Patterns and clinical correlates of lifetime alcohol consumption in women and men with bipolar disorder: findings from the UK Bipolar Disorder Research Network

Running head: Alcohol consumption in bipolar disorder

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Abstract

Objectives: Despite previous literature on comorbid alcohol use disorders (AUDs) in bipolar disorder (BD), little is known about patterns of alcohol use more widely in this population. We have examined lifetime heaviest average weekly alcohol consumption levels in a large well-characterised UK sample including lifetime clinical correlates of increasing levels of alcohol use. **Methods:** Participants were 1203 women and 673 men with bipolar I disorder interviewed by semi-structured interview who had consumed alcohol regularly at any point in their life. **Results:** Over half of both women (52.3%) and men (73.6%) had regularly consumed over double the current UK recommended guideline for alcohol consumption. In women and men increasing levels of lifetime alcohol consumption were significantly associated with presence of suicide attempts (women: OR 1.82, $p<0.001$; men: OR 1.48, $p=0.005$) and rapid cycling (women: OR 1.89, $p<0.001$; men: OR 1.88, $p<0.001$). In women only, increasing levels of alcohol consumption were significantly associated with more episodes of depression (OR 1.35, $p<0.001$) and mania (OR 1.30, $p<0.004$) per illness year, less impairment in functioning during the worst episode of mania (OR 1.02, $p<0.001$), fewer psychiatric admissions (OR 0.51, $p<0.001$), comorbid panic disorder (OR 2.16, $p<0.001$) and eating disorder (OR 2.37, $p<0.001$). **Conclusions***:* Our results highlight the clinical importance of obtaining detailed information on levels of alcohol consumption among patients with BD. Increased levels of alcohol use, not necessarily reaching criteria for AUD, may be helpful in predicting BD illness course, in particular eating disorders comorbidity in women.

Keywords: Bipolar disorder, alcohol consumption, clinical characteristics

1. Introduction

Several epidemiological studies have shown a strong association between lifetime alcohol use disorders (AUDs) and bipolar disorder (BD) [1–3]. A number of clinical studies have confirmed these findings with the pooled lifetime prevalence of AUDs in BD calculated in a meta-analysis to be around 35% (22% and 44% in women and men respectively) [4]. This compares to around 13% in the general population [5]. There are a number of explanations for this association including shared genetic risk factors [6–8] and the self-medication hypothesis [9].

The presence of AUDs in BD has been associated with a more severe and unstable illness course characterised by higher rates of lifetime suicide attempts [10–13], a younger age of onset of illness [12,13], more depressive symptoms [13], increased risk of depressive relapse [14] lifetime comorbid post-traumatic stress disorder (PTSD) [12,15], worse psychosocial functioning [13], heightened inter-episodic affective lability [16] , impulsivity and risk taking behaviour [17,18] and additional substance use disorders [12,19].

Despite the previous literature on comorbid AUDs in BD, little is known about the pattern of lifetime alcohol consumption more widely in this population and whether there are clinical correlates of increasing levels of alcohol use irrespective of whether or not the criteria for AUD are met. The limited research examining such relationships has mixed findings. Among 148 'non heavy drinkers' with BD in Canada, increased number of standard drinks per week was associated with more lifetime manic episodes and more emergency department visits in men. Among women, increased frequency of alcohol use was associated with more lifetime episodes of depression and hypomania [20]. In

contrast, in a Dutch prospective follow up study of 137 outpatients with BD, levels of alcohol use (defined as either no/incidental, moderate or excessive based on the average number of units of alcohol per week over the past 4 weeks) was not associated with lifetime clinical characteristics measured at baseline or any 12-month clinical course or outcome variables in women or men [21].

Due to differences in study designs and patient populations, it is difficult to draw conclusions from the small number of previous studies examining the relationship between levels of alcohol consumption and lifetime clinical features in BD. Further investigations into these relationships and patterns of alcohol consumption more broadly are likely to have implications for the management of BD as well as improving understanding of factors contributing to lifetime heterogeneity in BD illness course. In this study of a large and well-characterised UK sample of individuals with BD, we aimed firstly to describe lifetime heaviest regular alcohol consumption, and secondly to examine lifetime clinical correlates of increasing levels of alcohol use, including comorbid anxiety and eating disorders which are known to commonly co-occur with AUDs [22,23]. Our large sample enabled us to examine these relationships in women and men separately, which we did in light of the findings of recent systematic reviews and meta-analyses which found an effect of gender on the comorbidity between AUDs and BD. [4,24]

2. Methods

Data were collected as part of an ongoing UK-based programme of research into the genetic and non-genetic determinants of BD and related mood disorders (Bipolar Disorder Research Network, BDRN; bdrn.org) which has UK National Health Service (NHS) Research Ethics Committee approval (MREC/97/7/01) and local Research and Development approval in all participating NHS Trusts/Health Boards.

2.1. Recruitment of participants

Participants were recruited using both systematic and non-systematic recruitment methods. Systematic recruitment involved screening for potential participants through Community Mental Health Teams (CMHTs) and lithium clinics. Non-systematic recruitment included advertisements on the research team website, in local media and via patient support organisations (such as Bipolar UK).

Participants were required to: i) be 18 years or older; ii) have mood symptoms that started before the age of 65 years; and, iii) be of UK white ethnicity, due to a focus on genetic analysis. Individuals were not eligible if they: i) experienced affective illness only as a result of alcohol or substance dependence; or ii) experienced affective illness only secondarily to medical illness or medication.

Participants were interviewed using the Schedule for Clinical Assessments in Neuropsychiatry (SCAN) [25], which provides detailed information about lifetime psychopathology. Psychiatric and general practice case-notes where available were also reviewed. Best-estimate main lifetime diagnosis was made according to DSM-IV criteria and key clinical variables, such as age at illness onset, history of psychiatric

admissions and lifetime suicidal behaviour were rated. Level of function during each participant's lifetime worst episode of depression and mania was assessed using the Global Assessment Scale (GAS)[26] . The GAS measures overall functioning during a specified time-frame on a continuum from illness to health with scores ranging from 1-100 (lowest-highest level of functioning). Information on lifetime diagnoses of other psychiatric illnesses was collected from participant self-report of a formal clinical diagnosis and from medical notes.

In cases where there was doubt, diagnostic and clinical ratings were made by at least two members of the research team blind to each other's rating. Inter-rater reliability was formally assessed using 20 cases. Mean kappa statistics were 0.85 for DSM-IV diagnoses and ranged between 0.81 and 0.99 for other key clinical variables; mean intra-class correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables. Team members involved in the interview, rating and diagnostic procedures were all research psychologists or psychiatrists.

2.2 Alcohol consumption

This study was carried out on 1876 participants (1203 women and 673 men) with a DSM-IV main lifetime diagnosis of bipolar I disorder (BDI) who had consumed alcohol regularly at any point in their lifetime. Participants, who were all interviewed between 2001 and 2013, were asked at interview how much alcohol on average they had consumed per week at their heaviest ever regular use which was converted into an average heaviest units/week [a UK unit of alcohol refers to 10ml pure alcohol].

2.3 Statistical analysis

Statistical analyses were carried out using R version 3.3. Descriptive statistics were first carried out to describe heaviest average weekly alcohol consumption in women and men, including the proportion consuming over the UK weekly recommended guideline for alcohol consumption (14 units per week for both women and men since 2016, 21 units for men prior to the 2016 UK guideline change). In order to examine the relationship between levels of alcohol consumption and lifetime clinical characteristics, participants were divided into five ordinal groups of equal size according their heaviest average regular weekly alcohol consumption (level 1 = lowest alcohol consumption to level 5 = highest alcohol consumption) in women and men separately. Demographic and lifetime clinical characteristics were compared between groups using one-way analysis of variance (parametric continuous variables), Kruskal–Wallis tests (non-parametric continuous variables) and chi-squared tests (categorical variables).

Ordinal regression models were then used to analyse the relationship between levels of alcohol consumption and each clinical characteristic significant at $p<0.05$ in the univariate analyses. Each characteristic was examined separately adjusting for potential confounding demographic variables found to be significantly associated with the levels of heaviest average regular weekly alcohol consumption among women and men in the sample respectively. The proportional odds assumption for the ordinal regression models were met, which justified the calculation of a single adjusted odds ratio for each clinical characteristic variable.

3. Results

The distribution and patterns of heaviest average regular weekly alcohol consumption among women and men with BD who had consumed alcohol regularly at any point in their lifetime are presented in Table 1 and Figure 1. The median heaviest average weekly units of alcohol consumed was 30 in women and 50 in men. Heaviest average regular weekly alcohol consumption was in excess of the current UK weekly recommended guideline among 71% of women and 88% of men, and was at least twice over the recommended guideline (30 units or more per week) among 52% and 74% of women and men respectively. 79% of men had consumed over the previously higher recommended UK guideline of 21 units per week which were in place at the time of data collection, with 55% of men consuming over twice the previous recommended guideline (45 units or more per week).

Relationships between levels of heaviest regular alcohol consumption and lifetime clinical characteristics in women and men are shown in Tables 2 and 3 respectively. Within women, after controlling for potential demographic confounders (age at interview and level of education) odds of increasing levels of alcohol consumption were significantly associated with having a younger age of illness onset (OR 0.97, 95% CI 0.95-0.98, $p<0.001$), history of rapid cycling (OR 1.89, 95% CI 1.45-2.47, $p<0.001$), more episodes of depression per illness year (OR 1.35, 95% CI 1.16-1.58), $p<0.001$), more episodes of mania per illness year (OR 1.30, 95% CI 1.10-1.58, $p<0.004$), less impairment in functioning during the worst episode of mania (OR 1.02, 95% CI 1.01-1.03), $p<0.001$), history of suicide attempts (OR 1.82, 95% CI 1.48-2.26, $p<0.001$), fewer psychiatric admissions (OR 0.51, 95% CI 0.38-0.67, $p<0.001$), and history of panic disorder (OR 2.16, 95% CI 1.61-2.91, $p<0.001$) and eating disorder (OR 2.37,

95% CI 1.64-3.44, p<0.001). In men, after controlling for age at interview, increasing levels of alcohol consumption were significantly associated with history of rapid cycling (OR 1.88, 95% CI 1.30-2.72, p<0.001) and suicide attempts (OR 1.48, 95% CI 1.12-1.96, p= 0.005). A trend was however observed for increasing levels of alcohol consumption to be associated with a younger age of illness onset and history of panic disorders in men with stratified group sizes for eating disorder history being too small for statistical analysis.

4. Discussion

This is the first study to examine patterns and clinical correlates of increasing levels of lifetime alcohol consumption among individuals with BD in a large UK sample. Among both women and men a large proportion of the sample who had consumed alcohol regularly at any point in their life had, at their heaviest, regularly consumed over the recommended UK guideline at the time for alcohol consumption. In fact approximately half of both women and men had consumed over double the recommend guideline. This figure is increased in men when considering the new UK guideline in place since 2016 which lowered the recommend weekly units of alcohol consumption for men from 21 to 14 in line with the guideline for women. While there are no directly comparable general population lifetime figures available, these high proportions further highlight the importance of routinely screening for level of alcohol use among individuals with BD. In the UK at least, rates of recording alcohol consumption in primary care among adults with BD are high [27]. However, the extent to which effective interventions are implemented are unknown.

Our results extend previous research which has predominantly focused on correlates of lifetime AUDs in BD and not considered levels of lifetime alcohol consumption more broadly. We did find differences between women and men which is in keeping with previous research that has found gender-specific differences in clinical correlates of lifetime AUDs in BD [15,28]. Although different gender-specific patterns were observed, among both women and men markers of a more severe and unstable BD illness course (rapid cycling and suicidal attempts) were associated with increasing levels of alcohol consumption. Despite this, increasing levels of alcohol consumption were not found to be associated with number of admissions in men and were associated with fewer psychiatric admissions in women. These findings are surprising given the high rates of history of suicide attempts among individuals in the highest level of heaviest average regular alcohol consumption (74% in women and 54% in men). However they do support results from a previous study that found that despite a more frequent history of suicidal behaviours, those with comorbid BD and AUDs were no more likely to receive any more, or more intensive, treatment than those without [10]. Increasing levels of alcohol consumption in women were significantly associated with less impairment in functioning during the worst episode of mania which may in part explain our finding of fewer psychiatric admissions. In contrast, impairment during the worst episode of depression was not significantly associated with increasing levels of alcohol consumption. Unfortunately, we were unable to stratify hospital admissions into those for the treatment of depression and mania which may have revealed different patterns. Interestingly our results are in contrast to the previous finding in a prospective Dutch study that found levels of alcohol use, assessed over the past four weeks, were not associated with a number of baseline lifetime clinical characteristics of BD including history of suicide attempts [21]. However, the studies are not directly comparable due to

the different timeframes used (lifetime compared to past four weeks) and different methods of categorising levels of alcohol consumption based on average weekly units.

Among women in our sample, increasing levels of heaviest average regular weekly alcohol consumption were additionally significantly associated with a younger age of illness onset and self-reported formal clinical diagnosis of panic disorder and eating disorder. Among these disorders, differing patterns were observed with increasing levels of alcohol consumption. Prevalence of eating disorder comorbidity increased more steadily across the levels of alcohol consumption compared to panic disorder comorbidity which was notably more prevalent at higher levels of alcohol consumption. Although lifetime AUDs have been found to be associated with panic disorder in general population epidemiological studies [29], previous studies have not found this association specifically in BD samples [12,15]. The presence of a lifetime anorexia nervosa diagnosis has previously been found to be significantly associated with AUD in univariate analyses in a BD sample [12]. However due to small stratified group sizes the association did not remain significant in multivariate analyses and was not examined separately in women and men. The relationship between alcohol consumption and specific eating disorder comorbidities warrants investigation in further larger samples of women with BD.

Due to the cross-sectional study design we are unable to comment on the causal direction of the relationship between alcohol consumption levels and lifetime clinical characteristics of BD in our sample. Prospective studies, in particular focusing on levels of alcohol consumption in women and the relationship with anxiety symptoms are required. Furthermore, we did not collect data on family history of AUD or drinking

patterns including the onset of alcohol use in relation to the onset of BD and the lifetime frequency or duration of periods of alcohol consumption, which would be important factors to measure in future studies in both BDI and BDII. Our sample also does not reflect the gender distribution of BD in the general population. [30] This is due to female volunteer bias in our wider BDRN research programme and a result of our use non-systematic, in addition to systematic, recruitment methods. An additional limitation is that were unable to explore the relationship between increasing levels of alcohol use and other medical and psychiatric comorbidities that have been found to co-occur with AUDs, for example, post-traumatic stress disorder.

In addition to highlighting patterns of lifetime alcohol consumption in a large sample of individuals with BD, our findings suggest obtaining information about both current and past levels of alcohol consumption, particularly in women, may be helpful in identifying eating disorders comorbidity. Our results also highlight the importance of collecting quantifiable data on amount of alcohol consumption in future BD samples, particularly in those intended for international consortium collaborations where guidelines both between and within countries overtime may differ and affect AUD diagnostic practises.

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Table 1 Heaviest average regular weekly units of alcohol consumed in women and men with bipolar I disorder who had consumed alcohol regularly at any point in their lifetime

	Women (n=1203)	**Men (n=673)**
Median (IQR)	30 (48)	50 (72)
Mean (SD)	49.32 (62.5)	74.8 (78.3)
Range	1-560	1-560
Heaviest average regular consumption over current UK weekly recommended guideline † , % (n)	70.6 (849)	87.8 (591)
Heaviest average regular consumption over UK weekly recommended guideline prior to change for men in 2016 ‡, % (n)	-	79.2 (533)

† over 14 units per week for both women and men, ‡ over 21 units per week for men. IQR = interquartile range, SD= standard deviation.

Table 2 Comparison of lifetime demographic and clinical characteristics according to levels of heaviest average regular weekly alcohol consumption in women

	Alcohol consumption						
	Level 1 (n=222)	**Level 2 (n=256)**	**Level 3 (n=219)**	**Level 4 (n=277)**	**Level 5 (n=229)**	**Unadjusted p-value**	**Adjusted OR ‡ (95% CI), p-value**
Heaviest average regular alcohol units/week consumed: median (range)	5 (1-9)	14 (10-20)	30 (21-39)	50 (40-70)	112 (75-800)	-	-
Demographic variables							
Age at interview, years: mean (SD)	49.5 (12.0)	45.8 (11.3)	43.8 (12.0)	43.8 (11.6)	43.7 (10.1)	**<0.001**	-
Completed higher education *n* (%)	65 (30.5)	122 (49.0)	94 (43.7)	136 (51.1)	80 (36.7%)	**<0.001**	-
Has never married / never lived as married *n* (%)	19 (8.7)	37 (15.0)	33 (15.4)	32 (12.0)	29 (13.4%)	0.215	-
Systematically recruited *n* (%)	70 (31.7)	65 (25.6)	47 (22.0)	75 (27.3)	62 (27.7)	0.237	-
Lifetime clinical characteristics							
Age at illness onset, years: median (IQR) range	23.5 (11) 9-56	21 (12) 4-59	20 (10) 7-55	18 (10) 4-58	18 (7) 7-51	**<0.001**	**0.97 (0.95-0.98), <0.001**
Rapid cycling present *n* (%)	39 (23.9)	50 (27.2)	43(26.5)	77 (40.7)	78 (51.0)	**<0.001**	**1.89 (1.45-2.47), <0.001**
No. episodes depression per illness year: median (IQR) range	0.33 (0.39) 0.02-6.0	0.38 (0.47) 0.03-10.0	0.40 (0.51) 0.04-3.08	0.50 (0.64) 0.04-14.29	0.57 (0.78) 0.04-8.33	**<0.001**	**1.35 (1.16-1.58), <0.001**
No. episodes mania per illness year: median (IQR) range	0.25 (0.33) 0.02-2.78	0.28 (0.38) 0.03-10.0	0.29 (0.37) 0.03-3.08	0.36 (0.46) 0.03-14.29	0.44 (0.67) 0.02-4.62	**<0.001**	**1.30 (1.10-1.58), 0.004**
GAS score during worst depression: median (IQR) range	35 (10) 5-65	40 (13) 12-77	40 (14) 10-51	40 (14) 10-60	38 (10) 10-60	**<0.001**	1.00 (0.99-1.01), 0.688
GAS score during worst mania: median (IQR) range	28 (15) 10-50	22 (15) 10-51	30 (20) 5-50	30 (20) 10-55	30 (21) 10-51	**<0.001**	**1.02 (1.01-1.03), <0.001**
Suicide attempt present *n* (%)	106 (50.2)	104 (42.4)	113 (52.6)	153 (57.5)	169 (74.4)	**<0.001**	**1.82 (1.48-2.26), <0.001**

Psychiatric admission *n* (%)	207 (95.4)	223 (88.1)	187 (86.2)	210 (76.9)	181 (80.8)	**<0.001**	**0.51 (0.38-0.67), <0.001**
Psychotic symptoms present *n* (%)	157 (77.3)	194 (84.7)	149 (77.2)	179 (79.2)	140 (74.5)	0.112	-
Family history of bipolar disorder *n* (%)	26 (13.1)	11 (5.3)	26 (14.3)	29 (12.1)	20 (10.2)	**0.035**	1.12 (0.79-1.61), 0.520
Panic disorder present *n* (%)	19 (17.8)	24 (13.6)	30 (19.1)	59 (27.6)	63 (34.4)	**<0.001**	**2.16 (1.61-2.91), <0.001**
Eating disorder † present *n* (%)	5 (4.7)	8 (4.4)	24 (14.4)	32(14.4)	40 (21.2)	**<0.001**	**2.37 (1.64-3.44), <0.001**

IQR= inter quartile range, OR=odds ratio, CI= confidence interval, GAS=Global Assessment Scale. Totals vary due to unknown/missing data. Bolded values are statistically significant at $p<0.05$. † Anorexia nervosa and/or bulimia nervosa and/or binge eating disorder, ‡ Ordinal regression models adjusted for age at interview and completed higher education.

Table 3 Comparison of lifetime demographic and clinical characteristics according to levels of heaviest average regular weekly alcohol consumption in men

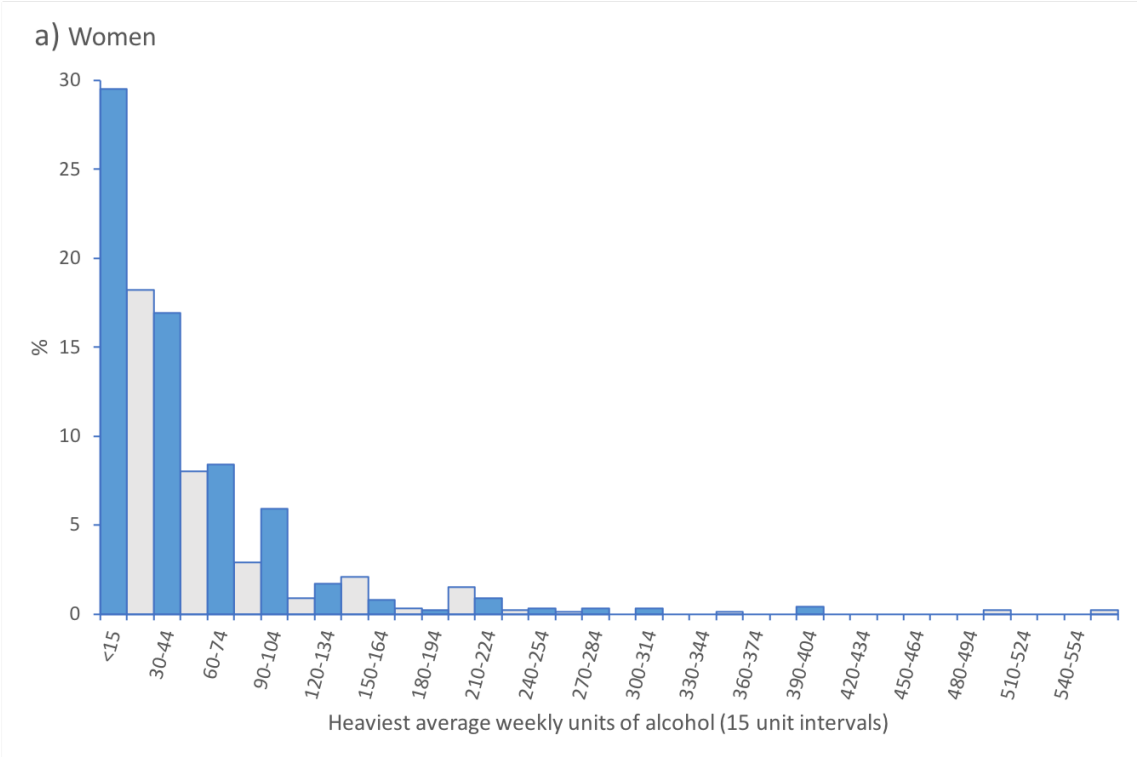
	Alcohol consumption level						
	Level 1 (n=133)	**Level 2 (n=155)**	**Level 3 (n=121)**	**Level 4 (n=138)**	**Level 5 (n=126)**	**Unadjusted p-value**	**Adjusted OR ‡ (95% CI), p-value**
Heaviest average regular alcohol units/week consumed: median (range)	12 (1-20)	30 (21-40)	50 (42-60)	84 (63-100)	171.5 (101-560)	-	-
Demographic variables							
Age at interview, years: mean (SD)	50.3 (13.0)	47.9 (11.9)	46.6 (11.5)	47.5 (11.8)	46.6 (11.0)	**0.033**	-
Completed higher education *n* (%)	52 (41.9)	66 (45.2)	49 (41.9)	54 (41.5)	49 (40.5)	0.950	-
Has never married / never lived as married *n* (%)	32 (25.2)	32(22.1)	19(16.7)	30(23.8)	21(17.9)	0.417	-
Systematically recruited *n* (%)	51(38.9)	49(32.2)	45(37.2)	48(35.3)	40(32.8)	0.753	-
Lifetime clinical characteristics							
Age at illness onset, years: median (IQR) range	23.5 (17) 10-54	22 (12) 7-58	21 (12) 9-63	22.5 (13) 12-53	21 (11) 7-47	0.083	-
Rapid cycling present *n* (%)	16 (17.0)	26 (24.5)	23 (25.3)	24 (23.8)	41(44.1)	**0.001**	**1.88 (1.30-2.72), <0.001**
No. episodes depression per illness year: median (IQR) range	0.22 (0.39) 0.03-4.29	0.33 (0.55) 0.03-8.33	0.37 (0.57) 0.02-3.18	0.4 (0.53) 0.03-20.0	0.5 (0.64) 0.00-3.33	**<0.001**	1.10 (0.98-1.28), 0.126
No. episodes (hypo) mania per illness year: median (IQR) range	0.29 (0.38) 0.03-4.29	0.30 (0.36) 0.04-2.85	0.31 (0.50) 0.04-2.94	0.35(0.45) 0.05-5.26	0.4 (0.47) 0.03-3.33	0.139	-
GAS score during worst depression: median (IQR) range	40 (12) 10-66	40 (15) 12-55	40 (14) 15-63	40 (15) 19-70	40 (16) 15-57	0.156	-
GAS score during worst mania: median (IQR) range	26 (9-50)	27 (15-53)	21.5 (8-50)	26 (10-56)	30 10-50)	0.153	-
Suicide attempt present *n* (%)	43(34.1)	59(39.1)	50(43.5)	52(39.1)	67 (53.6)	**0.024**	**1.48 (1.12-1.96), 0.005**

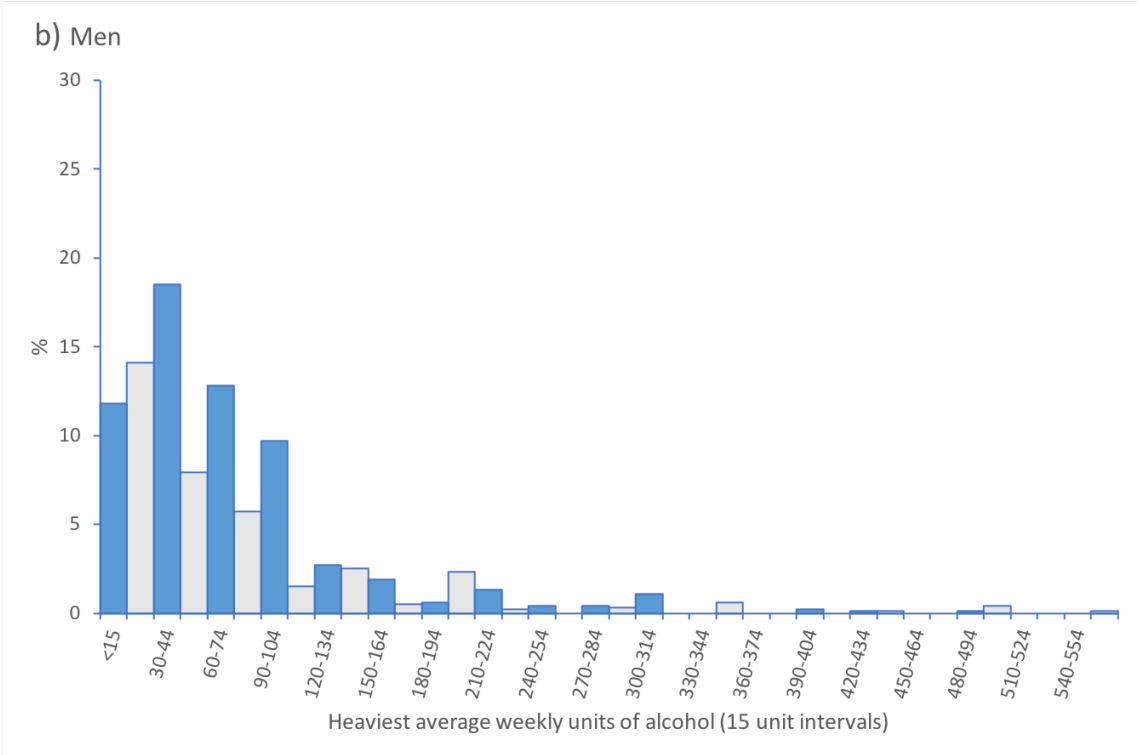
Psychiatric admission *n* (%)	113(86.9)	141(91.0)	100(84.0)	119(86.9)	105(84.7)	0.455	-
Psychotic symptoms present *n* (%)	86(73.5)	104(76.5)	80(74.1)	85(72.6)	77(74.0)	0.969	-
Family history of bipolar disorder *n* (%)	11 (9.5)	10 (7.9)	7 (6.9)	15 (14.0)	11 (10.3)	0.440	-
Panic disorder present *n* (%)	9(10.8)	19(17.6)	7(8.1)	14(15.9)	20(21.1)	0.105	-
Eating disorder † present *n* (%)	0 (0.0)	2 (1.9)	2 (2.2)	1 (1.1)	4 (4.2)	§	-

IQR= inter quartile range, OR=odds ratio, CI= confidence interval, GAS=Global Assessment Scale. Totals vary due to unknown/missing data. Bolded values are statistically significant at $p<0.05$. † Anorexia nervosa and/or bulimia nervosa and/or binge eating disorder, ‡ Ordinal regression models adjusted for age at interview, § Cells expected less than 5

FIGURE LEGEND

Figure 1 Proportions and distribution of heaviest average regular weekly units of alcohol consumed in women (n=1203) and men (n=673) with bipolar I disorder who had consumed alcohol regularly at any point in their lifetime




b) Men
30
25
20
15
10
5
0
%
<15
30-44
60-74
90-104
120-134
150-164
180-194
210-224
240-254
270-284
300-314
330-344
360-374
390-404
420-434
450-464
480-494
510-524
540-554
Heaviest average weekly units of alcohol (15 unit intervals)