Temporal patterns of recovery across eating disorder subtypes


Objective: To compare patterns of recovery in individuals with index episodes of anorexia nervosa (AN) and bulimia nervosa (BN).

Method: Using Kaplan-Meier methods and Cox proportional hazards models, comparisons were conducted that were conditional on duration of eating disorder from onset and included a conservative recovery criterion of 3 asymptomatic years. Data collection was retrospective and from two of the international Price Foundation genetic studies on 901 individuals with eating disorders.

Results: Using Kaplan-Meier methods, 11% of those with index AN and 10% of those with index BN met recovery criteria at 10 years. At 15 years, 16% of those with index AN and 25% of those with index BN met recovery criteria. In a Cox proportional hazards model the index BN group had three times the rate of recovery at 10–14 years (p = 0.01) than the index AN group.

Conclusions: Initially the probability of recovery was greater for those with index AN, but as the duration of the eating disorder lengthened those with BN had higher probabilities of recovery. Replication of these results with prospective data using similarly stringent recovery criteria and methods is required to confirm trends.

Key words: eating disorders, recovery, remission.


Anorexia nervosa (AN) and bulimia nervosa (BN) are serious psychiatric illnesses. Follow-up studies of eating disorders suggest a spectrum of outcomes ranging from recovery to death [1,2] Community studies suggest shorter durations of illness [3,4], whereas clinical studies generally indicate a more protracted course [1]. The standardized mortality ratio for AN is 10.5 [5]. Relapse rates range from 22% to 51% across outcome studies of AN and BN [6].

No consensus definition of remission, recovery, and relapse exists in the field [1]. Moreover, rates of remission or recovery vary across eating disorder subtypes. Estimates of remission or recovery for AN range from 31% to 76% [6–12]. A review of 119 AN studies found that on average less than one-half fully recover [13]. Estimates of remission for BN range between 21% and 75% [6,11,12,14–17]. A review of 88 BN studies found that 50% of women were fully...
recovered after 5–10 years [18]. The wide range of estimates reflects varying diagnostic and assessment measures, duration of follow up, and nature of the sample (e.g. community, clinic, tertiary care). Although longer follow-up studies exist, the longest duration of follow up for studies using survival analysis was 15 years [8].

Reported recovery rates also vary as a function of the duration of time that an individual is required to be symptom free in order to be declared remitted or recovered. By definition, recovered and remitted refer to varying lengths of time a person remains asymptomatic. Remission typically indicates that symptoms are absent for a brief period of time. Maintenance of remission for a longer period of time is considered durable. Remission typically indicates that symptoms have subsided from extremely short (i.e. 8 weeks) [8,12] to a more substantive 12 months [20]. In addition, the level of symptomatology assessed also affects outcome statistics [8,11].

Field et al. argue that asymptomatic periods of less than 1 year should be considered remissions, not recoveries [14]. They obtained estimates of the probability of relapse in a prospective study from 106 treatment-seeking women with BN, who had abstained from binge eating and purging for 4 weeks. Few participants remained asymptomatic after 1 year (n = 40), and estimates of the probability of relapse were less stable due to sparse data. Likewise, Carter et al. encouraged observation periods exceeding 1 year to better capture the extended process of recovery [7]. The authors examined the timing and risk of relapse in 51 AN patients following weight restoration. The mean time to relapse was 18 months, with risk being greatest 6–17 months after discharge. Together these findings underscore that a large proportion relapse in clinical samples for both AN and BN within the first year after receiving treatment for the eating disorder.

Previous studies using survival analysis in eating disorders have approached the concept of time until remission or recovery differently. Definitions of remission or recovery included not exceeding 1 symptom-free year [20], 1 month [16], 8 symptom free weeks [8,12] and two studies included no time element to determine how long a person had to remain symptom free to be classified as remitted [10,11]. Collectively these studies had sample sizes not exceeding 250 people with maximum follow-up duration of 15 years.

We characterized and compare AN and BN recovery profiles in a large, carefully characterized sample of individuals with eating disorders. The precise characterization necessary for a genetic study has allowed for a detailed explication of course of illness among 901 participants. We used survival analysis to estimate proportions and rates with a conservative estimate of recovery requiring 3 symptom-free years.

Methods

Participants

The Price Foundation collaborative group ascertained a sample of BN-affected relative pairs (BN ARP) [21] from 1998–2000 and AN trios (affected individual plus parents) [22] from 2000 to 2003. Kaye et al. and Reba et al. have described the criteria for inclusion and exclusion for each study in detail [21,22]. These studies, designed to identify susceptibility loci for eating disorders, obtained informed consent from all study participants. All sites received approval from their local Institutional Review Board.

Combined, these data form a sample of 1502 individuals. After including only those who were female, a proband, and with complete age information permitting calculation of years with an eating disorder from onset, the analysis population was 901 women with 276 women from the BN ARP study and 625 from the AN Trios study.

Definition of recovery

Recovery was defined as at least 3 years without any eating disorders symptoms (i.e. low weight, dieting, binge-eating, compensatory behaviours). Subthreshold psychological features such as weight influencing self-evaluation were allowed based on the fact that low levels of these features represent ‘normative discontent’ [23]. We chose 3 years in order to maximize the chances of observed recoveries truly representing recoveries rather than temporary remissions. It is known that the majority of those in clinical samples relapse within the first year after discharge [7,12] and few data exist in the literature to guide the optimal definition of recovery. In addition, the present study relied on retrospective recall and we believed that requiring longer symptom-free periods would improve accuracy of reports of recovery. We therefore opted for a conservative definition of 3 years.

Assessments

Lifetime histories of eating disorders in probands were assessed with the Structured Interview for Anorexia Nervosa and Bulimic Disorders (SIAB) [24]. Additional eating disorder symptom information was obtained by an expanded version of Module H of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) [25].

Retrospective questions identifying the onset and offset (if not currently ill) of the eating disorder were used to calculate the
duration of the eating disorder. The duration of eating disorder symptoms was the age at onset subtracted from the age at last reported symptoms.

At onset, an index diagnosis of either AN or BN based on initial symptoms was assigned. If cross-over occurred they were shifted from the index subtype and designated as having a mixed eating disorder diagnosis from that point forward until the end of observation. For participants reporting cross-over, the duration of time with an eating disorder included two components instead of one. The first component was time spent in the index eating disorder. The second component included time with the mixed eating disorder, following the index eating disorder, until recovery or end of observation. An AN index diagnosis followed by a mixed diagnosis was defined as AN-mixed, and a BN index diagnosis followed by a mixed diagnosis was defined as BN-mixed. These characterizations make four mutually exclusive eating disorder subtype categories: index AN, index BN, AN-mixed and BN-mixed.

Statistical methods

SAS/STAT, version 9.1.3 of the SAS System for Windows (SAS Institute, Cary, NC, USA) was used for data handling and statistical analyses. Graphics were created using the R software package (R Foundation for Statistical Computing, Vienna, Austria). Percent recovery by eating disorder subtype was estimated by Kaplan–Meier (KM) analyses. The KM estimates using these data account for time spent in the index eating disorder only. Time with an eating disorder in these data consists of time both in an index eating disorder and after cross-over. Thus the KM estimates are useful in that they offer descriptive information possible to characterize in plots, but unlike the subsequent method they do not characterize recovery for the complete length of time with an eating disorder. Thus, no testing was done using this method. Rates of recovery were compared and tested across eating disorder subtypes using a Cox proportional hazards (PH) model. The hazard in this context represents the rate at which recovery occurred they were shifted to index AN, index BN, AN-mixed and BN-mixed.

Results

Sample characteristics

The mean age at interview was 28 years (SD = 8.1). The mean age of onset was 16 years (SD = 3.3) with an interquartile range of 4 years. The time between onset of first eating disorder and the interview had a mean of 12 years with a range of 40 years (Table 1). More than 80% of participants had not experienced recovery prior to the assessment, and were censored at that point.

Kaplan–Meier curves

Those with index AN have the highest probability of recovering and conversely, the lowest probability of continuing with an eating disorder prior to year 10. Figure 1 indicates that the probability of a recovery event after 10 years is highest for those with BN. The probability of recovering by year 5 is 0.04 for those with index AN and 0.02 for those with index BN. By year 10 the probability of recovering is 0.10 for index BN, while the index AN group has a 0.11 probability of recovering. At year 15 the probability of recovering is 0.25 for those with an index BN diagnosis and 0.16 for those with index AN. Finally, the probability of recovering by year 20 is 0.30 and 0.19 for BN and AN, respectively. Initially, prospects of recovery are stronger for those with index AN, but as the duration of the eating disorder lengthens, those with index BN have higher probabilities of recovery (Figure 1).

Smoothed hazard curves

The plot of smoothed hazard function by eating disorder type shows the number of recovery events per unit time by eating disorder type. AN and BN in this context refer to the index eating disorder for each individual. There is a peak in the rate of BN recovery between years 10 and 14, with the BN group having a higher rate of recovery than AN after approximately 5 years with an eating disorder (Figure 2). The smoothed hazard curve indicates a consistent decline in the rate of recovery for the AN group after the 10th year. After ≥15 years the rate of recovery consistently declines for both AN and BN.

Cox proportional hazards

A semi-parametric model, the Cox PH regression, was used to test differences in the conditional rate of recovery by eating disorder subtype. Age at interview (<26, 26–31, 32–36, 37+ years) was a stratification variable in the analysis. In the first 5 years of an eating disorder those with index BN have an average hazard of recovery 30% lower than those with index AN (Table 2). The difference in hazards between the index BN group and the index AN group, the referent, varied over time, and covariates indicating a time interaction were added to the model. Between 5 and 9 years of duration, the hazard of recovery is 23% lower for index BN than index AN. After 10 years and before 15 years with an eating disorder, those with index BN show around a threefold higher hazard of recovery (p = 0.01) than the referent in the analyses, index AN. The hazard for index BN remains high in the following time intervals, but the number of people with information at this time is small and the estimates are not as reliable as for earlier times.

According to the fitted model, the AN-mixed group starts in the first 10 years with just a 7% lower rate of recovery relative to index
### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Index AN</th>
<th>AN-mixed</th>
<th>ANBN</th>
<th>Index BN</th>
<th>BN-mixed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<tr>
<td>(n = 526)</td>
<td>(n = 145)</td>
<td>(n = 15)</td>
<td>(n = 123)</td>
<td>(n = 92)</td>
<td>(n = 901)</td>
<td></td>
</tr>
<tr>
<td>Age at interview (years), Mean ± SE</td>
<td>27 ± 0.3</td>
<td>29 ± 0.7</td>
<td>29 ± 2.3</td>
<td>29 ± 0.7</td>
<td>31 ± 1.0</td>
<td>28 ± 0.3</td>
</tr>
<tr>
<td>Age at onset (years), Mean ± SE</td>
<td>16 ± 0.1</td>
<td>16 ± 0.3</td>
<td>18 ± 1.0</td>
<td>17 ± 0.3</td>
<td>17 ± 0.5</td>
<td>16 ± 0.1</td>
</tr>
<tr>
<td>Years between interview and eating disorder onset, Mean ± SE</td>
<td>11 ± 0.3</td>
<td>13 ± 0.6</td>
<td>11 ± 2.3</td>
<td>12 ± 0.7</td>
<td>13 ± 0.8</td>
<td>12 ± 0.3</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>337 (65)</td>
<td>74 (55)</td>
<td>6 (46)</td>
<td>69 (62)</td>
<td>44 (49)</td>
<td>530 (61)</td>
</tr>
<tr>
<td>Not currently married</td>
<td>75 (15)</td>
<td>21 (16)</td>
<td>3 (23)</td>
<td>23 (21)</td>
<td>16 (18)</td>
<td>138 (16)</td>
</tr>
<tr>
<td>Married</td>
<td>103 (20)</td>
<td>39 (29)</td>
<td>4 (31)</td>
<td>19 (17)</td>
<td>29 (33)</td>
<td>194 (23)</td>
</tr>
<tr>
<td>Highest grade completed, n (%)</td>
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<td></td>
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<tr>
<td>&lt;12th grade</td>
<td>37 (7)</td>
<td>9 (6)</td>
<td>0 (0)</td>
<td>4 (4)</td>
<td>7 (8)</td>
<td>56 (7)</td>
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<tr>
<td>High school</td>
<td>222 (43)</td>
<td>64 (48)</td>
<td>5 (39)</td>
<td>51 (48)</td>
<td>50 (56)</td>
<td>392 (46)</td>
</tr>
<tr>
<td>College</td>
<td>151 (30)</td>
<td>42 (31)</td>
<td>5 (38)</td>
<td>39 (37)</td>
<td>22 (25)</td>
<td>259 (30)</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>101 (20)</td>
<td>20 (15)</td>
<td>5 (23)</td>
<td>12 (11)</td>
<td>10 (11)</td>
<td>146 (17)</td>
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<tr>
<td>Ever have children, n (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>74 (14)</td>
<td>36 (26)</td>
<td>4 (29)</td>
<td>25 (23)</td>
<td>23 (26)</td>
<td>706 (81)</td>
</tr>
<tr>
<td>No</td>
<td>443 (86)</td>
<td>100 (74)</td>
<td>10 (71)</td>
<td>86 (77)</td>
<td>67 (74)</td>
<td>162 (19)</td>
</tr>
</tbody>
</table>

AN, anorexia nervosa; AN-mixed, anorexia nervosa followed by another eating disorder type; ANBN, onset of AN and BN reported in same year; BN, bulimia nervosa; BN-mixed, bulimia nervosa followed by another eating disorder type. First eating disorder diagnosis listed is the index eating disorder.
AN in the first 10 years. However, as duration of the eating disorder lengthens, the rate of recovery for this mixed group exceeds that of index AN by 1.5-fold and 2.6-fold after 10–14 years and 15+ years of duration, respectively. Those with a BN-mixed diagnosis do not show an upward trend as do those with an index eating disorder of AN. After 15 years the hazard of recovery for those with BN-mixed remains closer to that of index AN, if not lower.

Discussion

We explored recovery characteristics in 901 women with AN and BN using a conservative definition of recovery requiring 3 consecutive symptom-free years. After 15 years 16% of those with index AN and 25% of those with index BN reported recovery. Moreover, we identified different conditional rates of recovery across subtypes. Within the first 10 years the index BN group evidenced non-significantly lower rates of recovery than the index AN group. But following the 10th year of time until recovery, index BN individuals had more than double the hazard of recovery than individuals in the index AN group. The rate of recovery for AN-mixed and BN-mixed relative to the index AN referent group was lower in the first 10 years, but from years 10 to 14 both subtypes had higher rates. Unlike the BN-mixed group, those with AN-mixed show a consistent trend towards higher hazards of recovery after 10 years of eating disorder duration. None of these differences were statistically significant.
The recovery percentages reported here are lower than other studies that investigated long-term outcome in eating disorders using survival analysis [7,8,10−12,14,16,20,26]. In the present study, at 5 years of follow up, 2% of women with BN and 4% of women with AN had reported a recovery event. Vast differences emerge in the outcome literature for eating disorders secondary to differences in methodology and sample characteristics [1]. This can also render comparisons across studies problematic. Recovery rates vary substantially, depending on the definition of recovery used and the length of observation. The present definition of recovery was more conservative than that of other published studies. The length of observation in previous longitudinal studies with survival analysis also varied widely, ranging from 1 to 15 years. Studies with shorter length of follow up could not require longer symptom-free periods and might have reported higher recovery rates because they failed to capture the cyclicity and relapsing patterns of eating disorder symptoms.

Two previous studies have comparable methodology in terms of maximum symptom-free time required for recovery [20] or maximum length of observation [12]. Kordy et al. reported an observation period of 2.5 years and a recovery definition of 12 months symptom-free and found a 16% reported recovery for BN and 6% for AN [20]. By comparison, in the present analysis after 5 years, the index AN group percent recovered (4%) exceeded the index BN group (2%). Herzog et al. reported an observation period of 7.5 years and a definition of recovery of 8 consecutive symptom free weeks [12]. The observed recovery rates in BN were significantly higher than in AN (74% in BN and 33% in AN). By comparison, at the 7 year point in the present analysis, the index AN group had a higher recovery rate than index BN (9% vs 5%). It is only after the 10 year mark for this analysis that index BN exceeds index AN recovery rates.

These differences underscore the critical impact of the definition of recovery duration, in that the recovery rates were dramatically higher in the study with 8 week recovery duration, in comparison to that for the present 3 year definition. A second important factor is the average age at the start of the observation. For Kordy et al. and Herzog et al. the average age was approximately 25 years and reflected when individuals presented for treatment. In the present study the observation period began at between the ages of 16 and 18 years, which was the retrospectively reported age of onset of disorder. Moreover, because the probability of recovery increases over time up until a certain point, those studies that examine a truncated observation period excluding the early years of illness might be expected to yield higher recovery rates.

Keel and Mitchell highlighted the important fact that a subgroup of women with BN are at risk for experiencing additional episodes of the disorder [18]. Using a brief recovery definition could give the false impression of complete recovery, when in reality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Years</th>
<th>Parameter Estimate</th>
<th>SE</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td>Index BN</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt;5</td>
<td>−0.356</td>
<td>0.749</td>
<td>0.70</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>−0.267</td>
<td>0.401</td>
<td>0.77</td>
<td>0.51</td>
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<tr>
<td>10-14</td>
<td>1.087</td>
<td>0.432</td>
<td>2.97</td>
<td>0.01</td>
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<tr>
<td>15-19</td>
<td>0.821</td>
<td>0.802</td>
<td>2.27</td>
<td>0.31</td>
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</tr>
<tr>
<td>20+</td>
<td>1.415</td>
<td>1.061</td>
<td>4.12</td>
<td>0.18</td>
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</tr>
<tr>
<td>AN-mixed</td>
<td>&lt;10</td>
<td>−0.073</td>
<td>0.338</td>
<td>0.93</td>
<td>0.83</td>
</tr>
<tr>
<td>10-14</td>
<td>0.423</td>
<td>0.486</td>
<td>1.53</td>
<td>0.38</td>
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<tr>
<td>15+</td>
<td>0.967</td>
<td>0.582</td>
<td>2.63</td>
<td>0.10</td>
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<tr>
<td>BN-mixed</td>
<td>&lt;10</td>
<td>−0.901</td>
<td>0.590</td>
<td>0.41</td>
<td>0.13</td>
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<td>10-14</td>
<td>0.231</td>
<td>0.540</td>
<td>1.26</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>15+</td>
<td>−0.532</td>
<td>1.102</td>
<td>0.59</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

AN, anorexia nervosa; AN-mixed, anorexia nervosa followed by another eating disorder type; BN, bulimia nervosa; BN-mixed, bulimia nervosa followed by another eating disorder type.; Adjusted for age in a Cox proportional hazards regression. Referent is index AN in all cases.
individuals could be temporarily remitted. Even with the more conservative recovery definition of 3 asymptomatic years the possibility of relapse remains, but it is assumed to be low. An assumption in this particular analysis is that the recovery event occurs only once and none existed before the last reported symptoms. If this assumption is not met then recovery rates are biased downwards.

The majority of studies that have used survival analyses have recruited participants at the time of entry to a treatment programme. Generally this creates heterogeneity at entrance, with some individuals being early in the disease and others being further along or even in a relapsing state. The present design offered both advantages and disadvantages to that approach. First, given that the present samples were ascertained for participation in a genetic study, they could have been interviewed at any point in the course of their illness independent of treatment status (during the illness, remitted, recovered, relapsed). Moreover, the careful reconstruction of their disorder from onset to the time of evaluation provided a detailed analysis of course of illness.

This interview process provides a complete retrospective longitudinal profile of illness course. But the variation inherent in this retrospective design results in a situation in which some individuals are recalling information from earlier in their personal history than others. Although varying duration of recall can bias estimates within an eating disorder subtype, comparisons between subtypes should be valid, assuming that recall duration does not vary between subtypes. Ascertaining this bias through a medical record review is problematic in that the potential exists for variation across records. Participants span multiple countries and multiple health systems. While the potential for bias exists in this study method, the uniformity of interviews in the study design ensures consistency.

In addition to the conservative recovery criterion, another explanation for the lower recovery rates seen in the present sample is that cases ascertained for a genetic study may differ systematically from clinical or community samples in terms of eating pathology, comorbidity, and course of illness. Although we have considered this possibility in previous reports in which we included participants from multiplex families only, the present sample included a large proportion of individuals from a study that was sampled on the basis of a trio design (i.e. affected proband plus parents), from families that were not necessarily multiplex. Second, the comorbidity patterns of the present sample were examined in previous reports [27–29] and are on par with other clinical samples of individuals with eating disorders, but somewhat higher than that observed in community samples [30].

We also evaluated rates of recovery for four subtypes in this paper: AN, BN, and mixed diagnoses (AN to BN and BN to AN). Incorporating these unidirectional shifts between subtypes over the course of the eating disorder provides unique recovery estimates for mixed eating disorder diagnoses. In accounting for a shift to a mixed category, the index AN group may have higher rates of recovery than expected. Both AN-mixed and BN-mixed have lower rates of recovery than does the index AN group in the first 10 years after onset. Because diagnostic crossover can occur at any time, individuals continue to leave the AN group for the AN-mixed group over time. Thus, higher estimates of recovery for the AN group could emerge than if those individuals had remained in the original AN group.

Ten years from illness onset appears to be a meaningful marker. At that point the number of recovery events per unit time declines for all eating disorders subtypes, especially for index AN. Concretely, recovery is most likely within the first 10 years after symptom onset, which leads to both questions and cautions.

First, 10 years is a substantial amount of time to be ill. Both AN and BN have considerable physical, psychological, social and developmental consequences [31–34]. AN is particularly ravaging physically [35] and is associated with poor quality of life [36,37], which may contribute to decreasing chances of recovery with increasing duration of illness. Second, although one cannot automatically make assumptions about secondary and tertiary prevention from analyses such as these, the issue of early intervention cannot be ignored. Given that the average duration of illness of eating disorders prior to presentation for treatment is approximately 6 years [38], and given that 10 years represents a meaningful point at which the probability of recovery begins to decrease, an argument for earlier detection and intervention can be made.

Similarly, although recovery events occur 10 years after the onset of illness, the rate at which events occur decreases. Additional treatment strategies that focus on rehabilitation models (although always allowing for the possibility of recovery) may be warranted in helping these individuals to manage their illness in the face of potential chronicity.

The present results must be considered within the context of several limitations. First, data were collected retrospectively. Although the assessment
approach was developed to ensure a careful reconstruction of eating disorders history as necessary for genetic studies, various recall biases cannot be ruled out. Second, the assumption of one recovery event biases estimates downwards. Third, sample recruitment was not exclusively through treatment centres. While recruitment through clinical centres was the predominant means of subject enrolment [21,22], advertisements for genetic studies were also used. Although on one hand this provides an advantage over studies that have relied on treatment presentation for ascertainment, it also introduces sample heterogeneity. Fourth, women with a more severe illness who might have died from an eating disorder are not captured in the sample thus biasing the recovery estimates upwards.

Although a longitudinal prospective study is ideal, the retrospective approach allowed for certain characteristics, difficult to obtain in prospective studies and adding to the strength of the conclusions. Some strengths of the present study include the sample size of 901 participants, broad ages at time of interview (15–58 years), age of onset range from 8 to 36, and a conservative definition of recovery. Also unique to the survival analysis is the specification of cross-over between the two eating disorder subgroups. In addition, we analysed duration of the eating disorder from first onset rather than duration of eating disorder from presentation for treatment.

Viewing the present results in the context of extant studies using similar methodology underscores the critical importance of developing consensus definitions of relapse, remission, and recovery for eating disorders [1]. When conservative definitions of recovery are used over long observation periods, the outcome of eating disorders is less favourable than previously believed. Requiring a 3 year asymptomatic period excludes individuals from the recovery sample who experience temporary remissions followed by subsequent episodes of illness. Future analyses that use prospective designs coupled with similarly stringent recovery criteria and analytic approaches will assist with verifying and extending the present results while eliminating recall bias. In the mean time, efforts to enhance early detection and referral may assist with shifting recovery statistics toward more favourable outcomes.

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References

19. Frank E, Prien RF, Jarrett RB et al. Conceptualization and rationale for consensus definitions of terms in major


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