

# Is the female preponderance in major depression secondary to a gender difference in specific anxiety disorders?

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## ABSTRACT

**Background.** While a female preponderance in unipolar depression is a consistent finding in community-based studies, determinants remain speculative. This study aimed to examine whether a female preponderance in certain anxiety disorders drives a gender difference in depression.

**Method.** The relevant data from the National Comorbidity Study (NCS) are analysed.

**Results.** We observed a biphasic pattern in the emergence of a female preponderance in the depressive and anxiety disorders, with an initial pre-pubertal or early adolescent onset, and after attenuation in early to middle adulthood, re-emergence in mid- to late-adulthood. Analyses focused on determinants of the initial female preponderance. Female gender, presence of an anxiety disorder and variable ages of onset in the anxiety disorder all contributed to the increased chance of an initial depressive episode. Some specificity in linking the onset of depressive temporally in early adolescence with two anxiety disorders was demonstrated, specifically generalized anxiety disorder and panic disorder.

**Conclusions.** The separate anxiety disorders and their age of onset had variable links with depression, but female gender remained a significant predictor of depression after accounting for the effects of prior anxiety.

## INTRODUCTION

Community-based studies around the world invariably report higher lifetime rates of major depression in women (Weissman *et al.* 1996). Reasons proposed include artefactual factors (such as women being more willing to report or acknowledge depression) and 'real' factors (whether biological or psychosocial).

In general, the female preponderance in depression has been assumed to be primary, rather than secondary to other determinants. We pursue an alternative hypothesis: that it is a secondary phenomenon, linked to anxiety. The coexistence of anxiety and depression is common and

there are striking epidemiological consistencies between the two groups of conditions. For example, in the US National Comorbidity Study (NCS) the lifetime rates for major depression were 21.3% for females and 12.7% for males (Kessler *et al.* 1994), a ratio of 1.6:1. By comparison, the rates for any lifetime anxiety disorders were 30.5% and 19.2% respectively, a ratio of 1.7:1. Lifetime rates were higher for females across each separate anxiety disorder examined.

Several possible mechanisms might explain any such linkages, including a higher-order common cause (existing or expressed 'more strongly' in women) predisposing independently to the female preponderance in both lower-order anxiety and depression. An alternative sequencing model supposes that a gender-dimorphic higher-order variable predisposes to

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a primary female preponderance of anxiety that may, in turn, dispose to both the onset, and female preponderance, of depression.

Two studies have pursued the possibility that the female preponderance in depression may be secondary to a female preponderance in anxiety disorders. Breslau *et al.* (1995) studied young adults randomly selected from a health maintenance organization. They found that prior anxiety disorders increased the risk for subsequent major depression in both men and women, with differences in the prevalence of anxiety disorders accounting for much of the observed gender difference in major depression. We (Parker & Hadzi-Pavlovic, 2001) analysed the National Comorbidity Survey (NCS) database to determine whether gender and the existence of 'any' prior anxiety disorder influenced the risk of subsequent depression. Survival analyses established that prior anxiety made a stronger contribution than gender, both in regard to major depression (risks of 1.40 and 1.25 respectively) and to dysthymia (risks of 1.49 and 1.24). Interaction effects indicated that the influence of preceding anxiety on depression onset was similar for both males and females.

This paper extends our previous study by specifically investigating the contribution of individual anxiety disorders rather than simply 'any' lifetime anxiety disorder, as each anxiety disorder may have quite different links with depression. If specific or non-specific pathways could be identified, aetiological pursuit of the female preponderance in depression might be assisted.

## METHOD

### Sample

We used the NCS database for our study (see the National Comorbidity Survey homepage at <http://www.hcp.med.harvard.edu/ncs>). The NCS study (Kessler *et al.* 1994), undertaken between 1990 and 1992, involved a stratified, multistage survey of non-institutionalized persons aged 15–54 years in the 48 coterminous states of the United States. More than 8000 people (82.4% response rate) completed the Composite International Diagnostic Interview or CIDI (WHO, 1990), administered by lay interviewers, to generate lifetime and 12-month prevalence data for DSM-III-R psychiatric

disorders. The raw prevalence data were weighted to adjust for non-responders, for selection probability, and to reflect national socio-demographic distributions such as age, gender and ethnicity.

The standard CIDI question on the age of onset of disorders was extended, with subjects asked whether they could 'clearly remember' the exact age of their first episode of the disorder (Kessler *et al.* 1998). If not, additional questions were used to pursue the approximate age of onset and the earliest age of remembering an episode, in order to generate an 'upper bound' on the age of onset of any episode. Subjects were clearly able to have developed multiple disorders in the same year.

In all our analyses we used subject weights ( $p2wtv3$ ) required by the NCS, reducing the sample size to 5877 subjects (2939 females, 2938 males).

### Statistical analyses

For this paper we regard subjects as having been 'observed' from age 1 (earliest age at which an anxiety onset was recorded) up to the age at which they were either interviewed or had an onset of a depressive disorder. Consistent with other analyses of the NCS dataset (e.g. Kessler *et al.* 1998) discrete-time survival analyses were carried out using a logistic regression approach (Efron, 1988; Singer & Willett, 1993). Hence, for each subject, a separate record was created for each age from 1 up to either the age of censoring (i.e. interview) or onset. As there were very few people interviewed at ages 55 to 58 these were treated as censoring at 54 years of age.

### Depressive disorder definition

A case of 'DEP' was defined as those whose first onset of a depressive disorder was major depression (but allowing a concurrent first onset of dysthymia). A case of 'DYS' was defined as those whose first onset of a depressive disorder was dysthymia (but allowing a concurrent first onset of major depression). A case of 'DEPDYS' was defined as anyone who was a case of DEP and/or DYS. A total of 938 (16.0%) people were DEP cases (of whom 14.5% were also cases of DYS due to onsets in the same year); 317 (5.4%) were DYS cases (of whom 57.1% were also same-year cases of DEP); and 1119 (19.0%) were DEPDIS cases.

### *Anxiety disorder coding*

Lifetime diagnosis for each of the anxiety disorders was scored as a variable indicating whether there had been an onset of the anxiety disorder prior to onset of a depressive disorder or prior to censoring. When entered into analyses these variables were coded as dummy variables with 'no' as the reference category. If the onset of an anxiety disorder occurred at the same age as the onset of the depressive disorder it was coded as 'no'. Theoretically, individuals could have moved in or out of caseness over time, so that caseness was potentially a time-varying covariate. Except for the 12 months prior to interview, however, this information was not available, so that such variables were carried forward into subsequent years as indicators of past occurrences.

We used lifetime diagnostic criteria for the following anxiety conditions (numbers of subjects and percentage of sample in parentheses): (i) simple phobia (654, 11.1%); (ii) social phobia (795, 13.5%); (iii) panic attacks (422, 7.2%); (iv) panic disorder (200, 3.4%); (v) agoraphobia (386, 6.6%); and generalized anxiety disorder (GAD) (295, 5.0%).

### *Onset of anxiety*

To examine stages of onset, we created a variable indicating whether the very first anxiety onset had been 'age 1–12', 'age 13–20' or 'age 21+', as against 'no onset'. In analyses, this variable was dummy coded 0|1 with 'no onset' as the reference level. Onsets of separate anxiety conditions were deemed to be concurrent if they occurred in the same year.

### *Coding of age*

In calculating the basic survival and hazard functions for Figs 1 and 2, each age between 1 and 54 was dummy coded. This coding is, however, not practical more generally as there are as many variables as years (i.e. 54) – which is unmanageable when it comes to interactions between time and other variables. To allow for this in subsequent analyses, time was modelled using restricted cubic splines (Harrell, 2001), which provided a reasonable approximation. The knots for the splines were determined from inspection of the hazard function for males and females combined.

Basic data management was undertaken in SPSS (SPSS, 1999), while all calculations used S-Plus 6 (Insightful Corporation, 2001). In particular, logistic regressions used the generalized linear model procedure.

## RESULTS

### **Hazard and survival functions**

A number of hazard functions (which give, approximately, the probability of first onset at a particular age, given survival to that age) and survival functions were calculated as described by Singer & Willett (1993). The hazard functions were smoothed to reduce spikiness; however, even with the large NCS sample it would be unwise to over-interpret the size of year to year fluctuations. Changes in the relative hazards are paralleled by changes in the rate at which survival curves diverge (or converge).

### **Onset of anxiety disorders**

Fig. 1 shows the hazard function for first onset of the anxiety disorders (with males and females shown separately). A pre-pubertal (i.e. prior to 10 years of age) emergence of a female preponderance is evident for agoraphobia, social phobia, simple phobia and panic attacks, but is not clearly evident for generalized anxiety disorder or panic disorder. In addition, there is the suggestion (varying in effect across the differing anxiety disorders) for a second separation by the genders occurring from mid-adulthood onwards. Survival curves similarly show initial separation either in early childhood or early adolescence, and (less clearly) the suggestion of a second trend break separation in adulthood.

### **Onset of depressive disorders**

Fig. 2 shows the hazard function for the first onset of depressive disorders (with males and females shown separately). The gender difference pattern for those with a first onset of major depression and/or dysthymia is very similar to that for a first episode of major depression only, presumably shaped by the much larger number of subjects in the latter group.

There is a close parallel between changes in the hazard for the genders, at least up to the mid-40s. Several peaks are evident, the first in mid-adolescence and the last in those over the

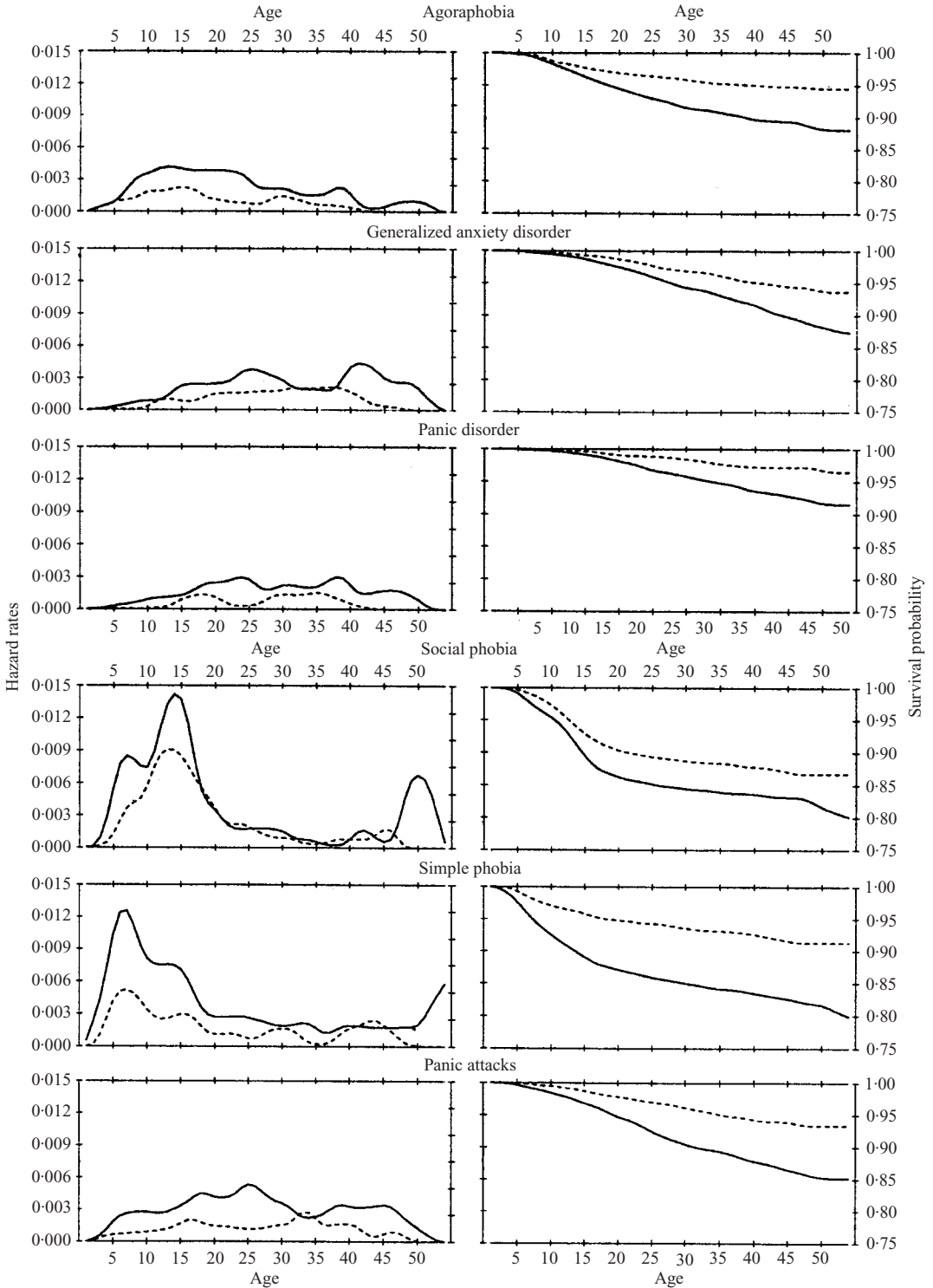


FIG. 1. Respective hazard rates and survival probabilities for onset of anxiety disorders (—, female; ---, male).

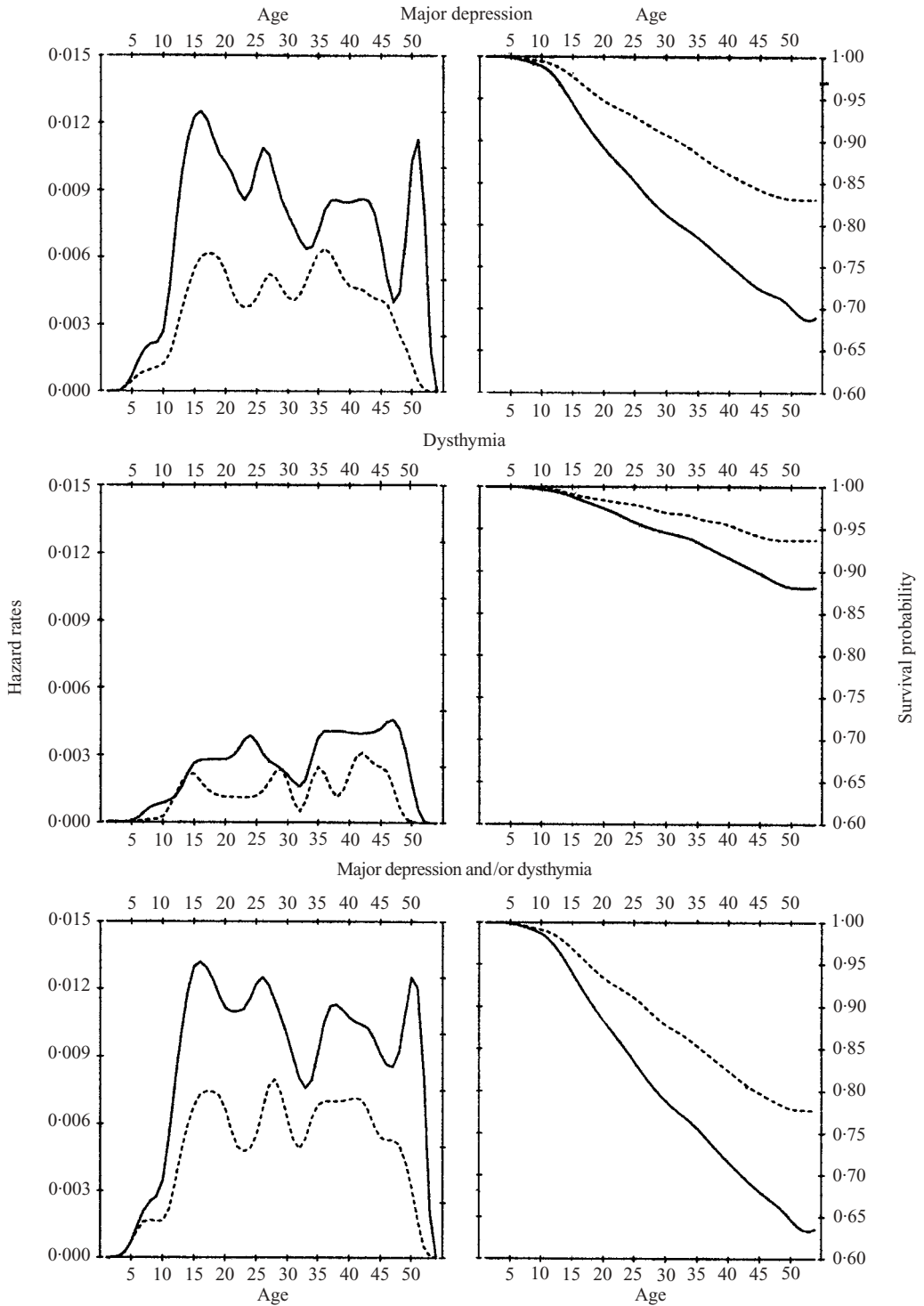


FIG. 2. Respective hazard rates and survival probabilities for first onset of depressive disorders (—, female; ---, male).

Table 1. Risks for first onset of DEP subsequent to onset of individual anxiety disorders (ADs)

Covariate	Agoraphobia		GAD		Panic disorder		Social phobia		Simple phobia		Panic attacks	
	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI
Model I												
Female	<b>1.88</b>	1.65–2.15	<b>1.89</b>	1.65–2.16	<b>1.89</b>	1.65–2.16	<b>1.84</b>	1.61–2.11	<b>1.72</b>	1.50–1.97	<b>1.82</b>	1.60–2.09
Onset of AD anytime	<b>2.76</b>	2.16–3.52	<b>2.78</b>	1.95–3.95	<b>2.49</b>	1.61–3.83	<b>2.45</b>	2.08–2.89	<b>2.98</b>	2.52–3.50	<b>3.59</b>	2.86–4.50
Model II												
Female	<b>1.91</b>	1.66–2.19	<b>1.92</b>	1.68–2.21	<b>1.91</b>	1.67–2.19	<b>1.91</b>	1.64–2.21	<b>1.83</b>	1.58–2.12	<b>1.87</b>	1.63–2.15
Onset of AD at ages 1–12	<b>3.45</b>	2.01–5.92	<b>5.39</b>	1.65–17.57	<b>8.63</b>	1.72–43.33	<b>3.00</b>	2.04–4.41	<b>3.27</b>	2.20–4.86	<b>5.37</b>	2.49–11.61
Onset of AD at ages 13–20	<b>2.89</b>	1.12–7.46	<b>7.49</b>	3.11–18.05	<b>8.19</b>	3.24–20.18	<b>2.86</b>	1.91–4.29	<b>8.13</b>	5.08–13.00	<b>6.28</b>	3.42–11.54
Onset of AD at ages >20	<b>3.81</b>	1.55–9.35	<b>3.08</b>	1.17–8.16	0.54	0.03–11.01	2.21	0.71–6.81	0.91	0.11–7.49	<b>3.22</b>	1.33–7.80
Onset 1–12 × Female	0.94	0.48–1.85	0.59	0.14–2.53	0.65	0.11–4.07	1.03	0.65–1.62	0.87	0.56–1.37	0.91	0.39–2.13
Onset 13–20 × Female	0.82	0.28–2.37	<b>0.29</b>	0.09–0.95	<b>0.11</b>	0.02–0.54	<b>0.58</b>	0.34–0.96	<b>0.30</b>	0.16–0.55	<b>0.42</b>	0.20–0.90
Onset >20 × Female	0.52	0.16–1.71	1.00	0.31–3.21	4.12	0.19–91.35	1.02	0.26–4.04	2.35	0.25–1.14	0.76	0.26–2.20

All models have spline functions for age included.  
Risks in bold are significant at  $P < 0.05$ .

age of 50 (though this second peak might be unreliable due to diminished numbers).

While the survival curve appears to suggest that a female preponderance in first onset of major depression only becomes evident in early adolescence, the hazard function shows a much earlier separation of the genders (i.e. prior to 10 years of age) – albeit with the separation trend break most distinct in early adolescence. In those developing a first episode of dysthymia, the picture is less complex, with the female preponderance indicated as developing later. Between about 25 and 35 years of age there is a convergence of hazard rates (parallel survival curves) but, outside this period, the female preponderance is more distinctive. Thus, the female preponderance reflects increased relative rates across two periods: (i) adolescence and early adulthood; and (ii) following middle-age.

### Correspondence of depression and anxiety patterns

The marked changes in hazard rates to a female preponderance in the depressive disorders from puberty onwards occur just after or concurrently with changes in two anxiety disorders (generalized anxiety disorder and panic disorder) consistent with our hypothesis. However, as noted, the female preponderances develop further over time. The two stages at which the survival curves ‘pull apart’ indicates that determinants are not necessarily the same at each point, although the existence of the biphasic pattern for both the anxiety and depressive conditions argues for common mechanisms or mechanisms having

similar impact on the onset of anxiety and depression, whether reflecting a shared higher order variable influencing both disorders or a sequencing model – where one disorder impacts on the emergence of the other.

### Quantifying the comparative impact of gender and specific anxiety disorder on the onset of depression

Table 1 reports the risks of DEP associated with each anxiety disorder separately; that is, the risk of subsequent DEP in those who developed an anxiety disorder relative to those who did not. Risks are not adjusted as to whether the onset of the particular anxiety disorder was the first onset of any anxiety disorder or not. Model I in Table 1 examines female gender and the onset of the disorder, while Model II divides onset into three periods and includes period-by-gender interactions. From Model I it can be seen that the risks of DEP in those with a predisposing anxiety disorder range from 2.5 to 3.6 – but with differences across differing anxiety disorders not being great. As the unadjusted risk for gender is 1.91, it is clear that the covariates make little difference to this effect. The closeness of the risks for GAD and panic attacks reflects all cases of GAD also having an onset of panic attacks.

Model II also shows gender having a stable effect over time on DEP. Agoraphobia aside, onsets of DEP after age 20 showed reduced or negligible risks. Of particular note is the large increase associated with simple phobia onsets at 13–20 years, suggesting that, if these develop after childhood (a period during which there is



Table 2. Risks for first onset of early-onset DEP (age &lt; 21) subsequent to onset of individual anxiety disorders (ADs)

Covariate	Agoraphobia		GAD		Panic disorder		Social phobia		Simple phobia		Panic attacks	
	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI
Model I												
Female	<b>1.90</b>	1.56–2.31	<b>1.92</b>	1.58–2.34	<b>1.92</b>	1.58–2.34	<b>1.86</b>	1.53–2.27	<b>1.73</b>	1.42–2.12	<b>1.86</b>	1.52–2.26
Onset anytime	<b>3.18</b>	2.21–4.56	<b>3.76</b>	1.98–7.14	<b>3.41</b>	1.49–7.79	<b>2.73</b>	2.13–3.49	<b>3.16</b>	2.48–4.03	<b>4.40</b>	3.06–6.31
Model II												
Female	<b>1.92</b>	1.56–2.36	<b>1.99</b>	1.63–2.42	<b>1.96</b>	1.61–2.40	<b>2.03</b>	1.63–2.52	<b>1.99</b>	1.60–2.47	<b>1.93</b>	1.57–2.37
Onset of AD at ages 1–12	<b>3.83</b>	1.83–8.05	<b>11.69</b>	3.50–39.02	<b>11.41</b>	1.60–81.27	<b>3.79</b>	2.29–6.26	<b>4.55</b>	2.74–7.55	<b>8.40</b>	3.62–19.5
Onset of AD at ages 13–20	3.25	0.83–1.28	<b>9.47</b>	2.79–32.33	<b>9.89</b>	2.45–39.84	<b>3.97</b>	2.15–7.36	<b>14.17</b>	7.17–28.03	<b>6.19</b>	2.69–16.89
Onset 1–12 × Female	0.76	0.30–1.89	0.32	0.06–1.70	0.35	0.03–3.52	0.86	0.47–1.57	0.58	0.32–1.04	0.60	0.23–1.57
Onset 13–20 × Female	1.03	0.22–4.79	0.15	0.02–1.17	—	—	<b>0.26</b>	0.11–0.63	<b>0.15</b>	0.06–0.39	0.33	0.09–1.26

All models have spline functions for age included.

Risks in bold are significant at  $P < 0.05$ .

—, Indicates a risk not reported due to poor numerical accuracy.

Table 3. Risks for first onset of late-onset DEP (age &gt; 30) subsequent to onset of individual anxiety disorders (ADs)

Covariate	Agoraphobia		GAD		Panic disorder		Social phobia		Simple phobia		Panic attacks		
	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI	Risk	95% CI	
Model I													
Female	<b>1.77</b>	1.49–2.11	<b>1.77</b>	1.49–2.11	<b>1.78</b>	1.49–2.12	<b>1.73</b>	1.46–2.06	<b>1.61</b>	1.35–1.92	<b>1.72</b>	1.44–2.05	
Onset anytime	<b>2.52</b>	1.83–3.48	<b>2.79</b>	1.85–4.21	1.68	0.92–3.05	<b>2.32</b>	1.88–2.88	<b>3.03</b>	2.45–3.74	<b>3.14</b>	2.34–4.20	
Model II													
Female	<b>1.81</b>	1.51–2.17	<b>1.78</b>	1.49–2.13	<b>1.79</b>	1.50–2.13	<b>1.79</b>	1.48–2.18	<b>1.62</b>	1.34–1.96	<b>1.73</b>	1.45–2.08	
Onset 1–12	<b>3.88</b>	2.00–7.51	<b>5.87</b>	1.34–25.67	4.48	0.26–77.18	<b>3.02</b>	1.83–4.97	<b>2.51</b>	1.42–4.44	<b>4.26</b>	1.34–13.52	
Onset 13–20	1.06	0.15–7.50	<b>5.89</b>	1.67–20.78	<b>5.39</b>	1.37–21.25	<b>2.58</b>	1.54–4.32	<b>6.99</b>	3.85–12.68	<b>5.56</b>	2.51–12.32	
Onset > 20	<b>4.00</b>	1.62–9.88	<b>2.90</b>	1.02–8.23	0.55	0.03–11.20	2.33	0.75–7.23	—	—	—	2.24	0.76–6.56
Onset 1–12 × Female	0.84	0.34–2.03	0.80	0.14–4.51	0.33	0.01–13.44	0.91	0.49–1.67	1.29	0.68–2.43	1.38	0.40–4.74	
Onset 13–20 × Female	2.08	0.27–1.63	0.25	0.04–1.47	0.15	0.02–1.30	0.75	0.40–1.41	<b>0.38</b>	0.18–0.80	<b>0.27</b>	0.09–0.80	
Onset > 20 × Female	0.37	0.10–1.38	1.19	0.34–4.09	3.94	0.17–89.25	0.52	0.10–2.64	—	—	1.16	0.33–4.06	

All models have spline functions for age included.

Risks in bold are significant at  $P < 0.05$ .

—, Indicates a risk not reported due to poor numerical accuracy.

probably a developmental vulnerability to simple phobias), there is a significant risk to subsequent depression. The interactions show that the onset of any anxiety disorder between 13–20 reduces the risk to DEP for females by a half or more; that is, adolescent/early-adulthood onset of anxiety is a stronger risk factor to DEP for males than for females. Whether this is just developmental lag or indicative of other determinants cannot be clarified with these data.

The analyses were repeated for early-onset DEP (prior to age 21) and late-onset DEP (after age 30). Table 2 shows the risks associated with anxiety disorders for the onset of DEP before age 21. Allowing for the fact that anxiety onsets closer to 20 have less time to result in depression, there is little variation by age of onset, though

simple phobia is again an exception. The onset by gender interactions, while not as consistently significant, are again in the direction of a reduced influence in females.

Turing to late-onset DEP, Table 3 shows the risks associated with anxiety disorders for the onset of DEP after age 30. If we ignore the confidence intervals, the pattern of risks is essentially the same as that for the overall sample in Table 1. While there is some diminution in the associated risk for some anxiety disorders, and other than for agoraphobia, late-onset depression is more strongly associated with anxiety occurring before the age of 20 years.

We specifically examined the effects of several other covariates on gender-by-onset interactions for two disorders with marked interactions with

gender: social phobia and panic disorder. For each, we fitted a model which included: (i) onset of the other disorders; and (ii) time of onset covariates for the particular disorder, looking to compare the latter risks with their counterparts in Table 1. Results indicated that the particular interactions were unaffected by the addition of the other disorders, even when, as with panic disorder, the risks associated with main effects for onset were reduced markedly.

## DISCUSSION

The NCS study design had much to commend its use for testing our hypotheses. It provided a large sample size, subjects had a similar female preponderance of both anxiety and depressive disorders, and the researchers went to considerable trouble to establish the exact age of onset for disorders. In terms of study limitations, data clearly relied on subjects' memories, and obvious limitations must be conceded, particularly in recalling onset of disorders that do not necessarily commence abruptly and which might have occurred decades previously. Secondly, our modelling analyses considered each disorder in isolation and assumed it was not influenced by any other disorder. In reality, co-morbidity of anxiety disorders is common, and was common here (about 30% of the sample were positive on more than three disorders), and may well distort both the reporting of the disorders and their expression. Thirdly, the onset of a major depressive episode or a seriously perturbing anxiety disorder might cause an individual to under-report the symptoms or significance of an earlier condition so that it might not reach the criteria for caseness. Fourthly, we have relied on a single cross-sectional interview, rather than undertaking a longitudinal study where the sequence of onset of disorders might well be more readily clarified. Finally, even with a survey the size of the NCS, doubts must remain about the power to detect some effects involving rarer disorders and interactions.

Our investigation focused on whether the emergence of a female preponderance in major depression and/or dysthymia was linked temporally with a similar emergence in all or certain anxiety disorders. Examining depressive patterns alone first, the first phase of a biphasic female preponderance occurred in early adolescence

and with the female preponderance less evident for dysthymia than for major depression. However, the weighted numbers of those meeting criteria for dysthymia only was relatively small (74 females, 50 males) and risks erroneous interpretation. Thus, we did not pursue analyses in this small subset.

The pattern for onset of major depression – alone or in conjunction with dysthymia – is thus our focus for consideration.

Most of the anxiety disorders (i.e. agoraphobia, social phobia, simple phobia and panic attacks) showed a trend for a female preponderance emerging well before the pubertal period. Only two anxiety disorders (i.e. GAD and panic disorder) had a pattern suggesting a pubertal emergence in early adolescence and thus in temporal correspondence with the emergence of the female preponderance in depressive disorders. While multiple pubertal influences must be conceded, we have argued (Parker & Brotchie, in press) for the greater salience of gender hormone effects rather than socialization or gender role influences.

Our quantitative analyses were informative, particularly in suggesting that similar temporal patterning (for depression, generalized anxiety disorder and panic disorder) were insufficient for confirming the hypothesis. First, we established that female gender provides an independent risk to depression (i.e. above and beyond any influence of anxiety). Secondly, our analyses did not support a specificity model, whereby only certain anxiety disorders contribute to depression. Instead, the risks effected by each anxiety disorder on the onset of depression were quite similar, despite earlier analyses suggesting the emergence of female preponderances in the anxiety disorders emerging at seemingly differing periods. While not central to our hypothesis – which focuses on a possible determinant of the gender difference in depression rather than determinants of depression onset *per se* – such findings are of general relevance. Our Model II analyses more closely addressed the hypotheses being pursued. By trichotomizing age of onset of the separate anxiety disorders to putative prepubertal (i.e. 1–12 years), adolescence (i.e. 13–20 years) and adulthood (i.e. more than 20 years) periods, we were able to examine period, gender and period-by-gender interactions. In these analyses, gender alone had a relatively stable



effect over the three periods on depression onset. In the analyses of period-by-gender interaction, the risk of initial onset of pre-pubertal depression was effectively close to unity across most of the anxiety disorders (being somewhat lower for GAD and for panic disorder). However, onset of an anxiety disorder in adolescence reduced the risk of depression in females, so that the development of an anxiety disorder at that time was a stronger risk to later depression for males.

Such analyses showed: (i) a gender effect; (ii) time of anxiety onset effects; and (iii) time by gender interactions (i.e. differential effects due to gender). While we found interesting relationships between gender and time of onset, analyses did not support our hypothesis that the female preponderance in depression is simply secondary to a female preponderance in (all or specific) anxiety disorders. This could reflect the reality or a too parsimonious hypothesis that cannot be readily tested because of a range of complexities (e.g. definition of separate anxiety disorders, the heterogeneity of anxiety and depressive disorders). The imposition of a cut-off in determining 'caseness' will always be somewhat arbitrary and thus influence studies of this nature. Dimensional measures of trait anxiety and of 'neuroticism' might be more useful markers for pursuit of the hypothesis. Furthermore, even if the hypothesis was valid, gender would only cease to be a predictor if there was no error of measurement – with the potential for measurement error being high in a study of this type.

In a study of patients with clinical depression (Parker *et al.* 1999), we established the distinctly greater relevance of a preceding anxiety disorder in those who developed their first episode of depression at an early age (both when cut-off ages were  $\leq 25$  years, and  $\leq 20$  years). In our current study we examined the comparative impact of gender and onset of separate anxiety disorders at differing age periods (and their interaction) on the chance of both early-onset (i.e. prior to 21 years) and late-onset (i.e. after 30 years) depression. In our Model I analyses there was a general trend whereby all pre-existing anxiety disorders were associated with a greater risk of early-onset rather than late-onset depression, confirming the high risk effected by early-onset anxiety.

An unexpected finding was a suggested bimodal distribution in the female preponderance in onset of both anxiety and depressive disorders. In addition to a first pre-pubertal or adolescent separation, and following some approximation of onset risk across the genders in early to mid-life, there was a second phase where a female preponderance in onset re-emerged for the depressive disorders and for several of the anxiety disorders (most clearly for GAD and social phobia), commencing variably from the late 30s to the late 40s. We are not aware of such a pattern being previously identified in community studies. If not artefactual, the temporal confluence of the phenomenon across the anxiety and depressive conditions again argues for a shared higher-order common factor or a sequencing model to explain the links. Again, if not artefactual, interesting questions are raised as to whether the later separation in onset rates might be determined more by social or biological factors.

While our analyses failed to find any one (or set) of anxiety disorders that might drive – and possibly determine – the emergence of female preponderances in depression, they have revealed a range of complexities in testing the impact of anxiety on depression. Findings are reported in some detail to assist shaping of future studies assessing determinants of the female preponderance in unipolar depression.

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