Article

A Longitudinal Investigation of Mortality in Anorexia Nervosa and Bulimia Nervosa

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Objective: Although anorexia nervosa has a high mortality rate, our understanding of the timing and predictors of mortality in eating disorders is limited. The authors investigated mortality in a long-term study of patients with eating disorders.

Method: Beginning in 1987, 246 treatment-seeking female patients with anorexia nervosa or bulimia nervosa were interviewed every 6 months for a median of 9.5 years to obtain weekly ratings of eating disorder symptoms, comorbidity, treatment participation, and psychosocial functioning. From January 2007 to December 2010 (median follow-up of 20 years), vital status was ascertained with a National Death Index search.

Results: Sixteen deaths (6.5%) were recorded (lifetime anorexia nervosa, N=14; bulimia nervosa with no history of anorexia nervosa, N=2). The standardized mortality ratio was 4.37 (95% CI=2.4–7.3) for lifetime anorexia nervosa and 2.33 (95% CI=0.3–8.4) for bulimia nervosa with no history of anorexia nervosa. Risk of premature death among patients with lifetime anorexia nervosa peaked within the first 10 years of follow-up, resulting in a standardized mortality ratio of 7.7 (95% CI=3.7–14.2). The standardized mortality ratio varied by duration of illness and was 3.2 (95% CI=0.9–8.3) for patients with lifetime anorexia nervosa for 0 to 15 years (4/119 died), and 6.6 (95% CI=3.2–12.1) for those with lifetime anorexia nervosa for >15 to 30 years (10/67 died). Multivariate predictors of mortality included alcohol abuse, low body mass index, and poor social adjustment.

Conclusions: These findings highlight the need for early identification and intervention and suggest that a long duration of illness, substance abuse, low weight, and poor psychosocial functioning raise the risk for mortality in anorexia nervosa.

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Mortality rates are higher in anorexia nervosa than in other psychiatric disorders (1), but few studies have examined when death is more likely to occur in the course of this eating disorder. Most commonly, rates of premature death are described by the standardized mortality ratio, calculated as the number of observed deaths during a given period in a specific population of interest divided by the number of deaths expected in the general population, matched for age, race, and sex. A meta-analysis of 25 studies of patients with anorexia nervosa found a standardized mortality ratio of 5.9 in studies with a mean follow-up duration of 12.8 years (1). A similar standardized mortality ratio of 6.2 over 13.4 years of follow-up has also been reported (2). Although both are elevated, there was considerable variability in standardized mortality ratios across studies included in the meta-analysis (1), and these standardized mortality ratios are lower than those reported in studies with shorter follow-up periods (3, 4). Such variability across studies might be accounted for by ascertainment rates, sample size, severity of illness, and duration of follow-up, which may differ substantially from study to study. Thus, it would be instructive to examine the standardized mortality ratio in relation to the duration of follow-up as well as the duration of illness to understand whether there are high-risk periods for premature death in eating disorders.

Six longitudinal studies, including three in adolescents (5–7) and three in adults (8–10), have examined mortality rates over time. All of these investigations assessed anorexia nervosa patients at inpatient admission and again at multiple varying time points, ranging from 2 to 20 years after admission. Four of these studies found that the number of deaths increased with increasing duration of follow-up, with greater consistency in the adult studies than in the adolescent studies. However, it is unclear whether risk of death remained constant during follow-up because at least three studies (5, 9, 10) detected a majority of recorded deaths earlier in the follow-up period.

In the literature, it remains unknown at what point in the progression of the disorder death is more likely to occur and whether there are differences between patients with anorexia nervosa who die relatively early in the follow-up period (or early in the course of the disorder) and those who die later (after a more protracted or chronic course). These two variables, timing of follow-up assessment and duration of illness, are distinct; individuals with eating disorders do not necessarily seek treatment or enter a study at the exact point when they meet full diagnostic criteria. To

This article is featured in this month's AJP Audio, is the subject of a CME course (p. 935), and is discussed in an Editorial by Dr. Crow (p. 824)

clarify this distinction, our first aim in this longitudinal study was to examine standardized mortality ratios at two time points as well as at varying years of duration of illness. Such data might be informative as to whether there is a peak period for death in eating disorders. Our second aim was to examine factors that might increase vulnerability to premature death. Studies have indicated that older age at hospital admission, longer duration of eating disorder, history of attempted suicide, use of diuretics, more severe eating disorder symptoms, desire for lower weight at admission, repeated admission, and psychiatric comorbidity predict mortality (2–4, 11). We address the question of which variables predict mortality when examined at a later follow-up point in this longitudinal study. Predictor variables included eating disorder symptoms, comorbidity, treatment, and psychosocial functioning assessed both at intake and through interviews conducted over the study period.

Method

Participants

The sample consisted of females recruited for participation in the Massachusetts General Hospital Longitudinal Study of Anorexia and Bulimia Nervosa between 1987 and 1991. Most participants were seeking outpatient treatment for their eating disorder. Participants who met the following inclusion criteria were invited to participate: DSM-III-R diagnosis of anorexia nervosa or bulimia nervosa; female; age ≥12 years old; reside within 200 miles of Boston; English speaking; and no evidence of organic brain syndrome or terminal illness. Of the 294 individuals who met the study criteria, 250 (85%) agreed to participate; four dropped out after their intake interview, resulting in a sample size of 246. Participants were reclassified according to DSM-IV criteria, resulting in 51 with anorexia nervosa, restricting type, 85 with anorexia nervosa, binge eating/purging type, and 110 with bulimia nervosa. Of these, 186 (76%) were identified as having lifetime presence of anorexia nervosa, which was defined as 1) being diagnosed at study intake with anorexia nervosa (N=136), 2) having a history of anorexia nervosa prior to study intake (N=26), or 3) developing anorexia nervosa over the course of the study (N=24). Given our previous observations that individuals with lifetime anorexia nervosa who die continue to be at risk even when not actively ill and our previous analyses suggesting that deaths observed among individuals with intake diagnoses of bulimia nervosa might be attributable to a lifetime diagnosis of anorexia nervosa (11), we chose to analyze mortality by lifetime presence (not just intake diagnosis) of anorexia nervosa.

Procedure

This study was approved by the institutional review board at Massachusetts General Hospital. After brief telephone screening, individuals were scheduled for a face-to-face interview to confirm eating disorder diagnoses, assess other psychiatric disorders and treatment history, and measure height and weight. Follow-up interviews were conducted every 6 to 12 months until 2000.

Measures

During intake interviews, participants' lifetime axis I psychiatric history was assessed using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (12), modified to include DSM-III-R diagnostic criteria for anorexia nervosa and bulimia nervosa. The 1983 Metropolitan Insurance Company (13) height and weight norms were used to calculate percent ideal body weight.

Over the course of the study, the Longitudinal Interval Follow-Up Evaluation, adapted for eating disorders (14), was used to assess eating pathology, treatment, and comorbid psychiatric disorders. Once a diagnosis was determined, the course of psychopathology was coded on a week-by-week basis using the Psychiatric Status Rating Scale (11), with scores ranging from 1 (no symptoms) to 6 (full diagnostic criteria). Major depressive disorder and substance use disorders were rated similarly.

Psychosocial functioning was assessed longitudinally using semistructured interviews to examine interpersonal relationships and functioning at work, in household chores, and in recreational activities, as well as global life satisfaction and overall functioning (15, 16). Ratings were made on a 5-point scale ranging from 1, no impairment, to 5, severe impairment. We refer to the global score measuring overall psychosocial functioning as the "social adjustment score." The Global Assessment of Functioning Scale was used to evaluate overall level of symptom severity and impairment, with higher scores indicating better functioning. Further study details have been presented elsewhere (17).

Ascertainment of Vital Status

Vital status was ascertained in 2010 by searching the National Death Index (18). This index represents a branch of the National Center for Health Statistics with a national death certificate database updated through December 31, 2008, at the time of this investigation (19). Cause of death was obtained from death certificates, and, whenever possible, interviews were conducted with the deceased participant's relatives to collect data concerning the participant immediately prior to her death.

The median time from study intake to last study visit was 9 years (range, 13 weeks–12 years), and the median time from last study visit to ascertainment of vital status was 11 years (range, 9 weeks–11 years), resulting in a median total follow-up time of 20 years (range, 13 weeks–23 years).

Statistical Data

To summarize mortality, we calculated crude mortality ratios, annual mortality rates (deaths per person-years), and standardized mortality ratios quantifying the excess number of deaths in our study population compared with what would be expected after adjusting for age, sex, and duration of follow-up. The expected number of deaths for a general white female population, adjusted for age, was derived from U.S. decennial life tables for Massachusetts from 1989 to 1991 (20). Fisher's exact 95% confidence intervals around the standardized mortality ratios were calculated using chi-square centile cutoffs (21). We examined how risk of death changed over time by comparing the standardized mortality ratio by years of follow-up (0–10 years compared with >10–20 years) and by total duration of eating disorder (0–15 years compared with >15–30 years; from full-onset eating disorder through last study visit, excluding weeks with full eating disorder recovery). Formal comparison of the standardized mortality ratios by years of follow-up was not conducted because the ratios are not independent, and comparison by duration of illness is not recommended because our standardized mortality ratios were obtained by indirect standardization (because of the small number of deaths).

Cox proportional hazards regression was used to identify predictors of mortality. The proportional hazards assumption and functional form of the continuous covariates were verified using the methods of Lin et al. (22). Because mortality status was ascertained for many participants after the last study measurement of the course variables, use of time-varying covariates was not possible. Instead, we summarized the variability in course variables using mean scores for continuous

TABLE 1. Summary of Covariates Analyzed for Female Patients With Lifetime Anorexia Nervosa[a]

Variable	Alive (N=172)		Died (N=14)[b]	
	Mean	SD	Mean	SD
Intake covariate				
Age (years) at eating disorder onset	17	4.6	17	5.9
Age (years) at study intake	24	6.7	30	7.7
Years of eating disorder prior to study intake	7	5.7	13	6.9
Body mass index (BMI)	19	3.2	16	3.4
Percent ideal body weight	84	14.0	74	15.9
	N	%	N	%
Eating disorder diagnosis				
Anorexia nervosa, restricting type	44	26	7	50
Anorexia nervosa, binge eating/purging type	79	46	6	43
Bulimia nervosa	49	28	1	7
History of hospitalization for an eating disorder	77	45	9	64
History of alcohol abuse	25	15	4	29
History of drug use disorder	19	11	4	29
History of bipolar disorder	13	8	2	14
Any suicidal gestures or attempts	49	28	7	50
	Mean	SD	Mean	SD
Course covariate				
Years from study intake to last visit	9	2.0	6	3.1
Years from last visit to last follow-up or death	12	1.7	3	4.2
Total years of eating disorder	13	6.8	17	7.0
Number of changes in eating disorder diagnosis	2	2.0	1	1.6
Psychiatric Status Rating Scale				
Anorexia nervosa score, percent of weeks ≥5	23	32.7	54	42.3
Anorexia nervosa score, last visit	2.3	1.9	4.3	1.8
Weight loss, percent of weeks ≥21%–29% below ideal body weight	20	32.6	50	43.4
BMI, percent of 13-week periods <16	2	5.8	9	12.1
Last visit covariate				
BMI, last visit	21	3.0	17	3.9
Psychiatric Status Rating Scale				
Alcohol abuse score, percent of weeks ≥3	2	6.6	18	29.3
Alcohol abuse score, last visit	0.2	0.5	0.9	1.2
Major depressive disorder score, percent of weeks ≥5	12	19.5	28	32.5
Major depressive disorder score, last visit	2	1.6	3	2.0
Manic score, last visit	0.1	0.4	0.3	0.8
Social adjustment rating[c]				
Average during study	3	0.7	4	1.0
Last visit	3	0.9	4	1.1
Global Assessment of Functioning Scale score				
Average during study	56	9.0	43	11.7
Last visit	57	10.4	42	12.2

[a] Other course variables analyzed included the percent of study weeks meeting the following criteria: bulimia psychiatric status rating score ≥5 (percent of weeks dichotomized as above compared with at or below the median); binge eating/purging (including vomiting, laxative use, and diuretic use); other compensatory behavior (including diet pill use, fasting, and vigorous exercise); drug abuse psychiatric status rating score ≥3; hospitalized for an eating disorder; and suicidal gestures or attempts. Also analyzed were sessions of individual therapy received (mean over time) and marital status at last visit (single; married or living with a partner; or separated, divorced, or widowed).
[b] A total of 16 patients died during the course of the study; two of the 16 had bulimia nervosa with no history of anorexia nervosa.
[c] The ratings for social adjustment were as follows: 1=very good; 2=good; 3=fair; 4=poor; 5=very poor.

covariates and percentage of weeks below or above a cutoff for ordinal or categorical covariates. All covariates analyzed are listed in Table 1.

Univariate analyses were conducted first to ensure that relationships were not obscured by collinearity among the covariates; consistent with methods used previously (11), we conservatively applied a Bonferroni-corrected significance threshold of 0.0011, adjusting for the 46 individual comparisons made. Significant covariates were then entered into multivariate models, and stepwise variable selection (with alpha=0.01 to enter and alpha=0.05 to remain) was used to identify a final model. To facilitate comparison with cross-sectional studies that examined only intake covariates, we performed automated selection separately on variables measured at intake, over the course of the study, and at last study visit. All analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, N.C.).

TABLE 2. Clinical Characteristics of 16 Women With an Eating Disorder Who Died During the Course of the Study

Participant	Eating Disorder Diagnosis at Intake	Lifetime Anorexia Nervosa	Age at Intake (Years)	Age at Death (Years)	Years of Eating Disorder at Intake	Total Years of Eating Disorder	Number of Changes in Eating Disorder Diagnosis	Percent Below Ideal Body Weight at Last Visit	Years From Intake to Death	Years From Last Visit to Death	Cause of Death
1	Anorexia nervosa, restricting type	Yes	39	39	19.9	20.4	0	30–39	0.8	0.4	Suicide
2	Anorexia nervosa, restricting type	Yes	32	44	20.6	22.1	0	21–29	12.5	11.0	Complications of resuscitated cardiac arrest; acute methadone, diazepam, and chloral hydrate intoxication
3	Anorexia nervosa, restricting type	Yes	21	29	0.9	5.7	6[a]	6–9	8.2	0.7	Suicide
4	Anorexia nervosa, restricting type	Yes	43	52	7.4	15.4	0	≥40	9.1	1.1	Respiratory failure due to amyotrophic lateral sclerosis
5	Anorexia nervosa, restricting type	Yes	29	36	9.7	17.0	0	10–14	7.7	0.5	Suicide
6	Anorexia nervosa, restricting type	Yes	26	43	11.0	19.5	0	21–29	17.1	8.7	Gastrointestinal hemorrhage, esophageal ulceration
7	Anorexia nervosa, restricting type	Yes	30	48	13.2	21.5	0	10–14	18.0	9.7	Anoxic brain injury, septic shock
8	Anorexia nervosa, binge eating/ purging type	Yes	29	38	15.3	23.6	2	10–14	9.1	0.9	Fungal pneumonia
9	Anorexia nervosa, binge eating/ purging type	Yes	20	24	8.1	10.6	1	6–9	4.9	2.4	Cardiac arrhythmia, seizure disorder
10	Anorexia nervosa, binge eating/ purging type	Yes	43	45	24.9	27.2	2	21–29	2.4	0.2	Acute ethanol intoxication
11	Anorexia nervosa, binge eating/ purging type	Yes	30	39	12.9	14.0	2[a]	10–14	9.8	0.3	Cardiopulmonary arrest, cardiovascular disease, diabetes mellitus
12	Anorexia nervosa, binge eating/purging type	Yes	30	35	16.8	20.1	1	≥40	5.3	2.0	Suicide

continued

TABLE 2. Clinical Characteristics of 16 Women With an Eating Disorder Who Died During the Course of the Study (*continued*)

Participant	Eating Disorder Diagnosis at Intake	Lifetime Anorexia Nervosa	Age at Intake (Years)	Age at Death (Years)	Years of Eating Disorder at Intake	Total Years of Eating Disorder	Number of Changes in Eating Disorder Diagnosis	Percent Below Ideal Body Weight at Last Visit	Years From Intake to Death	Years From Last Visit to Death	Cause of Death
13	Anorexia nervosa, binge eating/purging type	Yes	33	38	17.6	22.9	1	≥40	5.8	0.5	Cardiorespiratory failure, hepatic failure, cirrhosis
14	Bulimia nervosa	Yes	18	35	2.5	2.5	1[b]	6–9	17.3	9.1	Chronic ethanol abuse with early cirrhosis of liver
15	Bulimia nervosa	No	20	35	0.9	10.2	0	6–9	15.2	6.0	Acute bronchopneumonia; cerebral glioma
16	Bulimia nervosa	No	30	40	20.2	29.7	0	6–9	10.5	1.0	Mitral valve prolapse

[a] Participant recovered from eating disorder during follow-up but subsequently relapsed.
[b] Participant had recovered from eating disorder by the time of her last study visit.

Results

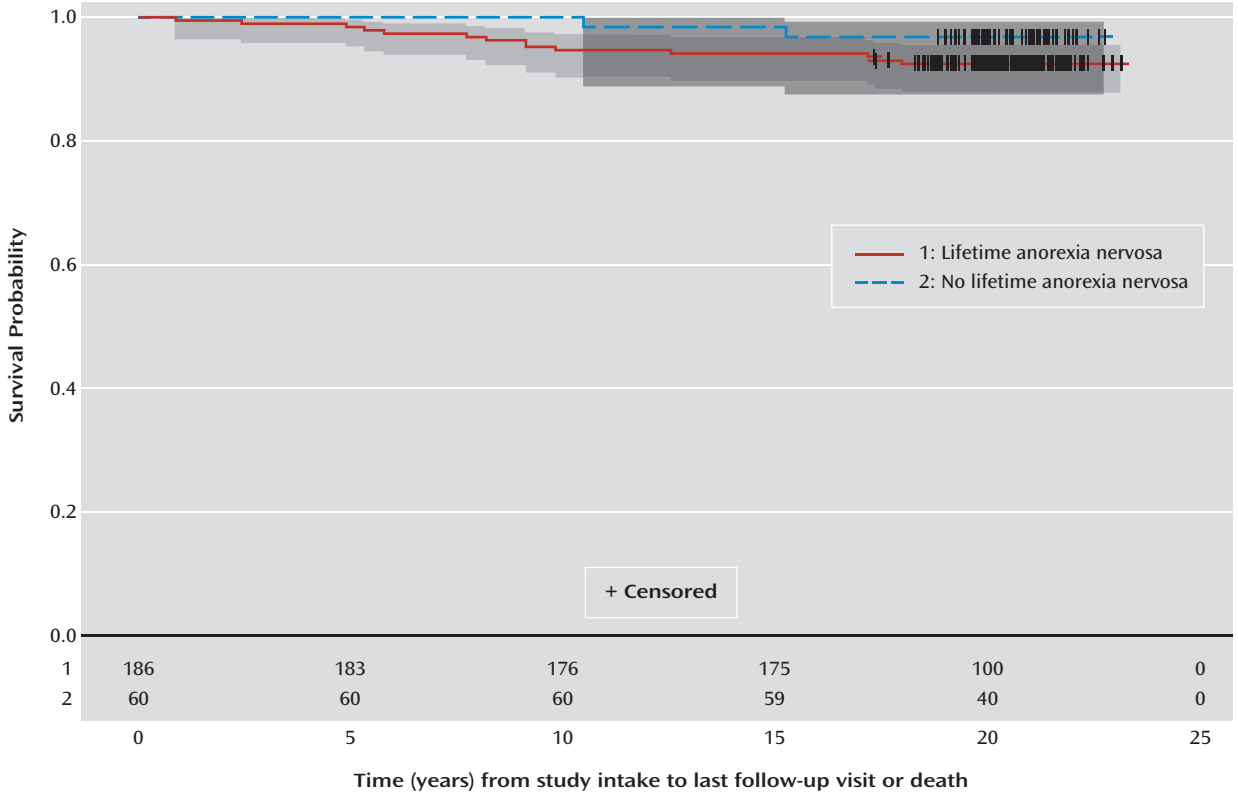
Overall, 16 deaths (6.5%) were observed among the 246 participants (Table 2). Among the 186 individuals with a lifetime history of anorexia nervosa, 14 (7.5%) died, which translated to an annual mortality rate of 3.87 deaths per 1,000 person-years. After adjusting for age, sex, and race, the standardized mortality ratio for individuals with lifetime anorexia nervosa was 4.37 (95% exact confidence interval [CI]=2.4–7.3). Among the 60 participants with bulimia nervosa and no history of anorexia nervosa, two (3.3%) died, which translates to an annual mortality rate of 1.63 deaths per 1,000 person-years and a standardized mortality ratio of 2.33 (95% CI=0.3–8.4). When standardized mortality ratios were calculated by intake diagnosis rather than presence of lifetime anorexia nervosa, findings were consistent in that individuals with anorexia nervosa at intake had significantly elevated mortality (6.2 times the expected rate), while those with an intake diagnosis of bulimia nervosa did not (1.5 times the expected rate, with the confidence interval overlapping 1.0). Given the small number of deaths in the bulimia nervosa group, and the fact that the confidence interval for the standardized mortality ratio includes 1.0 (no elevated mortality), additional analyses focused primarily on participants with lifetime anorexia nervosa.

Of the 16 deaths, four occurred by suicide (all four of these patients had anorexia nervosa). We previously reported the standardized mortality ratio for suicide in our sample to be 56.9 (11). With no new completed suicides in the sample, but an increased number of expected suicides in the demographically matched population since our last analysis, the standardized mortality ratio for suicide among individuals with lifetime anorexia in this sample is now substantially lower, calculated to be 25.2 [95% CI=6.9–64.5].

Risk of premature mortality appeared to decrease over time among individuals with lifetime anorexia nervosa. Within the first 10 years of follow-up, the annual mortality rate for this group was 5.49 deaths per 1,000 person-years, compared with 1.13 deaths per 1,000 person-years thereafter. The standardized mortality ratio also varied substantially by follow-up time. For the follow-up duration from 0 to 10 years (10/186 died), the standardized mortality ratio was 7.7 (95% CI=3.7–14.2), and for the follow-up duration >10 to 20 years (4/176 died), the ratio was 0.7 (95% CI=0.2–1.7). When we examined the standardized mortality ratio by illness duration, we again found considerable variation. The standardized mortality ratio for those with an eating disorder for 0 to 15 years (4/119 died) was 3.2 (95% CI=0.9–8.3), and for those with an eating disorder lasting >15 to 30 years (10/67 died), the ratio was 6.6 (95% CI=3.2–12.1). In other words, the standardized mortality ratio was higher within the first decade of the study compared with the second decade and for those with a longer duration of illness. Specifically, seven of the 10 patients with a longer duration of illness died in the first decade of the study (Table 2), although three of the four patients who died in the second decade also had a longer duration of illness. Thus, the 10 patients who died in the first decade were not the same 10 patients with >15 years of an eating disorder, suggesting that these covariates capture somewhat different information.

The number of changes in eating disorder diagnosis over the course of the study is presented in Table 2. Our previous work indicated that over time, the majority of

FIGURE 1. Survival Curve Comparing Female Patients With and Without a Lifetime History of Anorexia Nervosa



patients with an intake diagnosis of anorexia nervosa in the entire sample experienced crossover between the anorexia nervosa subtypes or from anorexia nervosa to bulimia nervosa; crossover was recurrent and bidirectional with the subtypes (23, 24). In contrast, crossover from bulimia nervosa to anorexia nervosa in individuals without a history of anorexia nervosa at intake was less common (23). It is noteworthy that two of the three individuals with an intake diagnosis of bulimia nervosa who died did not meet criteria for anorexia nervosa during the course of follow-up, nor did they have a history of anorexia nervosa at intake. It is possible that associations between mortality and eating disorder diagnoses depend on when in the course of illness diagnostic status is assessed. Importantly, however, an examination of diagnostic crossover in our predictor analyses indicated that it was not a significant predictor of mortality.

Values of covariates ascertained at intake and course variables examined as predictors of mortality are summarized in Table 1. Although the mean age at eating disorder onset was similar between participants who were still alive at last follow-up and those who died prematurely, those who were still alive at last follow-up entered the study at a much earlier age than those who died prematurely, indicating that those who died had a longer duration of illness prior to study intake, which may reflect delays between disorder onset and seeking treatment.

As shown in the survival curve (Figure 1), whereas individuals without lifetime anorexia nervosa were more likely to die later in the study, most deaths among those with lifetime anorexia nervosa occurred at varying times within the first 10 years of follow-up. Furthermore, while lifetime anorexia nervosa appeared to confer greater risk of mortality, the overall mortality rate was still low in both groups (survival at 20 years after study intake among individuals with and without lifetime anorexia nervosa was 92% and 97%, respectively).

Significant univariate predictors (before and after Bonferroni correction) are presented in Table 3. After applying automated model selection separately to the significant intake, course, and last visit variables, duration of illness was the only significant intake variable to predict mortality. Among course variables, percent of weeks with alcohol abuse and percent of weeks with low body mass index (BMI) (<16) remained in the model. Among last visit covariates, alcohol abuse, BMI, and social adjustment score remained significant. To determine which of the intake, course, and last visit variables together best predicted mortality, we conducted one final automated stepwise selection, which resulted in three variables remaining significant: percent of weeks with alcohol abuse, BMI at last visit, and social adjustment score at last visit. Finally, to account for the fact that, by definition, the last study visit was closer to the time of death than to the time of

TABLE 3. Significant Univariate Predictors of Mortality Among Female Patients With Lifetime Anorexia Nervosa

Univariate Predictor	Time Point	Estimate	Standard Error	Hazard Ratio	95% CI	p
Age (years)	Intake	0.10	0.031	1.68	1.2–2.3[a]	0.0009**
Eating disorder diagnosis	Last visit	–	–	–		0.04*
Eating disorder diagnosis	Last visit (bulimia nervosa compared with anorexia nervosa, restricting type)	−2.15	1.049	0.12	0.02–0.9	0.04*
Eating disorder diagnosis, last visit	Last visit (full eating disorder recovery compared with anorexia nervosa, restricting type)	−2.38	1.049	0.092	0.01–0.7	0.02*
Years of eating disorder	Intake	0.13	0.036	1.94	1.4–2.8[a]	0.0002**
Years of eating disorder	Total	0.078	0.034	1.47	1.0–2.1[a]	0.03*
Anorexia nervosa Psychiatric Status Rating Scale score	Percent of weeks ≥5	0.020	0.0065	1.22	1.1–1.4[b]	0.002*
Anorexia nervosa Psychiatric Status Rating Scale score	Last visit	0.64	0.20	1.89	1.3–2.8	0.002*
Bulimia nervosa Psychiatric Status Rating Scale score	Percent of weeks ≥5–above compared with at or below median (6.5%)	−1.33	0. 65	0.27	0.1–0.9[b]	0.04*
Percent ideal body weight	Intake	−5.68	2.17	0.57	0.4–0.9[b]	0.009*
Weight loss	Percent of weeks ≥21%–29% below ideal body weight	0.019	0.0063	1.21	1.1–1.4[b]	0.003*
Weight loss	Last visit	–	–	–		0.04*
Weight loss	Last visit; 6%–9% compared with 21%–29% below ideal body weight	−2.01	0.69	0.13	0.0–0.5	0.004*
BMI	Intake	−0.29	0.10	0.75	0.6–0.9	0.005*
BMI	Percent of 13-week periods <16	0.077	0.022	2.15	1.4–3.3[b]	0.0004**
BMI	Last visit	−0.39	0.084	0.68	0.6–0.8[b]	<0.0001**
Alcohol abuse Psychiatric Status Rating Scale score	Percent of weeks ≥3	0.048	0.0096	1.61	1.3–1.9[b]	<0.0001**
Alcohol abuse Psychiatric Status Rating Scale score	Last visit	0.94	0.24	2.55	1.6–4.1	<0.0001**
Major depressive disorder Psychiatric Status Rating Scale score	Percent of weeks ≥5	0.021	0.0082	1.23	1.0–1.4[b]	0.01*
Major depressive disorder Psychiatric Status Rating Scale score	Last visit	0.44	0.14	1.56	1.2–2.0	0.001*
Social adjustment score	Average during study	1.41	0.31	4.10	2.2–7.5	<0.0001**
Social adjustment score	Last visit	1.29	0.27	3.64	2.21–6.2	<0.0001**
Global Assessment of Functioning Scale score	Average during study	−0.11	0.027	0.32	0.2–0.5[b]	<0.0001**
Global Assessment of Functioning Scale score	Last visit	−0.11	0.023	0.34	0.2–0.5[b]	<0.0001**

[a] The hazard ratio is calculated for a 5-year increase in the covariate.
[b] The hazard ratio is calculated for a 10-unit increase in the covariate.
* Indicates significance at an alpha level of 0.05; ** indicates significance at a Bonferroni-corrected alpha level of 0.0011.

the last follow-up for those still alive, we forced age at intake into the final model to account for the passage of calendar time. Both the significance and the direction of effect of the covariates were maintained in the final model after adjusting for age.

To understand the factors captured by the social adjustment score, we compared social adjustment components at last visit by mortality status. Women who died had moderate to severe impairment in employment (t=–4.92, df=160, p<0.0001), mild to moderate impairment in household functioning (t=–4.24, df=174, p<0.0001), and fair to poor interpersonal relationships with friends (t=–2.96, df=184, p=0.003) and siblings (t=–2.35, df=184, p=0.02) and were more likely to be single (Fisher's exact p=0.07). They also had fair to poor enjoyment of recreational activities (t=–3.00, df=184, p=0.003) and low global satisfaction (t=–2.88, df=184, p=0.004). There were no significant differences in interpersonal relationships with partners or with parents.

Discussion

Our analyses revealed that patients with lifetime anorexia nervosa had higher premature mortality rates than the general population and that risk of premature death was highest in the first 10 years of follow-up and among

individuals with the longest duration of illness. This finding may be explained by the fact that most of the women who died came into the study with a long duration of illness. With one exception, those who died reported an illness duration spanning 7 to 25 years before entry into the study. It may be that their deaths tended to come early in the study because they had already suffered a long period of time with an eating disorder. Thus, while mortality rates in anorexia nervosa varied based on when in the course of this longitudinal study mortality was assessed as well as by the duration of the disorder, it seems likely that chronicity is a crucial factor in premature death.

In some (25) but not all (26, 27) studies, the standardized mortality ratio for bulimia nervosa has been reported to be lower than that for anorexia nervosa. Interestingly, however, two of the three women with bulimia nervosa in our study who died had never been diagnosed with anorexia nervosa. Future research might investigate causes of death in bulimia nervosa, as well as potential predictors, by combining data sets in order to achieve adequate sample sizes.

The age and cause of death in this sample of patients with anorexia nervosa are noteworthy. All deaths occurred in middle adulthood, with all but three deaths occurring between ages 35 and 48 years, suggesting that for women with long-standing histories of eating disorders, middle adulthood is a particularly high-risk period for dying. Furthermore, the causes of death, with a few exceptions (e.g., amyotrophic lateral sclerosis), may have been related to eating disorder symptoms, although given the time lapse between the last interview and death, we are not able to address this issue definitively. In the case of the four suicides, the causes of death represent extreme methods with high lethality (28).

Although a number of predictor variables were significant in univariate analyses, alcohol abuse over the course of the study and BMI and social adjustment at the last interview remained significant in multivariate analyses. Our earlier analyses at the 10-year follow-up found that longer duration of illness at intake and severity of alcohol use disorder during follow-up increased the risk of mortality (11). Over the longer follow-up period, the degree of low weight and the social adjustment score at the last visit also emerged as significant multivariate predictors of mortality.

Social adjustment has been linked to mortality in depression and substance abuse (29, 30). While it is difficult to know in what ways poor social adjustment may be related to mortality (i.e., directly, in concert with comorbidity, or as a reflection of eating disorder severity), our findings indicate that assessing the quality of relationships, the capacity for work and play, and the degree of impairment in psychosocial functioning is vital when working with patients with anorexia nervosa. Recent efforts examining the care of individuals with long-term anorexia nervosa are important, given how little is known about how to treat patients with a chronic eating disorder (31, 32).

Strengths of our study include the large well-maintained sample, the long duration of follow-up, and the careful assessment of diagnoses. Limitations include that the assessment of comorbidity was limited to substance abuse and depression and that no longitudinal data were available between the last study visit and the assessment of mortality, which constituted a lengthy period in some cases. Thus, it is possible that mortality was affected by unobserved life events that occurred between the last study visit and death. Furthermore, the National Death Index does not report deaths that occur outside the United States.

In conclusion, anorexia nervosa continues to be a disorder with high mortality rates and one for which effective treatment remains elusive (33). Our findings highlight the need for early identification and intervention and suggest that among those with a long duration of illness, particularly when substance abuse, low weight, or poor psychosocial functioning are also present, the risk for mortality increases substantially.

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