current findings point to the potential need for sex-specific prevention and treatment responses.

Received 20 April 2013; Revised 13 September 2013; Accepted 16 September 2013; First published online 15 November 2013

Key words: Comorbidity, anxiety disorders, mood disorders, substance use disorders, gender.

Psychiatric comorbidity is the presence, simultaneously or in sequence, of two or more distinct mental disorders in an individual and is widely recognised as the norm rather than the exception among people with mental disorders (Cerdeira *et al.* 2008). Community studies indicate that around one-half to two-thirds of people with a mental disorder experience comorbidity over their lifetime (Merikangas & Kalaydjian, 2007; Kessler & Wang, 2008; Teesson *et al.* 2009). People with comorbid mental disorders suffer significant disability, experience a more complex and chronic course of illness and often remain untreated in the community (de Graaf *et al.* 2004; Coryell *et al.* 2012).

Comorbidity between anxiety and mood disorders (MDs) is typically investigated from the perspective of shared aetiology *v.* direct causation, with some researchers proposing that anxiety and affective disorders exist along a continuum and share vulnerability and risk factors, and others suggesting that they

are separable disorders with distinct vulnerability, natural history and symptom profiles (Wittchen *et al.* 2000; Matthew *et al.* 2011). The relationships between internalising disorders [i.e., mood and anxiety disorders (ADs)] and substance use disorders (SUDs) have been explained by the self-medication hypothesis, where a SUD is thought to develop to cope with the symptoms of a primary mood or AD (Martins *et al.* 2009; Leeies *et al.* 2010; Robinson *et al.* 2011). It has also been proposed that substance use may exert physiologic efforts that increase vulnerability to mood and ADs (Falk *et al.* 2008), that both disorders are initially unrelated but exacerbate each other, or that an unknown antecedent factor gives rise to both (Compton *et al.* 2007; Hasin *et al.* 2007; Liang & Chikritzhs, 2011).

Examining patterns of comorbidity over lifetime as well as temporal relationships between disorders has the potential to guide the timing and targeting of prevention and treatment (Glantz *et al.* 2009) as well as inform nosologic debates about the underlying structure of psychopathology (Forbush and Watson, 2012). To date, very few studies have examined the bi-directional temporal sequencing of MDs, ADs and SUDs simultaneously and none have comprehensively examined the

* Address for correspondence: Dr Tim Slade, National Drug and Alcohol Research Centre, University of New South Wales, 22–32 King Street, Randwick, NSW 2032, Australia.
Email: (tims@unsw.edu.au)

relationship between sex and the development of these disorders over lifetime in a large representative population sample. The present study therefore aimed to: (1) determine the rates and patterns of comorbidity of the common MDs, ADs and SUDs across lifetime and (2) describe the onset and temporal sequencing of these classes of mental disorder, by sex, in a representative general population sample in Australia.

Methods

Sample

Data came from the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB), a nationally representative population survey with a sample size of 8841 (Slade *et al.* 2009). Respondents were selected at random from a stratified, multistage area probability sample of persons aged 16–85 years living in private dwellings and data were weighted according to the inverse probability of being selected. Interviews were carried out by trained lay-interviewers from the Australian Bureau of Statistics (ABS) and were conducted in the respondent's own household using a Computer-Assisted Personal Interview (CAPI) questionnaire that took, on average, 90 min to complete. The ABS operates under Australian National Legislation that mandates strict provisions for the ethical conduct of the agency's research. Survey participation was voluntary and not remunerated. The survey achieved a response rate of 60%, with an intensive non-response follow-up study demonstrating that mis-estimation at the aggregate level is likely to be small (Slade *et al.* 2009).

Measures

Experience of DSM-IV disorders over lifetime was assessed using a modified version of the World Health Organization's Composite International Diagnostic Interview (WMH-CIDI; (Kessler & Ustun, 2004), a structured interview with questions designed to operationalise the diagnostic criteria for each mental disorder. The survey assessed the prevalence of 13 individual mental disorders across the three classes of mental disorder; MDs (major depressive disorder, bipolar disorder and dysthymia), ADs (panic disorder, agoraphobia, social phobia, generalised AD, post-traumatic stress disorder and obsessive-compulsive disorder) and SUDs (alcohol abuse, alcohol dependence, drug abuse and drug dependence). Note that abuse and dependence were assessed with reference to four separate classes of illicit drugs – cannabis, sedatives, stimulants and opioids). Comorbidity was examined between each of these three classes of disorder,

rather than at the individual disorder level. The rationale for this was twofold: first, cell sizes at the individual disorder level were not adequate across all disorder combinations to allow comparisons of temporal sequencing. Second, there are reasonable theoretical grounds to argue that comorbidity across different disorder class combinations (e.g., MDs and ADs *v.* MDs and SUDs) may reflect different causal mechanisms and may have different implications for research and treatment (Cerdeira *et al.* 2008).

Age of onset and temporal sequencing of disorders

Respondents were asked about the age at which they first experienced symptoms of each mental disorder and this was defined as the age of onset for that disorder. A series of prompts similar to those used in the World Mental Health Survey Initiative were used to increase the accuracy of retrospective recall of onset (Kessler *et al.* 2007). Because this analysis was limited to disorder groups or classes, the earliest disorder onset for each class was used. For example, if a respondent met criteria for panic disorder and social phobia, the earlier of these two onsets was used to define the age at onset of ADs. When considering temporal sequencing of MDs and ADs, respondents were classed as having a temporally primary AD if their earliest onset AD preceded the onset of all MDs.

Statistical analysis

Survey procedures in STATA Release 12 were used for all analyses. Prevalence estimates were weighted to conform to independent population estimates and 95% confidence intervals were based on, and standard errors obtained through, the delete-a-group jack-knife variance technique. Comparisons across comorbidity classes were made using adjusted Wald chi-squared tests and odds ratios (ORs) for gender comparisons were obtained using binary logistic regression analyses. Median ages of onset were obtained using Kaplan–Meier survival estimates stratified by sex (Hosmer & Lemeshow, 1989). This method of analysis allows for data to be modelled over time to retain all respondents including those who had not developed the disorder at the time of interview, often referred to as 'censored' cases. Survival time was defined as the number of years from birth to onset of disorder or to age at interview, whichever came first. The relationship between temporal sequencing of disorder classes and sex was examined using discrete-time survival analysis where sex and pre-existing disorders were treated as covariates and examined in interaction in models that predicted subsequent onset of either MDs, ADs or SUDs. Hierarchy rules were not applied.

For each of the six disorder class combinations (ADs prior to MDs, SUDs prior to MDs, MDs prior to ADs, SUDs prior to ADs, MDs prior to SUDs and ADs prior to SUDs) six separate discrete-time survival analyses (labelled Model 1 to Model 6) were carried out. Each analysis modelled the conditional probability of transitioning from not having the target disorder to having the target disorder in any given year. Model 1 included sex as a single predictor variable to examine the odds of developing the target disorder class for females compared with males. Model 2 included pre-existing disorder class as a single predictor variable to examine the odds of developing the target disorder class for those with compared with those without the pre-existing disorder class. Model 3 included both sex and pre-existing disorder class in a model together to determine whether pre-existing disorder class was associated with increased odds of developing the target disorder class controlling for sex and vice versa. In addition to the main effects, Model 4 included the interaction between sex and pre-existing disorder class to determine whether the association between the pre-existing disorder class and the odds of

developing the target disorder class differed for males and females. To further understand the interaction terms, Models 5 and 6 examined the sex-specific odds (males in Model 5 and females in Model 6) of the target disorder class for those with compared with those without the pre-existing disorder class. The effect of time in all discrete-time survival models was approximated by a model including linear, quadratic and cubic terms. Preliminary modelling ensured that models met the assumption of proportionality of hazards and where this assumption was not met models included interaction terms between covariates and time. All models controlled for age at interview, divided into three categories (16–29, 30–49, 50+).

Results

Comorbidity of mental disorders over lifetime

The lifetime prevalence of DSM-IV mental disorders and mental disorder comorbidity in the Australian population is presented in Table 1. Of the total population, 41.5% (95% CI=39.9–43.1) met criteria for a

Table 1. Lifetime prevalence of mental disorder classes and mental disorder class comorbidity for males and females in the Australian population

	Males			Females			Females v. males		Total		
	N	%	95% CI	N	%	95% CI	OR	95% CI	N	%	95% CI
Any anxiety ^a	649	16.1	14.5–17.9	1176	24.6	22.7–26.6	1.7**	1.4–2.0	1825	20.4	19.2–21.7
Any mood ^b	483	12.1	10.6–13.7	899	18.3	16.8–19.9	1.6**	1.3–2.0	1382	15.2	14.3–16.2
Any substance use ^c	1356	34.7	32.7–36.8	687	13.9	12.6–15.3	0.3**	0.3–0.4	2043	24.2	23.0–25.5
Any mental disorder	1763	45.3	43.2–47.4	1804	37.7	35.7–39.8	0.7**	0.7–0.8	3567	41.5	39.9–43.1
One disorder class	1222	32.1	30.1–34.2	1047	22.6	20.8–24.6	1.0	–	2269	27.3	25.9–28.8
Two disorder classes	369	9.1	7.9–10.4	568	11.3	10.1–12.5	1.8**	1.4–2.2	937	10.2	9.3–11.1
Three disorder classes	176	4.2	3.4–5.2	193	3.9	3.2–4.7	1.3	1.0–1.8	369	4.1	3.5–4.7
One disorder class:											
Anxiety disorder only	198	5.2	4.2–6.5	474	10.7	9.4–12.3	4.6**	3.3–6.5	672	8.0	7.1–9.0
Mood disorder only	107	2.7	2.1–3.4	263	5.5	4.6–6.6	3.5**	2.6–4.7	370	4.1	3.6–4.8
Substance use disorder only	917	24.2	22.2–26.3	310	6.4	5.4–7.4	0.1**	0.1–0.2	1227	15.2	14.1–16.4
Two disorder classes:											
Anxiety and mood disorders	106	2.7	2.1–3.6	384	7.6	6.7–8.7	4.8**	3.0–7.4	490	5.2	4.6–5.9
Anxiety and substance use disorders	169	3.9	3.1–4.9	125	2.4	1.9–3.0	0.4**	0.2–0.6	294	3.1	2.6–3.7
Mood and substance use disorders	94	2.4	1.7–3.4	59	1.3	0.9–1.8	0.4*	0.2–0.7	153	1.8	1.5–2.3

^aIncludes panic disorder, agoraphobia, social phobia, generalised anxiety disorder, post-traumatic stress disorder and obsessive-compulsive disorder.

^bIncludes major depressive disorder, dysthymia and bipolar disorder.

^cIncludes alcohol abuse, alcohol dependence, other drug (e.g., cannabis, ecstasy, methamphetamine, etc.) abuse and other drug dependence.

* $p < 0.05$; ** $p < 0.001$.

mental disorder, most commonly SUDs (24.2%, 95% CI=23.0–25.5) or ADs (20.4%, 95% CI=19.2–21.7). Compared with males, females were less likely to meet criteria for SUDs (OR 0.3, 95% CI= 0.3–0.4) but more likely to meet criteria for ADs (OR 1.7, 95% CI = 1.4–2.0) or MDs (OR 1.6, 95% CI= 1.3–2.0).

Of the total population 10.2% (95% CI= 9.3–11.1), or a quarter of those with a mental disorder met criteria for two disorder classes and 4.1% (95% CI= 3.5–4.7) met criteria for all three disorder classes. Comorbidity differed by sex with females more likely to meet criteria for two disorder classes compared with males (OR 1.8 95% CI= 1.4–2.2).

Among those with only one disorder class females were more likely than males to meet criteria for ADs (OR 4.6, 95% CI= 3.3–6.5) or MDs (OR 3.5, 95% CI= 2.6–4.7) but less likely than males to meet criteria for SUDs (OR 0.1, 95% CI= 0.1–0.2). Among those with two disorder classes, females were more likely than

males to meet criteria for anxiety and MDs (OR 4.8, 95% CI= 3.0–7.4) but less likely to meet criteria for anxiety and SUDs (OR 0.4, 95% CI= 0.2–0.6) or mood and SUDs (OR 0.4, 95% CI= 0.2–0.7).

Age of onset of mental disorder classes over lifetime

Median age at onset of ADs was 20 (Interquartile range (IQR) 12–40) for males and 19 (IQR 12–36) for females. Median age at onset of MDs was 38 (IQR 22–49) for males and 32 (IQR 20–52) for females and median age at onset of SUDs was 20 for both males and females (IQR 18–26 and 18–28, respectively).

Temporal sequencing of mental disorders over lifetime

Data on the temporal sequencing of mental disorders for people with different disorder class combinations are shown in Table 2. ADs were reported as temporally

Table 2. Temporal ordering of mental disorder classes over lifetime for males and females with two or three classes of mental disorders^a

	Males			Females					Total		
	N	%	95% CI	N	%	95% CI	OR	95% CI	N	%	95% CI
Anxiety and Mood Disorders	105			381					486		
Anxiety disorder primary	50	41.7	29.9–54.6	213	58.0	51.9–63.9	1.7	0.7–4.2	263	53.7	47.9–59.4
Mood disorder primary	22	19.3	10.0–33.9	66	15.5	11.8–20.0	0.8	0.3–2.5	88	16.5	12.9–20.8
Anxiety and mood disorders simultaneous ^b	33	39.0	25.2–54.8	102	26.5	21.6–32.1	1.0	–	135	29.8	24.6–35.6
Anxiety and Substance Use Disorders	167			124					291		
Anxiety disorder primary	115	66.4	55.5–75.9	77	67.1	55.5–77.0	1.1	0.5–2.2	192	66.7	58.6–73.9
Substance use disorder primary	43	27.7	18.9–38.7	37	25.6	17.4–36.1	1.3	0.3–5.3	80	26.9	20.4–34.7
Anxiety and substance use disorders simultaneous ^b	9	5.8	2.6–12.6	10	7.2	3.3–14.9	1.0	–	19	6.4	3.7–10.8
Mood and Substance Use Disorders	93			59					152		
Mood disorder primary	24	20.3	11.8–32.7	19	46.3	26.3–67.5	4.1*	1.4–12.4	43	29.4	18.9–42.7
Substance use disorder primary	60	70.7	55.8–82.2	29	39.3	23.5–57.7	2.9	0.8–10.4	89	59.7	46.6–71.5
Mood and substance use disorders simultaneous ^b	9	8.9	3.8–19.4	11	14.5	7.1–27.2	1.0	–	20	10.9	6.4–17.9
Anxiety, Mood and Substance Use Disorders	172			192					364		
Anxiety disorder primary	93	53.4	42.1–64.3	111	57.6	48.6–66.2	1.1	0.5–2.2	204	55.4	47.8–62.8
Mood disorder primary	17	11.4	6.2–20.2	23	11.4	7.0–17.8	1.0	0.4–2.6	40	11.4	7.4–17.1
Substance use disorder primary	34	21.5	12.4–34.6	30	17.3	11.5–25.2	0.8	0.3–2.2	64	19.5	13.7–26.9
Anxiety, mood and substance use disorders simultaneous ^c	28	13.7	9.0–20.2	28	13.7	8.7–21.0	1.0	–	56	13.7	10.0–18.4

^aA small number of respondents ($N=13$) were missing age of onset for at least one of their lifetime disorders. They are not included in this table.

^bOnset of both disorder classes occurred within the same 12-month period.

^cOnset of at least two disorders occurred within the same 12-month period, and before the onset of the third class of disorder, or all three classes of disorder had their onset within the same 12-month period. For the majority of this group (63%) onset of anxiety and mood disorders occurred within the same 12-month period, but before the onset of substance use disorders. Onset of all three classes of disorder within the same 12-month period was uncommon.

* $p < 0.05$; ** $p < 0.001$.

primary for 53.7% (95% CI=47.9–59.4) of people with comorbid ADs and MDs, and for 66.7% (95% CI=58.6–73.9) of people with comorbid ADs and SUDs. When SUDs were comorbid with MDs over lifetime SUDs were reported as temporally primary for 59.7% (95% CI=46.6–71.5) of people. When all three classes of disorder were comorbid over lifetime, ADs were most commonly the primary disorder (55.5%, 95% CI=47.8–62.8), followed by SUDs (19.5%, 95% CI=13.7–26.9). ADs and MDs were the most common combination to have their onset in the same year (29.8%, 95% CI=24.6–35.6). There were no differences in temporal ordering of disorder classes for males and females among those with comorbid ADs and MDs, ADs and SUDs, or all three disorder classes. However, when MDs and SUDs were comorbid females were more likely than males to report their MDs as temporally primary (OR 4.1, 95% CI=1.4–12.4).

Development of lifetime mental disorders by sex and pre-existing disorder

The above analyses are restricted to the 14.3% of people meeting criteria for more than one class of mental disorder thus excluding the majority (85.7%) of the total sample. To understand the relationship between sex, pre-existing mental disorders and the development of comorbidity across the lifetime of *all* respondents (including

those who do not go on to develop comorbid disorders), discrete-time survival analyses were carried out.

The results of the discrete-time survival analyses are found in Table 3. The results of Model 1 analyses showed that for all six pre-existing and target disorder combinations sex was associated with the target disorder class in predictable ways (i.e., females had a higher odds of developing MDs and ADs and a lower odds of developing SUDs compared with males). The results of Model 2 analyses showed MDs were predicted by pre-existing ADs (OR=8.1, 95%CI=5.1–12.8) but not SUDs. Similarly, ADs were predicted by pre-existing MDs (OR=3.4, 95%CI=2.6–4.5) but not SUDs. Last, SUDs were predicted by both a pre-existing MDs (OR=4.9, 95%CI=2.2–11.0) and pre-existing ADs (OR=1.8, 95%CI=1.6–2.2). Results of Model 3 analyses confirmed that, when entered into a model together, both sex and the presence of a pre-existing disorder remained as significant predictors of the development of the target disorder with minimal attenuation of ORs. With sex in the model, pre-existing SUDs became significantly associated with an increased odds of developing both MDs (OR=1.5, 95%CI=1.2–2.0) and ADs (OR=1.3, 95%CI=1.0–1.7).

Model 4 results showed that statistically significant interactions were present for three out of the six disorder class combinations. The results suggest that the nature and/or extent of the association between a pre-existing disorder and the development of the target

Table 3. Results of discrete-time survival analyses examining the risk of developing a target mental disorder class given the presence of a pre-existing mental disorder class

Target disorder	Mood disorder				Anxiety disorder				Substance use disorder			
	Anxiety disorder ^a		Substance use disorder		Mood disorder		Substance use disorder ^a		Mood disorder		Anxiety disorder	
Pre-existing disorder	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
M1: sex (female)	2.2**	1.6–3.2	1.6**	1.3–1.9	1.6**	1.4–1.9	1.6**	1.4–1.9	0.3**	0.3–0.4	0.3**	0.3–0.4
M2: pre-existing disorder	8.1**	5.1–12.8	1.3	1.0–1.7	3.4**	2.6–4.5	1.1	0.9–1.5	2.0**	1.6–2.6	1.8**	1.6–2.2
M3: sex (female)	1.9*	1.3–2.8	1.7**	1.4–2.0	1.6**	1.4–1.8	1.7**	1.4–1.9	0.3**	0.3–0.4	0.3**	0.3–0.4
pre-existing disorder	7.4**	4.6–11.9	1.5*	1.2–2.0	3.2**	2.4–4.3	1.3*	1.0–1.7	2.5**	2.0–3.5	2.2**	1.8–2.7
M4: sex(female)	0.8	0.6–1.1	1.0	0.6–1.5	0.6*	0.3–1.0	1.5*	1.1–2.1	1.7*	1.2–2.5	1.3	1.0–1.8
*pre-existing disorder interaction												
M5: pre-existing disorder in males	10.7**	4.6–24.6	1.5*	1.0–2.2	4.7**	3.1–7.0	1.2	0.8–1.6	2.0**	1.4–2.8	2.0**	1.6–2.5
M6: pre-existing disorder in females	6.1**	3.8–9.8	1.5*	1.1–2.0	2.6**	1.8–3.7	1.6*	1.2–2.2	3.1**	2.3–4.0	2.5**	2.0–3.2

* $p < 0.05$; ** $p < 0.001$.

^aEvidence of non-proportionality of hazards was found in some or all models within a given disorder pair, where appropriate, models include sex by time and pre-existing disorder by time interaction terms to account for non-proportionality.

disorder differed for males and females. When looking at the development of ADs the significant interaction between sex and pre-existing MDs indicated that the association between pre-existing MDs and the development of ADs was nearly half as strong in females as it was in males. Sex-specific models (Models 5 and 6) showed that males with pre-existing MDs were around five times more likely to develop subsequent ADs, while the odds of developing ADs in females given pre-existing MDs were increased by around two and a half. The association between pre-existing MDs and the development of SUDs also differed significantly in males and females. However, in this case the direction of the effect was opposite to that seen among pre-existing MDs and the subsequent development of ADs. Sex-specific models showed that females with pre-existing MDs were around three times more likely to develop subsequent SUDs, while males with pre-existing MDs were twice as likely to develop SUDs compared with those without pre-existing MDs. Last, the relationship between pre-existing SUDs and subsequent ADs again differed for males and females. While there was no significant relationship for males, females with pre-existing SUDs were at significantly increased odds of developing ADs compared with females without pre-existing SUDs.

Discussion

The current study used data from a large epidemiological survey of mental disorders in the Australian general population to examine the patterns and temporal sequencing of comorbidity both in the total sample and separately for males and females. In general, females were more likely than males to report comorbidity over lifetime. MDs were commonly temporally secondary when comorbid with other disorders. The exception to this pattern was for comorbid MDs and SUDs where females were more likely to report their MDs as primary. While contemporaneous onset was evident to a greater or lesser extent for all disorder combinations ADs and MDs were the most common of the comorbid disorder combinations to have their onset in the same year. Two findings were of note in the discrete-time survival analyses. First, all disorder classes were significantly related to each other regardless of the temporal direction. Second, the strength and direction of the association between pre-existing and target disorder classes in some cases differed between males and females.

The finding that females are more likely than males to report comorbidity is undoubtedly a result of the higher prevalence of MDs and ADs in females compared with males coupled with the higher prevalence

of comorbidity among the MDs and ADs compared with any other disorder combinations. Given the common finding that comorbidity *per se* is associated with more disability, higher rates of service utilisation, longer illness duration and other indicators of poor functional outcome (Merikangas & Kalaydjian, 2007), these findings point to the continued need to prevent and treat comorbidity in order to reduce the burden of mental disorders, particularly in females. Sex differences in the proportion reporting temporal primacy of MDs when MDs and SUDs are comorbid are consistent with previous epidemiological studies (Helzer & Pryzbeck, 1988; Kessler *et al.* 1997). Moreover, there is some evidence that the reasons for excessive/harmful drinking or drug use, the natural pre-cursors to SUDs, are different in males and females across early adulthood. Studies have shown that young adult males drink and use drugs more for social reasons, while females' use of alcohol and drugs is more closely related to emotional feelings such as stress, anxiety and loneliness (Lee *et al.* 2012).

One of the innovative aspects of the current study is the simultaneous examination of the bi-directional temporal sequences of mental disorder comorbidity. Past studies have tended to focus on pairs of individual disorders, sometimes examining associations that run in only one direction (Cerdeira *et al.* 2008). The few studies that have examined all three disorder classes have tended to focus on temporal ordering with respect to one disorder class (de Graaf *et al.* 2003; Falk *et al.* 2008). A strong finding that emerges from the current study is that the presence of *any* class of pre-existing mental disorder increases the risk of development of *any* other class of mental disorder. This pervasive finding suggests the existence of common mechanisms central to the development of comorbidity, regardless of the specific type of comorbidity. The findings underscore the need to further refine etiological models to account for the general increase in risk of any mental disorder given the prior existence of any other mental disorder. In fact, recent research by Lahey *et al.* (2012) proposes that a 'general factor of prevalent psychopathology' accounts for a significant degree of comorbidity in the general population. Understanding the psychological and neurobiological processes that underlie this general factor warrants further study.

When the target disorder class was MDs males and females were equally at risk given the pre-existence of either ADs or SUDs. However, males with pre-existing MDs were more likely to develop subsequent ADs than were females with pre-existing MDs, whereas females with pre-existing SUDs were more likely to develop subsequent ADs than were males with pre-existing SUDs. Both these findings are consistent with the so-called 'gender paradox' where in disorders

with an unequal sex prevalence ratio the sex with the lower prevalence is often more seriously affected in terms of comorbidity (Taylor & Ounsted, 1972). Males may require a larger genetic load than females to manifest MDs but once they do, this strong genetic load coupled with the robust genetic link between MDs and ADs substantially increases the risk of developing ADs in males. Similarly, females who engage in risky substance use, the natural pre-cursor to SUDs, are often more psychologically unhealthy than their male substance using counterparts (Pettinati & Plebani, 2009). These findings are important given recent evidence of a narrowing in the gap between males and females traditionally seen in the rates of risky substance use and SUDs (Keyes *et al.* 2011). With females in more recent birth cohorts appearing to drink at more risky levels the potential for increased rates of ADs may become realised in the near future.

While pre-existing MDs increased the risk of developing subsequent SUDs in both males and females the effect was stronger in females. These results are consistent with prospective studies, e.g. (Moscato *et al.* 1997), which demonstrate that depressive symptoms predict subsequent alcohol problems among females but not amongst males. Similarly, using data from the Epidemiologic Catchment Area study Gilman & Abraham (2001) demonstrated that the odds of developing alcohol dependence during a 1-year follow-up period increased according to the severity of baseline depressive symptoms and, critically, that this increase was much more pronounced among females. These findings highlight the need to screen for depressive symptoms not only as potential indicators of future MDs but also as possible markers for an increased risk of the development of SUDs in females.

Knowledge of the specific pre-existing/target disorder relationships that are most likely to occur in the general population can be used as markers for at-risk sub-groups. From this it may be possible to develop prevention programmes that target those with specific disorders early on in their developmental lifespan before they lead to the development of subsequent comorbid disorders. Within this context, the present study suggests that the exploration of sex-specific risk factors for the development of mental disorders may be of benefit. Gender-based violence represents one such sex-specific risk factor that is strongly associated with the development of individual and comorbid forms of mental disorder (Rees *et al.* 2011). While there is some doubt as to how much the treatment or prevention of a given mental disorder will prevent the subsequent onset of another mental disorder (Glantz *et al.* 2009) identification and characterisation of these vulnerable sub-groups still remains a public health priority.

Analyses like these provide evidence of the most common combinations of mental disorders, both how they exist at a given point in time and also, using self-reported age of onset, how they develop over time. Common combinations of disorders provide insight into novel and parsimonious ways of structuring mental disorder classification systems. A growing body of research is emerging that has identified a reduced number of core liabilities, often described as internalising, externalising and psychosis, that are thought to explain the high levels of comorbidity among a range of common and uncommon mental disorders (Kotov *et al.* 2011; Simms *et al.* 2012). The present study lends support to this line of investigation.

The above findings should be interpreted in the light of some limitations. The data come from a cross-sectional survey and hence are subject to biases typically associated with retrospective recall, including the general limitations of memory and the cognitive schemas people might have regarding the typical *v.* actual age of onset of mental disorders (Simon & VonKorff, 1995). It is most likely that males and females will have these biases to the same extent yet despite this we are still finding sex differences in temporal sequencing. We note that our findings are consistent with prospective studies that have assessed the development of comorbidity amongst specific mood and ADs (e.g., Moffitt *et al.* 2007). Our approach to identifying comorbidity meant that it was not possible to examine the comorbid patterns amongst the individual anxiety, mood and SUDs. Given the finding that individual disorders within a specific class differ greatly in their median age of onsets (particularly the ADs, (McEvoy *et al.* 2011)) future research should investigate disorder by disorder combinations to identify specific patterns that fall outside the patterns observed at the disorder class level. All data used in the current study come from a cross-sectional survey and hence limit the ability to draw causal conclusions. However, the data provide informative evidence of 'hot-spots' in the comorbidity matrix and are the first step in understanding risk pathways between one mental disorder and another.

The current study examined the onset and temporal sequencing of the common mental and SUDs across lifetime for males and females in a representative general population sample. It is one of the first studies to examine the sex-specific differences in development of comorbid disorders and one of the few to simultaneously consider bi-directional relationships across all three classes of disorders. It found that the presence of *any* class of pre-existing mental disorder increases the risk of development of *any* other class of mental disorder lending support to the notion of a general factor of psychopathology that accounts for the pervasive

prevalence of comorbidity in the general population. Second, it found evidence for several sex-specific differences in the temporal sequencing of comorbid disorders highlighting the potential benefit of sex-specific prevention and treatment programmes and underscoring the need for future longitudinal studies to examine development of comorbidity separately for males and females.

Acknowledgements

We would like to acknowledge the Australian Bureau of Statistics for carrying out the 2007 National Survey of Mental Health and Wellbeing and the respondents for participating in the survey.

Financial Support

This work was supported in part by an Australian National Health and Medical Research Council project grant (no. 630414).

Conflict of Interest

None.

Ethical Standard

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.

References

- Cerda M, Sagdeo A, Galea S (2008). Comorbid forms of psychopathology: key patterns and future research directions. *Epidemiologic Reviews* **30**, 155–177.
- Compton WM, Thomas YF, Stinson FS, Grant BF (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry* **64**, 566–576.
- Coryell W, Fiedorowicz JG, Solomon D, Leon AC, Rice JP, Keller MB (2012). Effects of anxiety on the long-term course of depressive disorders. *British Journal of Psychiatry* **200**, 210–215.
- de Graaf R, Bijl RV, Spijker J, Beekman AT, Vollebergh WA (2003). Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders-findings from the Netherlands Mental Health Survey and Incidence Study. *Social Psychiatry and Psychiatric Epidemiology* **38**, 1–11.
- de Graaf R, Bijl RV, Ten Have M, Beekman AT, Vollebergh WA (2004). Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *Journal of Affective Disorders* **82**, 461–467.
- Falk DE, Yi HY, Hilton ME (2008). Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. *Drug and Alcohol Dependence* **94**, 234–245.
- Forbush KT, Watson D (2012). The structure of common and uncommon mental disorders. *Psychological Medicine* **43**, 97–108.
- Gilman SE, Abraham HD (2001). A longitudinal study of the order of onset of alcohol dependence and major depression. *Drug and Alcohol Dependence* **63**, 277–286.
- Glantz MD, Anthony JC, Berglund PA, Degenhardt L, Dierker L, Kalaydjian A, Merikangas KR, Ruscio AM, Swendsen J, Kessler RC (2009). Mental disorders as risk factors for later substance dependence: estimates of optimal prevention and treatment benefits. *Psychological Medicine* **39**, 1365–1377.
- Hasin DS, Stinson FS, Ogburn E, Grant BF (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* **64**, 830–842.
- Helzer JE, Pryzbeck TR (1988). The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. *Journal of Studies on Alcohol* **49**, 219–224.
- Hosmer DW, Lemeshow S (1989). *Applied Logistic Regression*. John Wiley & Sons: New York.
- Kessler RC, Ustun TB (2004). The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research* **13**, 93–121.
- Kessler RC, Wang PS (2008). The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annual Review of Public Health* **29**, 115–129.
- Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Archives of General Psychiatry* **54**, 313–321.
- Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB (2007). Age of onset of mental disorders: a review of recent literature. *Current Opinion Psychiatry* **20**, 359–364.
- Keyes KM, Li G, Hasin DS (2011). Birth cohort effects and gender differences in alcohol epidemiology: a review and synthesis. *Alcoholism, Clinical and Experimental Research* **35**, 2101–2112.
- Kotov R, Ruggero CJ, Krueger RF, Watson D, Yuan Q, Zimmerman M (2011). New dimensions in the quantitative classification of mental illness. *Archives of General Psychiatry* **68**, 1003–1011.
- Lahey BB, Applegate B, Hakes JK, Zald DH, Hariri AR, Rathouz PJ (2012). Is there a general factor of prevalent psychopathology during adulthood? *Journal of Abnormal Psychology* **121**, 971–977.

- Lee JO, Kosterman R, McCarty CA, Hill KG, Hawkins JD** (2012). Can patterns of alcohol use disorder in young adulthood help explain gender differences in depression? *Comprehensive Psychiatry* **53**, 1071–1077.
- Leeies M, Pagura J, Sareen J, Bolton JM** (2010). The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. *Depression and Anxiety* **27**, 731–736.
- Liang W, Chikritzhs T** (2011). Affective disorders, anxiety disorders and the risk of alcohol dependence and misuse. *British Journal of Psychiatry* **199**, 219–224.
- Martins SS, Keyes KM, Storr CL, Zhu H, Chilcoat HD** (2009). Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence* **103**, 16–24.
- Mathew AR, Pettit JW, Lewinsohn PM, Seeley JR, Roberts RE** (2011). Co-morbidity between major depressive disorder and anxiety disorders: shared etiology or direct causation? *Psychological Medicine* **41**, 2023–2034.
- McEvoy PM, Grove R, Slade T** (2011). Epidemiology of anxiety disorders in the Australian general population: findings of the 2007 Australian National Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry* **45**, 957–967.
- Merikangas KR, Kalaydjian A** (2007). Magnitude and impact of comorbidity of mental disorders from epidemiologic surveys. *Current Opinion Psychiatry* **20**, 353–358.
- Moffitt TE, Harrington H, Caspi A, Kim-Cohen J, Goldberg D, Gregory AM, Poulton R** (2007). Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry* **64**, 651–660.
- Moscato BS, Russell M, Zielesny M, Bromet E, Egri G, Mudar P, Marshall JR** (1997). Gender differences in the relation between depressive symptoms and alcohol problems: a longitudinal perspective. *American Journal of Epidemiology* **146**, 966–974.
- Pettinati HM, Plebani JG** (2009). Depression and substance use disorders in women. In *Women and Addiction: A Comprehensive Handbook* (ed. KT Brady, SE Back and SF Greenfield), pp. 193–208. Guilford Press: New York.
- Rees S, Silove D, Chey T, Ivancic L, Steel Z, Creamer M, Teesson M, Bryant R, McFarlane AC, Mills KL, Slade T, Carragher N, O'Donnell M, Forbes D** (2011). Lifetime prevalence of gender-based violence in women and the relationship with mental disorders and psychosocial function. *Journal of American Medical Association* **306**, 513–521.
- Robinson J, Sareen J, Cox BJ, Bolton JM** (2011). Role of self-medication in the development of comorbid anxiety and substance use disorders: a longitudinal investigation. *Archives of General Psychiatry* **68**, 800–807.
- Simms LJ, Prisciandaro JJ, Krueger RF, Goldberg DP** (2012). The structure of depression, anxiety and somatic symptoms in primary care. *Psychological Medicine* **42**, 15–28.
- Simon GE, VonKorff M** (1995). Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiologic Reviews* **17**, 221–227.
- Slade T, Johnston A, Oakley Browne MA, Andrews G, Whiteford H** (2009). 2007 National Survey of Mental Health and Wellbeing: methods and key findings. *Australian and New Zealand Journal of Psychiatry* **43**, 594–605.
- Taylor DC, Ounsted C** (1972). The nature of gender differences explored through ontogenetic analyses of sex ratios in disease. In *Gender Differences: Their Ontogeny and Significance* (ed. C Ounsted and DC Taylor). Churchill Livingstone: Edinburgh.
- Teesson M, Slade T, Mills K** (2009). Comorbidity in Australia: findings of the 2007 National Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry* **43**, 606–614.
- Wittchen HU, Kessler RC, Pfister H, Lieb M** (2000). Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Psychiatrica Scandinavica. Supplementum*, 14–23.