Predictors of Mortality in Eating Disorders

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Background: Anorexia nervosa, but not bulimia nervosa, has one of the highest mortality rates among psychiatric disorders. However, potential predictors of mortality, such as comorbid psychiatric illnesses, remain unclear. We sought to determine mortality ratios and predictors of fatal outcome in women diagnosed as having anorexia or bulimia nervosa.

Methods: Women (N=246) diagnosed as having either *DSM-IV* anorexia nervosa (n=136) or bulimia nervosa (n=110) between January 1, 1987, and December 31, 1991, participated in a prospective longitudinal study. Vital status was determined by ongoing contact and a National Death Index search as of December 1998 (overall ascertainment, 99.8%) and telephone contact as of October 2000 (ascertainment, 95.0%).

Results: Eleven women died. Standardized mortality ratios were elevated for all causes of mortality (11.6; 95% confidence interval, 5.5-21.3) and suicide (56.9; 95% confidence interval, 15.3-145.7) in anorexia nervosa but not for death (1.3; 95% confidence interval, 0.0-7.2) in bulimia nervosa. Predictors of mortality in anorexia nervosa included severity of alcohol use disorder during follow-up (P<.001). Hospitalization for an affective disorder before baseline assessment seemed to protect women from a fatal outcome (P<.001).

Conclusions: Physicians treating patients with anorexia nervosa should carefully assess patterns of alcohol use during the course of care because one third of women who had alcoholism and died had no history of alcohol use disorder at intake.

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REVIEW OF MORTALITY in mental illness found that eating disorders were associated with one of the highest risks of premature death.1 This review used standardized mortality ratios (SMRs) (number of deaths observed in a sample to number of deaths expected in the population, correcting for age, sex, and duration of follow-up). Among patients with anorexia nervosa, primary causes of death include suicide and the direct effects of starvation.²⁻⁴ For bulimia nervosa, the most common causes of death have been automobile accidents and suicide.5 Given the limited sample sizes of most outcome studies, and the resulting limited number of deaths, few predictors of mortality have been revealed.

Two studies^{4,6} have reported that lower weight increases risk for fatal outcome in anorexia nervosa, likely because low weight is an indicator of starvation. Engel and colleagues⁷ reported that worse psychosocial functioning predicted mor-

tality in anorexia nervosa; patients with fatal outcome were more likely to be unemployed, unmarried, and living with their parents at the time of death. An association between inpatient treatment and mortality also has been suggested by eating disorders research^{2,4,8}; however, the nature of this association has been ambiguous. In one study,8 compulsory vs voluntary hospitalization represented a risk factor for death. A second study2 indicated that an older age at first psychiatric hospitalization increased risk of death. A third study⁴ suggested that having more than 1 hospital admission was associated with increased mortality. Two of these studies^{2,8} were restricted to inpatient samples, and it is unclear what proportion of women received inpatient treatment in the third study.4 Thus, the extent to which the mortality rate is elevated among patients ever hospitalized for their eating disorder is uncertain.

Mortality rates for anorexia nervosa are based largely on cohorts ascertained through inpatient settings. Because these

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patients could represent the most severe cases of anorexia nervosa, ¹⁰ it is unclear whether their mortality rates are increased relative to those of patients encountered in outpatient settings. Inpatient treatment has been associated with higher SMRs compared with outpatient treatment for mental disorders. ¹ This could explain the apparent discrepancy in mortality rates between women with anorexia vs bulimia nervosa, as most bulimia nervosa outcome studies are based on outpatient cohorts. ⁵ Inpatient treatment is used less for bulimia nervosa than for anorexia nervosa. ^{11,12} Thus, methodologic differences in treatment settings through which patients are ascertained may represent actual differences in illness severity that result in disparate mortality rates for anorexia and bulimia nervosa.

We found no other predictors of mortality in anorexia nervosa and no predictors of mortality in bulimia nervosa. Thus, clinicians encountering women with eating disorders have limited information concerning factors that increase risk of death in these patients. Potential predictors of mortality may include specific eating disorder symptoms that are associated with significant medical morbidity, such as low body weight leading to bradycardia¹³ or purging resulting in hypokalemia.¹⁴ In addition, comorbid psychiatric disorders that are associated with increased mortality may identify women at increased risk of death. For example, women with anorexia nervosa and those with bulimia nervosa have increased rates of major depression relative to the general population, 15,16 potentially contributing to an increased risk of suicide. Finally, treatment setting may predict mortality.1 For example, perhaps only anorexic patients requiring inpatient treatment display an increased risk of

The purpose of this study is to determine SMRs and predictors of fatal outcome in women diagnosed as having anorexia nervosa or bulimia nervosa. These women participated in a prospective longitudinal study that allows evaluation of intake and course variables as predictors of fatal outcome. Although participants were ascertained through outpatient and community settings, treatment history and prospective treatment utilization could range from no treatment to inpatient care.

METHODS

PARTICIPANTS

The study group comprised 246 women recruited for participation in a prospective longitudinal study of anorexia nervosa and bulimia nervosa between January 1, 1987, and December 31, 1991. Most of these women were seeking outpatient treatment for their eating disorder at the Massachusetts General Hospital Eating Disorders Unit and at other Boston area eating disorder programs. Most participants (n=235; 95.5%) received some form of treatment during follow-up, and a portion (n=90; 36.6%) received inpatient treatment. Retrospectively applying DSM-IV criteria to intake data concerning eating disorder symptoms, 136 women met the criteria for anorexia nervosa and 110 met the criteria for bulimia nervosa.

Invitations to participate in a longitudinal study of eating disorders were offered to women who met the following inclusion criteria: (1) *DSM-III-R* diagnosis of anorexia or

bulimia nervosa, (2) female, (3) minimum age of 12 years, (4) residence within 200 miles of Boston, (5) English speaking, and (6) no evidence of organic brain syndrome or terminal illness. Intake diagnoses were based on *DSM-III-R* criteria because *DSM-IV* criteria had not yet been established when the study began. Of the 294 women who met participation criteria, 250 (85.0%) agreed to participate in the longitudinal study. Four individuals dropped out of the study after the intake interview and before the first follow-up interview. Thus, the total size of the study group participating in the longitudinal follow-up study is 246.

PROCEDURE

This study was approved by the institutional review board at Massachusetts General Hospital. After brief telephone screening, individuals who seemed to meet the inclusion criteria were scheduled for a face-to-face interview to confirm eating disorder diagnoses and to assess other psychiatric disorders, treatment history, and height and weight. Participants completed written informed consent forms before this interview. Follow-up interviews were conducted, in person when possible, every 6 to 12 months. Mean and median duration of follow-up for collection of clinical data in the longitudinal study were 8.6 and 9 years, respectively.

MEASURES

During intake interviews, participants' lifetime Axis I psychiatric histories were assessed using the *Schedule for Affective Disorders and Schizophrenia–Lifetime Version*¹⁷ modified to include *DSM-III-R* diagnostic criteria for anorexia and bulimia nervosa. The 1983 Metropolitan Insurance Company height and weight norms were used to calculate percentage of ideal body weight. The *Structured Interview for DSM-III Personality Disorders*¹⁸ was used to assess Axis II disorders in individuals 18 years or older at intake or once participants had turned 18 years old during follow-up.

During follow-up interviews, the Longitudinal Interval Follow-up Evaluation¹⁹ adapted for eating disorders was used to assess eating disorders and comorbid psychiatric disorders according to Research Diagnostic Criteria. Once a diagnosis was given, the disorder's course was coded on a week-by-week basis using the Psychiatric Status Rating scale. Scores on this scale range from 1 to 6, with 1 indicating no symptoms and 5 or 6 indicating the presence of full diagnostic criteria. Further details on the use of this measure are presented elsewhere.²⁰ Social adjustment was evaluated on a 5-point scale, with 5 representing very poor psychosocial functioning. The Global Assessment of Functioning (GAF) scale of the DSM was used to evaluate overall level of symptom severity from all disorders and psychosocial function. Social adjustment, GAF scores, and treatment were rated on a week-by-week basis throughout follow-up.

ASCERTAINMENT OF VITAL STATUS

In addition to ongoing interviews for the longitudinal study group, follow-up telephone calls were conducted to determine vital status for all longitudinal study participants as of October 2000. Of the 246 study participants, vital status was confirmed for 234 (95.1%) via telephone contact. To assess the vital status of participants from the longitudinal study who were deemed out of contact, a National Death Index²¹ search was conducted. This index represents a branch of the National Center for Health Statistics with a national death certificate database updated through December 31, 1998, at the time of this investigation, providing ascertainment of vital status for 96.0%²² of

Table 1. Causes of Death in 11 Women With Eating Disorders

Participant, No.	Diagnosis at Intake	Age at Death, y	BMI (%IBW) at Death	NDI Underlying Cause of Death (<i>ICD-9</i> Code)
1	ANBP	39	19.2 (88)	Fungal pneumonia (486.0)
2	ANR	40	11.8 (55)	Suicide (950.9)
3	ANBP	24	21.3 (98)	Cardiac dysrythmias (427.9)
4	ANBP	46	17.4 (77)*	Alcohol poisoning (305.0)
5	ANBP	40	20.1 (88)*	Diabetes mellitus (E149†)
6	BN	40	40.2 (185)	Mitral valve prolapse (424.0)
7	ANR	29	19.9 (92)	Suicide (950.4)
8	ANR	52	12.8 (57)	Amyotrophic lateral sclerosis (335.20
9	ANR	37	18.2 (86)*	Suicide (958.9)
10	ANBP	35	14.6 (63)	Suicide (988.8)
11	ANR	39	9.4 (42)*	Heart and liver failure (571.5)

Abbreviations: ANBP, anorexia nervosa, binge-eating purging subtype; ANR, anorexia nervosa, restricting subtype; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BN, bulimia nervosa; %IBW, percentage of ideal body weight; NDI, National Death Index.

*Ascertained at last interview before death.

participants deemed out of contact. Thus, ascertainment was approximately 99.8% as of December 31, 1998. Cause of death was obtained from death certificates for all participants with a fatal outcome. Medical records and autopsy reports were reviewed when available. When possible, interviews were conducted with the deceased individuals' relatives to collect data concerning the individuals immediately before their death.

STATISTICAL METHODS

In addition to crude mortality rates, we calculated SMRs. The expected number of deaths for a general, white, female population was derived from US decennial life tables for 1989-1991. The expected number of suicides for a general female population was derived from the 1995 Annual Report: Vital Statistics of Massachusetts. Annual Report: Vital Statistics of Massachusetts.

Cox regression models were used to determine predictors of fatal outcome. We used time-varying proportional hazards (Cox) regression²⁵ to determine the effect of baseline and course variables on time to death. For the deceased participants, course variables were imputed as the last value carried forward from the last interview. For participants who were not deceased but discontinued participation in clinical assessments (n = 17), data were censored from analyses. Nested models were compared using the likelihood ratio test (LRT), which follows a χ^2 distribution. A Cox model produces a model coefficient (βi), hazard multiplier (exp[βi]), confidence interval for the hazard multiplier, LRT for the coefficient, and P value for the coefficient. Hazard multipliers greater than 1 increase hazard (shorten time to death), and multipliers less than 1 decrease hazard (lengthen time to death). A multiplier that does not differ significantly from 1 has no significant effect on time to death. Owing to the association between age and mortality, all Cox regression models controlled for age at intake. P<.05 was set for statistical significance. However, because of the large number of statistical tests, a conservative Bonferronicorrected P = .0016, reflecting 31 independent comparisons, is considered. The proportional hazards assumptions for the final models were tested using the procedure of Therneau and Grambusch (R function cox.zph).25

Finally, we developed a multivariate regression model to predict time to death using the methods suggested by Hosmer and Lemeshow. ²⁶ Briefly, this approach involves inclusion of variables demonstrating a univariate association with outcome at the $P \le .20$ level and any variables of clinical importance, regardless of their univariate association. After fitting this

initial multivariable model, each covariate of the model is removed. The significance of remaining covariates is evaluated to determine whether the new model has lost an important effect (a ≥20% change in the coefficient of any of the remaining covariates is evidence of an important interaction or confounding effect for the removed covariate). This process continues until no variables can be removed from the model. Statistical analyses were performed using the R statistical package.²⁷

RESULTS

Eleven women (4.5%) died. Of these, 10 women (91%) had intake diagnoses of anorexia nervosa and 1 (9%) had an intake diagnosis of bulimia nervosa according to DSM-IV criteria. Crude mortality for anorexia and bulimia nervosa was 7.4% and 0.9%, respectively. The SMRs were 11.6 (95% confidence interval, 5.5-21.3) for anorexia nervosa and 1.3 (95% confidence interval, 0.0-7.2) for bulimia nervosa. Thus, mortality rates seem to be elevated in anorexia nervosa but not in bulimia nervosa. Five women with anorexia nervosa met the criteria for the restricting subtype and 5 met the criteria for the binge-purge subtype at intake, and anorexia nervosa diagnostic subtype was not associated with mortality (coefficient, 0.04; LRT, 0.003; P=.96). Causes of death are reported in Table 1. Four deaths were due to suicide, all in women with anorexia nervosa. The SMR associated with suicide for anorexia nervosa was 56.9 (95% confidence interval, 15.3-145.7), representing a dramatically increased risk of death by suicide for these women.

Among intake variables, only longer duration of illness (coefficient, 0.11; LRT, 5.14; P=.02) and history of nonalcohol substance use disorders (coefficient, 0.56; LRT, 4.58; P=.03) were associated with increased risk of fatal outcome in anorexia nervosa. After controlling for age and duration of illness before intake, history of nonalcohol substance use disorders demonstrated only a trend level association with time to death (coefficient, 0.48; LRT, 3.52; P=.06).

Results from Cox regression models of course variables are given in **Table 2**. Significant predictors included greater severity of alcohol and substance use dis-

[†]ICD-10 code provided for underlying cause of death.

Table 2. Bivariate Models of the Association Between Course Variables and Mortality in Anorexia Nervosa Controlling for Age at Intake

Course Variable	Coefficient	LRT	P Value
Severity of anorexia nervosa	0.40	2.41	.12
Severity of bulimia nervosa	-0.09	0.28	.60
%IBW	0.21	1.03	.31
Self-induced vomiting	-0.13	0.04	.85
Laxative abuse	0.23	0.04	.83
Diuretic abuse	-4.41	0.30	.58
Diet pill abuse	-5.08	0.31	.58
Fasting	0.21	0.04	.85
Excessive exercise	-0.48	0.23	.64
Severity of depressive episodes	0.32	3.52	.06
Severity of manic episodes	0.54	2.00	.16
Severity of alcohol use	0.84	7.92	.005
Severity of substance use	0.87	3.97	.046
Social adjustment	0.82	6.62	.01
Global Assessment of Functioning score	-0.08	6.78	.009
Hospitalization	-5.62	0.52	.47
Individual therapy	-1.03	2.19	.14

Abbreviations: %IBW, percentage of ideal body weight; LRT, likelihood ratio test.

orders, worse social adjustment, and worse GAF scores during follow-up. After controlling for age and duration of illness before intake, severity of alcohol use disorder (coefficient, 1.05; LRT, 10.99; P<.001), severity of substance use disorders (coefficient, 1.04; LRT, 4.96; P=.03), social adjustment (coefficient, 0.80; LRT, 5.66; P=.02), and GAF scores (coefficient, -0.08; LRT, 6.36; P=.01) all demonstrated significant associations with time to death. Using the Bonferroni-corrected P=.0016, the association between mortality and severity of alcohol use disorder remained significant.

To build the multivariate regression model, we examined the significance of univariate associations for more than 40 variables with death. Of these, 17 variables demonstrated $P \le .20$ and were included in the initial model. Sequential elimination of each of these 17 variables revealed that 2 variables could be excluded from the model without producing a 20% or greater change in the coefficient of any variables remaining in the model. Table 3 gives the resulting multivariate regression model. Greater duration of illness at intake and severity of alcohol use disorder during follow-up increased risk of mortality, supporting results of Cox regression models. In addition, history of hospitalization for an affective disorder before intake significantly protected women with anorexia nervosa from death. Suicide gestures and attempts primarily related to alcohol and substance use demonstrated a trendlevel association with mortality.

COMMENT

Anorexia nervosa often has been cited as a psychiatric illness associated with high mortality. The present study provides insight into the features that increase risk of death in women with anorexia nervosa. One of the strongest and most consistent predictors of fatal outcome was severity of alcohol use disorder during follow-up. Indeed, based on

Table 3. Multivariate Regression Model of Time to Death*

Variable	Hazard Multiplier Coefficient (95% CI) LRT			<i>P</i> Value
Intake		(5575 55)		
Duration of illness	0.39	1.48 (1.11-1.99)	12.1	<.001
Affective disorder hospitalization	-6.56	0.001 (0.00-0.27)	12.9	<.001
Other suicidality†	3.17	23.92 (0.81-705.52)	3.9	.05
Course		,		
Severity of alcohol use	1.71	5.55 (1.68-18.29)	10.2	.001

Abbreviations: CI, confidence interval; LRT, likelihood ratio test. *Other covariates in the model included (1) the following variables from intake assessments: age, bipolar affective disorder, substance use disorder, any suicide attempts/gestures, suicide attempts/gestures associated with eating disorder, and hospitalization for reasons other than eating or affective disorders (primarily alcohol and substance use related) and (2) the following variables during follow-up: weight change, severity of anorexia nervosa, severity of depressive episodes, severity of manic episodes, severity of alcohol use, and severity of substance use. Model LRT = 44.3, df = 15, P < .001.

†Suicide attempts/gestures associated with mental illnesses other than eating and affective disorders (primarily alcohol and substance use related).

death certificates and interviews with the deceased women's relatives, alcohol seemed to play a direct role in the deaths of 2 women (participants 3 and 4). Of the 6 women with histories of alcoholism who died, one third had no history of alcohol use disorders at intake, potentially explaining the failure of this variable to predict mortality. Thus, clinicians should carefully assess alcohol use among their patients with eating disorders throughout treatment.

Previous investigations^{2,6,28} of mortality in anorexia nervosa have been based largely on inpatient samples, potentially representing the most severe cases of this disorder. However, neither history of hospitalization at intake nor during follow-up significantly increased risk of mortality in anorexia nervosa. Indeed, within the multivariate model, history of hospitalization for an affective disorder seemed to protect women from fatal outcome. Of the 11 women who died, all had a history of an affective disorder. However, only 1 of these women was hospitalized for an affective disorder before intake. Of the 4 women who committed suicide, none had been hospitalized for an affective disorder before intake, including 1 woman with a diagnosis of bipolar I affective disorder who had a suicide attempt during a previous major depressive episode. It is not possible to determine whether these women were less likely to be hospitalized for an affective disorder because they refused hospitalization or because the severity of their mood episode did not seem to warrant hospitalization at the time. However, our results suggest that the threshold for hospitalization during mood episodes may be justifiably lowered for women with anorexia nervosa.

Similar to findings from previous research,⁷ social adjustment during follow-up was associated with premature death (although not significantly after conservative Bonferroni correction). The associations among social adjustment, GAF scores, and mortality may reflect several patterns. First, factors that increase risk of death, such as alcohol use disorders, would also negatively im-

pact social adjustment and result in lower GAF scores. Second, problems in psychosocial functioning might increase the maladaptive use of alcohol and thus indirectly contribute to mortality or may directly increase the likelihood of death by suicide.

This study found no evidence of increased mortality in bulimia nervosa. To our knowledge, only one other study⁴ has reported an SMR for bulimia nervosa. Although this other study's SMR indicated that risk of death was elevated by a factor of 9 in women with bulimia nervosa, the SMR did not differ significantly from 1.⁴ Our finding is in agreement with those of most previous studies of bulimia nervosa outcome.⁵ Owing to the limited number of deaths, we could not determine predictors of mortality in bulimia nervosa.

Strengths of this study include the large sample, long duration of follow-up, careful assessment of eating disorder diagnoses at intake, and high retention rate. A further strength of this study was the careful prospective evaluation of eating disorders and comorbid psychiatric illnesses. Despite several strengths, certain weaknesses should be noted. We could not ascertain vital status as of October 31, 2000, for 5% of our participants. It is possible that the remaining women we were unable to locate had died. Additional deaths might alter the predictive significance of intake and course variables for mortality in anorexia nervosa. More important, additional deaths among women with bulimia nervosa would impact our conclusions concerning mortality in this disorder markedly. However, loss to follow-up did not differ between women with intake diagnoses of anorexia or bulimia nervosa, and using uniform sampling, assessment, and follow-up methods produced strikingly different results concerning mortality in anorexia nervosa compared with bulimia nervosa. Finally, approximately 15% of women who were eligible for the longitudinal study did not enroll, and it is unknown whether risk of premature death differs among these women compared with those who participated.

Given the high rate of suicide, lowering the threshold for hospitalization of anorexic patients during mood disorder episodes may reduce risk of death in these women. Future studies may benefit from evaluating the extent to which anorexia nervosa increases risk of mortality among patients with a primary diagnosis of alcohol use disorder. Physicians encountering patients with anorexia nervosa should be particularly concerned about those with a long history of the illness and ongoing problems with alcohol abuse or dependence.

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