

Mortality Rates in Patients With Anorexia Nervosa and Other Eating Disorders

A Meta-analysis of 36 Studies

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Context: Morbidity and mortality rates in patients with eating disorders are thought to be high, but exact rates remain to be clarified.

Objective: To systematically compile and analyze the mortality rates in individuals with anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS)

Data Sources: A systematic literature search, appraisal, and meta-analysis were conducted of the MEDLINE/PubMed, PsycINFO, and Embase databases and 4 full-text collections (ie, ScienceDirect, Ingenta Select, Ovid, and Wiley-Blackwell Interscience).

Study Selection: English-language, peer-reviewed articles published between January 1, 1966, and September 30, 2010, that reported mortality rates in patients with eating disorders

Data Extraction: Primary data were extracted as raw numbers or confidence intervals and corrected for years of observation and sample size (ie, person-years of observation). Weighted proportion meta-analysis was used

to adjust for study size using the DerSimonian-Laird model to allow for heterogeneity inclusion in the analysis

Data Synthesis: From 143 potentially relevant articles, we found 36 quantitative studies with sufficient data for extraction. The studies reported outcomes of AN during 166 642 person-years, BN during 32 798 person-years, and EDNOS during 22 644 person-years. The weighted mortality rates (ie, deaths per 1000 person-years) were 5.1 for AN, 1.7 for BN, and 3.3 for EDNOS. The standardized mortality ratios were 5.86 for AN, 1.93 for BN, and 1.92 for EDNOS. One in 5 individuals with AN who died had committed suicide

Conclusions: Individuals with eating disorders have significantly elevated mortality rates, with the highest rates occurring in those with AN. The mortality rates for BN and EDNOS are similar. The study found age at assessment to be a significant predictor of mortality for patients with AN. Further research is needed to identify predictors of mortality in patients with BN and EDNOS.

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EATING DISORDERS ARE INCREASINGLY recognized as an important cause of morbidity and mortality in young individuals. The lifetime risk of anorexia nervosa (AN) in women is estimated to be 0.3% to 1%, with a greater number of patients having bulimia nervosa (BN).^{1,2} Anorexia nervosa is a serious psychiatric illness characterized by an inability to maintain an adequate, healthy body weight. Bulimia nervosa is characterized by recurrent episodes of binge eating in combination with some form of unhealthy compensatory behavior. Eating disorder not otherwise specified (EDNOS) is a catchall DSM-IV diagnosis for patients with significant features of eating disorders that do not meet the criteria for AN or BN.³ Despite EDNOS being

a common presentation in eating disorders services, few published data exist regarding mortality rates in patients given this diagnosis.^{4,5} Anorexia nervosa is a serious illness in the young population, and outcome is often poor. Steinhausen⁶ showed that only 46% of patients fully recovered from AN, a third improved with only partial or residual features of the disorder, and 20% remained chronically ill for the long term. A low body mass index (BMI), a greater severity of social and psychological problems, self-induced vomiting, and purgative abuse have been identified as predictors of poor outcome in this disorder.⁷

Most mortality research in the eating disorders literature has focused on AN. Some authors have suggested that the mortality risk for BN is low.⁸ This conclusion

is surprising, given the medical complications associated with self-induced vomiting, laxative abuse, and other purging behaviors. The ratio of observed to expected deaths (ie, the standardized mortality ratio [SMR]) for AN has been reported to be between 0.71⁹ and 12.8.¹⁰ Also, it often has been reported that suicide is a particularly common cause of death in AN.^{11,12} Muir and Palmer¹³ suggested that official death certification may underestimate the incidence of suicide associated with this disorder. The wide variation of SMRs for eating disorders partly may depend on the length of follow-up. For example, Nielsen¹⁴ reported an SMR of 9.6 after approximately 10 years of follow-up, as opposed to 3.7 in 4 studies with a mean follow-up period ranging from 20 to 36 years. Other factors that correlate with a higher estimate of mortality are age, case severity, study period, and whether other eating disorders with a lower mortality rate were evaluated separately.¹⁵

Given this debate, the primary aim of our study was systematically to compile and to analyze mortality rates in individuals with eating disorders, taking into account variations in sampling, diagnosis, and length of follow-up of the study. Our hypothesis was that mortality rates would be elevated in all types of eating disorders. We also aimed to explore factors associated with mortality among individuals with AN, BN, and EDNOS.

METHODS

SEARCH STRATEGY

A systematic literature search, appraisal, and meta-analysis were conducted. The MEDLINE/PubMed, PsycINFO, and Embase abstract databases were searched from 1966 through September 30, 2010. Also, 4 full-text collections, ScienceDirect, Ingenta Select, Ovid Full text, and Wiley-Blackwell Interscience, were searched, and an article published online ahead of print was included.¹⁶ A broad range of subject headings was used to identify the relevant disorders and diagnoses. For each database search, 7 main search components (*eating disorders, anorexia nervosa, bulimia nervosa, eating disorder not otherwise specified [EDNOS], mortality, death, and survival*) were created by combining subject headings with the "OR" operator, and the same components then were combined by using the "AND" operator. Studies that followed up patients for a minimum of 1 year and included 15 or more participants at the time of analysis were included. Relevance was determined by screening titles and abstracts. Reference lists of relevant articles were screened for further potentially relevant studies, and citation searches were conducted. The results are reported for the exposure groups for AN, BN, and EDNOS (eTable 1: <http://www.archgenpsychiatry.com>)

STATISTICAL ANALYSIS

Primary data were extracted as raw numbers or confidence intervals (CIs) and corrected for years of observation and sample size (ie, person-years of observation). Weighted proportion meta-analysis was used to adjust for study size using the DerSimonian-Laird model to allow for heterogeneity inclusion in the analysis. We excluded articles without adequate data such as those in which no raw number was presented (or calculable), those that examined predictors of func-

tional decline only, and those that looked at other aspects of prognosis, such as hospitalization, without information regarding mortality rate. Mantel-Haenszel pooled risk ratios were estimated, with a χ^2 test for heterogeneity (I^2) used to assess between-study differences in effect.¹⁷ Random-effects models were fitted if heterogeneity existed, and risk ratios were presented as a forest plot.¹⁸ The forest plot shows study-specific risk ratios (and their 95% CIs) and the relative weighted contribution of each study, as well as the risk ratio estimate pooled across all studies. The analyses were performed with StatsDirect statistical software, version 2.7.7 (StatsDirect Ltd, Cheshire, England)

For the analysis, we collected data regarding the number of participants, the number of participants at follow-up, mean age of the population studied at first assessment, sex, mean BMI at first assessment, whether the population studied was inpatient or outpatient, SMR, the percentage of dead case individuals, diagnosis, and predictors of death, if available. We discuss findings for AN, BN, and EDNOS separately. The outcome of interest was mortality rate.

INCLUDED AND EXCLUDED STUDIES

Two independent assessors (J.A. and J.W.) identified 143 relevant articles that were screened in detail (**Figure 1**). In some cases, the authors of those articles were contacted to gather further information.^{19,22} After doing so, we excluded 78 articles because of inadequate duration of the study (< 1-year follow-up or case series) or inadequate sample size (< 15 patients). Review articles also were excluded from the analysis. Of the 65 articles retrieved for more detailed evaluation, 29 were excluded because of lack of description of cases resulting in death, same database used in other studies, or lack of diagnosis of death in cases. When investigators conducted multiple analyses reported in separate articles, we only selected the article with a longer follow-up; 7 studies were excluded for this reason.

SUMMARY OF RELEVANT STUDIES

Thirty-six relevant empirical quantitative studies of mortality in eating disorders were published between January 1, 1966, and September 30, 2010. All but 1 study²³ provided data regarding mortality rate in patients with AN. Twelve studies provided information regarding patients with BN, and 6 studies described mortality rate in patients with a diagnosis of EDNOS. Twenty-five studies provided sufficient data for analysis of SMR in AN. Across 36 studies, 17 272 unique patients had eating disorders. Reported deaths totalled 755. Considerable differences existed among the studies regarding design, group size, and methods. Few studies were prospectively organized. Diagnostic categories changed considerably during the period of the studies. In some cases, duration of follow-up also was difficult to compute from the original studies. Besides missing data, this problem occurred due to variations in the definition of the starting point or the general practice of providing only ranges instead of precise group parameters.

A general lack of control conditions and a scarcity of precise information regarding treatment was observed in these studies. Different treatment and psychotherapeutic approaches were used. The diversity of interventions precluded any definite evaluation of treatment effects.²⁴ Most outcome studies for AN reported crude mortality rates and SMRs. The crude mortality rates may have been inflated slightly, not all studies reported the cause of death, so causes other than the eating disorder might have led to patient death.

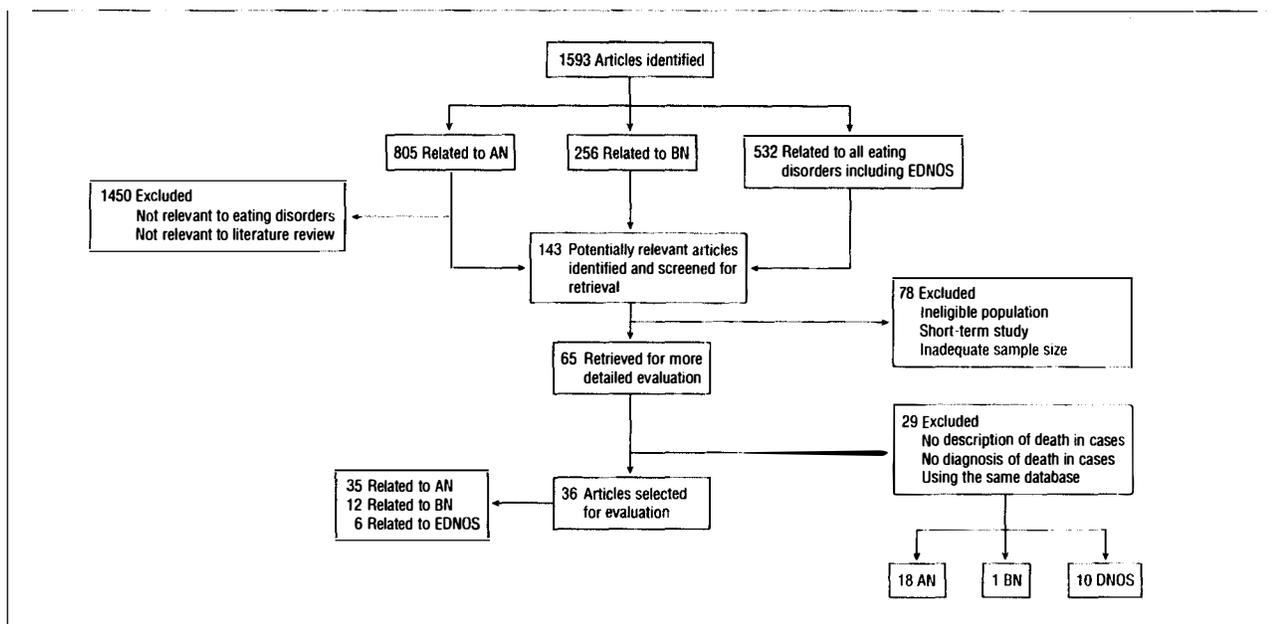


Figure 1. Literature review method used. AN indicates anorexia nervosa; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified.

RESULTS

ANOREXIA NERVOSA

Mortality Rate per Person-years

Thirty-five studies described the mortality rates of patients with AN (eTable 2). The mean (SD) follow-up period of the studies was 12.82 (7.39) years, with a maximum mean time of follow-up period of 36.2 years.²⁵ The mean (SD) sample size was 360.7 (954.1), with a maximum sample size at follow-up of 6009 cases.²⁶ The 35 studies subjected to bias assessment (eFigure 1) followed up a total of 12 808 individuals and reported 639 total deaths. The total follow-up time was 166 642 person-years. Overall, the weighted annual mortality for AN was 5.10 deaths (95% CI, 3.99-6.14) per 1000 person-years (**Figure 2**), of which 1.3 deaths resulted from suicide. We analyzed 14 studies that included only female patients with AN and found that the weighted annual mortality rate was 5.39 (95% CI, 3.57-7.59) per 1000 person-years. The weighted mortality rate was lower for studies (n=11) that selected inpatients (4.55; 95% CI, 3.09-6.28).

Standardized Mortality Ratio

Twenty-five studies involving 12 189 patients with AN examined SMRs compared with a reference population (eFigure 2). The mean follow-up period was 14.2 years. Heterogeneity was high ($I^2=91.2\%$; 95% CI, 88.9%-92.9%). The overall SMR using random-effects meta-analysis was 5.86 (95% CI, 4.17-8.26).

Predictors of Mortality

Meta-regression analysis was used to identify risk factors of death in AN. A priori (based in the literature), we

assumed that interstudy differences in age at assessment, sex, BMI, and comorbid conditions, such as alcohol intake, could be related to mortality in AN. Not enough studies reported comorbid conditions, and no studies observed male patients. Therefore, meta-regression analysis only could be conducted for age and BMI. This analysis showed significant positive correlation with age ($r=0.1$, $P=.01$) and nonsignificant correlation with BMI on assessment ($r=0.9$, $P=.11$). Results of the literature review regarding mortality in AN are presented in eTable 2.

BULIMIA NERVOSA

Mortality Rate per Person-years

Since the first study was reported in 1988, 12 studies described the mortality rates of patients with this diagnosis (eFigure 3 and eTable 3). Twelve studies followed up 2585 individuals with BN and reported 57 deaths. The mean (SD) sample size was 200.7 (252.6), and the mean (SD) follow-up period was 9.34 (3.8) years. The total person-years of follow-up was 32 798 years. The mean follow-up period was 9.74 years. The mortality rate for BN was lower than that reported for AN, with a relative risk of mortality of 2.11 (95% CI, 1.40-3.20). The weighted mortality rate was 1.74 (95% CI, 1.09-2.44) per 1000 person-years. We examined separately 5 studies that reported on a female population only. The analysis found a weighted mortality rate of 2.22 (95% CI, 0.73-4.72) per 1000 person-years of follow-up. No male-only studies were found.

Standardized Mortality Ratio

All 12 studies reported SMRs (although 3 studies reported no deaths) (**Figure 3**). Heterogeneity was low

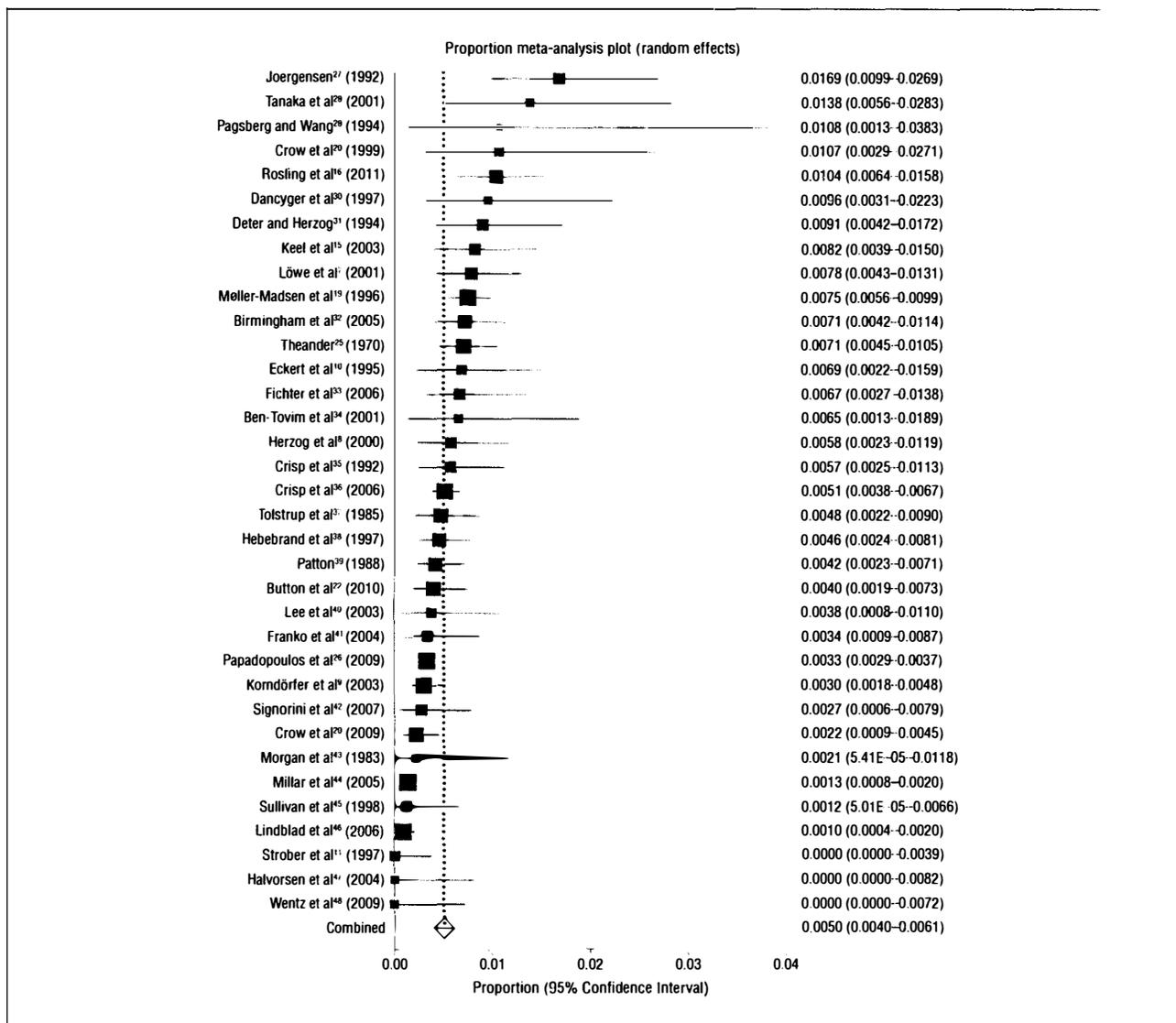


Figure 2. Annual mortality rate per 1000 person-years in anorexia nervosa. Studies include male and female patients.

($I^2=0\%$), and the overall SMR using random-effects meta-analysis was 1.93 (95% CI, 1.44-2.59), a significant difference from 1.00 ($P=.002$)

EDNOS Mortality Rate

Mortality Rate per Person-years

Only 6 studies described the mortality rate of patients with EDNOS (**Figure 4**). The difficulties defining EDNOS makes it more complicated to study this group. Despite the relatively small number of studies, the examination of this group is important to the inclusivity of the study, given that these patients represent such a large proportion of patients observed in practice. The mean (SD) sample size was 313 (391.7) patients, and the mean follow-up period of the studies was 9.1 (7.7) years. A total of 1879 individuals were followed up, and the reported total number of deaths was 59. The total person-years of follow-up was 22 644. Overall, the weighted annual mor-

tality rate for EDNOS was 3.31 deaths (95% CI, 1.48-5.75) per 1000 person-years.

Standardized Mortality Ratio

Only 4 studies involving 1812 individuals with EDNOS reported SMRs with CIs (eTable 4). The mean follow-up period was 10.9 years. Heterogeneity was low ($I^2=0\%$), and the overall SMR using random-effects meta-analysis was 1.92 (95% CI, 1.46-2.52), a significant difference from 1 ($P<.001$)

Because of the small number of studies, multiregression analysis was not used to explore prognostic factors for mortality rate in patients with BN and EDNOS. No difference in observed mortality (per 1000 person-years of follow-up) between BN and EDNOS was found, but AN had a 2.7-fold higher mortality rate than BN. Time series analysis showed no statistically significant effect for AN and BN but a negative correlation for EDNOS (adjusted $R^2=0.66$, $P=.01$), suggesting a smaller effect in more recent studies

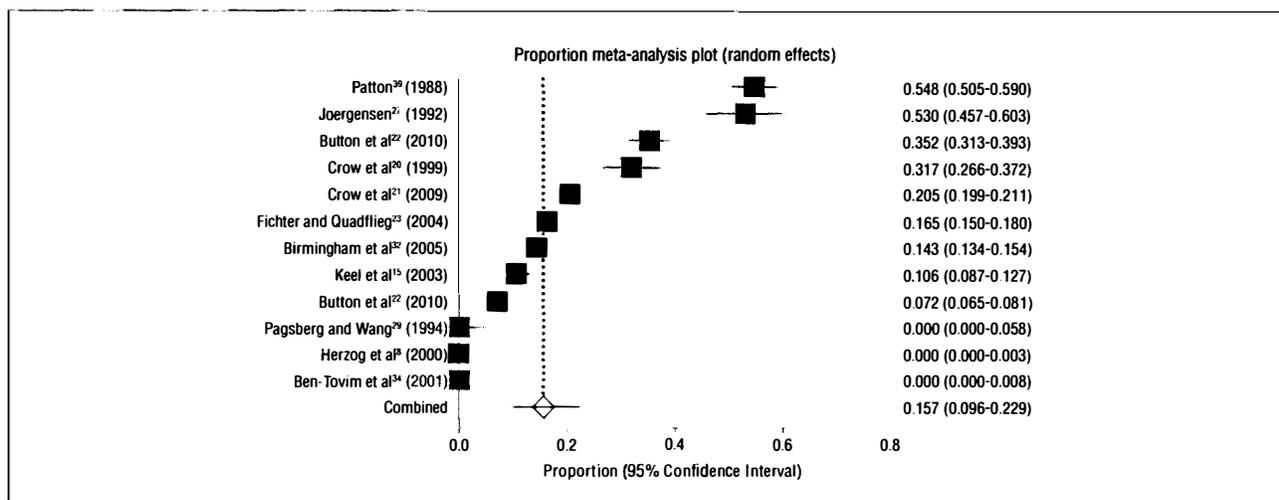


Figure 3. Standardized mortality ratios (95% confidence intervals) in patients with bulimia nervosa.

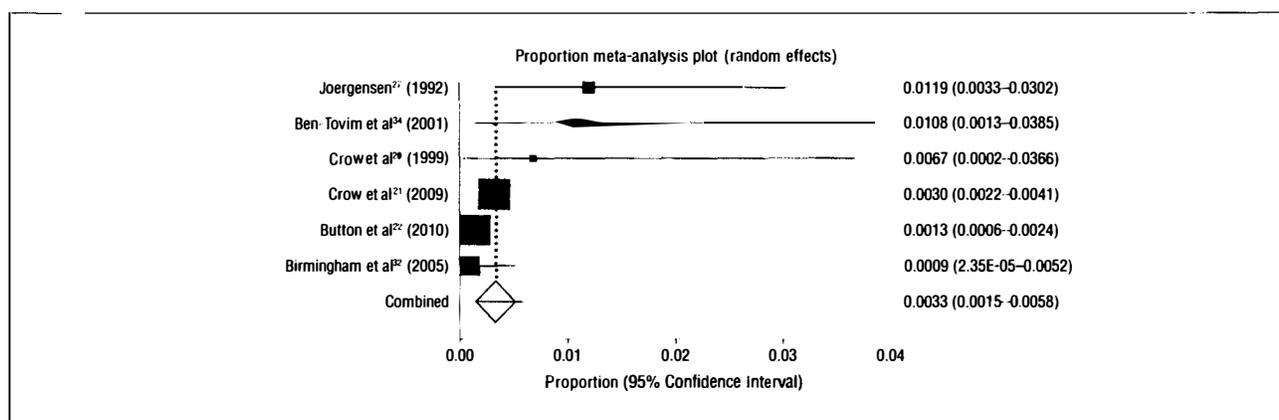


Figure 4. Mortality rates per person-years in patients with eating disorder not otherwise specified.

COMMENT

The aim of this study was to measure mortality rate in patients with eating disorders using meta-analysis. The existing literature regarding mortality rate from eating disorders has several limitations. First, length of follow-up has varied considerably. A second and probably more important limitation is low ascertainment rates. For example, in the BN studies reviewed by Keel and Mitchell,⁴⁹ some had ascertainment rates as low as 50%. Other limitations include the relatively small numbers of study patients with BN or EDNOS, the classification used in the study, and the population studied. A further limitation is that many studies have focused on indirect SMRs. Two major approaches to standardization, direct and indirect, have been used. Direct standardization is used when the study population is large enough that age-specific rates within the population are stable. When the population is small (or the outcome is rare), the number of events observed can be small. In that circumstance, indirect standardization methods can be used to produce an SMR. The indirect SMR presents a comparison with the general population, but it is unclear whether this population is comparable with that of individuals with eating disorders.

Indeed, it is equally useful to present the actual death rate per person-year.

The issue of diagnostic crossover also is important. A range of rates have been reported in the literature. For individuals with AN, it has been suggested that 20% to 50% will develop BN over time.^{10,11,50} A study by Eddy et al⁵¹ showed that one-third of patients with an intake diagnosis of AN crossed over to BN during 7 years of follow-up. This finding did not prevent patients from crossing back (ie, relapsing) into AN. Movement from an initial diagnosis of BN to AN is less common. A review by Keel and Mitchell⁴⁹ put this figure at less than 10%; Eddy et al⁵¹ found this rate to be 14.06% during a 7-year follow-up period. This finding is important when examining SMRs for the eating disorder groups because patients who had been diagnosed as having AN on assessment may have had BN by the time they died. Diagnostic crossover may have occurred; therefore, we cannot imply stability of diagnosis.

As hypothesized, we found an overall elevated mortality rate for patients with all types of eating disorders. This risk of death was highest for those with AN, with a weighted annual mortality rate of 5 per 1000 person-years (slightly higher in studies of females only), fol-

lowed by patients with EDNOS at 3 per 1000 person-years of follow-up and BN at 1.7 per 1000 person-years of follow-up. The mortality rate, particularly for AN, was considerably lower for those studies that had a long follow-up period, such as that by Korndörfer et al,⁹ which showed an SMR for AN of 0.71 and had 27.1 years of follow-up, or the study by Crow et al.²¹ with an SMR of 1.7 and a follow-up of 18.13 years. Studies^{15,19,40} with fewer years of follow-up generally showed a high SMR. Given the crossover observed between diagnoses, the actual duration of follow-up may be less important than the duration of illness.

The causes of patient deaths were not always available, and it is likely that many of the people who died may not have had AN or an eating disorder at the time of death. However, the rates of suicide were examined separately because this was mentioned in a number of studies. Twelve studies described deaths from suicide in patients with AN, and analysis showed that the weighted annual mortality due to suicide in AN was 1.39, which means that 1 in 5 individuals with AN who died had committed suicide.

The SMR values for BN and EDNOS are lower than for AN (ie, 5.86), giving individuals with EDNOS and BN SMRs of 1.92 and 1.93, respectively. It can be argued that reviews of SMR in BN can be highly selective because they only may include those studies that have found deaths at follow-up. In the present meta-analysis, we included all follow-up studies of patients with BN. Three of the studies did not find any case individuals who died, and 4 studies gave an SMR higher than 2. The low SMR suggests that a diagnosis of BN per se does not render an individual at increased risk of premature death, but this finding does not necessarily justify complacency, given that comorbid affective disorder and related behaviors may often accompany bulimic symptoms.

Little has been reported regarding the morbidity or mortality associated with EDNOS because this was not an accepted diagnosis until the *DSM-IV* criteria were published, although atypical eating disorders were noted before then. Our results for EDNOS suggest a possibly higher mortality risk than in BN. The SMR (ie, 1.92) reported in this meta-analysis is higher than that reported in the study by Birmingham et al,³² which found that SMR for patients with EDNOS was only 1.1. Eating disorder not otherwise specified is a mixture of atypical AN and atypical BN in *International Statistical Classification of Diseases, 10th Revision (ICD-10)*³² terms; therefore, those findings can be difficult to interpret. The question also exists of whether patients with EDNOS had previously been or were likely to become patients with AN. Based on the study by Eddy et al,⁵¹ this would appear to be so. The authors' depiction of the longitudinal course and crossover diagnoses for patients with an intake diagnosis of AN highlighted that some patients could be classified as having partial recovery. These figures ranged from 75% to 85% during the 7-year follow-up period, depending on subtype. Agras et al⁵³ examined the course of EDNOS and found that only 18% of this group had never had or did not develop another diagnosed ED during the 4-year study. Thus, any elevated mortality risk of EDNOS partly

could be explained by the assertion that EDNOS sometimes reflected the earlier stages of AN. Further studies are required before firm conclusions can be drawn.

Our study found that the mortality rates in patients with eating disorders are high. In some cases (ie, those involving AN), they are much higher than for other psychiatric disorders. Studies in other psychiatric disorders have found SMRs of 2.8 and 2.5 in males and females with schizophrenia,⁵⁴ 1.9 and 2.1 in males and females with bipolar disorder, and 1.5 and 1.6 in males and females with unipolar disorder, respectively.⁵⁵

PREDICTION OF DEATH

Our secondary objective was to examine the factors associated with mortality rate among the different diagnoses. Information regarding factors that predict outcomes was drawn from only a handful of studies and occasionally was conflicting. We anticipated that we would analyze predictors of death in the varying diagnoses. However, because an insufficient number of studies identified risk factors by meta-regression analysis for the EDNOS and BN groups, this was examined for the AN studies only. Few studies specifically examined predictors of mortality; instead, many examined predictors of poorer outcome. Based on the information from different studies, factors highlighted for poorer outcome, including mortality, in patients with AN included older age at first presentation,^{31,36,40} alcohol misuse,^{22,34,55} and low BMI at presentation.^{25,34,46} Other strong predictors of mortality involved comorbid disorders, such as affective disorder, suicidal behavior or self-harm, alcohol abuse, and a history of hospitalization for such mental health problems. Button et al²² found that only BMI at assessment and alcohol misuse reliably predicted mortality status, although evidence of an affective disorder almost was significant. Some studies^{24,46} also have found evidence of an association between alcohol misuse and increased mortality in AN. One of them²⁶ found that younger age and longer hospital stay at first hospitalization were associated with better outcome, and psychiatric and somatic comorbidity worsened the outcome of patients with eating disorders.

Unfortunately, because of the small number of studies that recorded different prognostic factors (such as somatic comorbidity, alcohol and drug abuse, and psychiatric comorbidity), meta-regression analysis for these factors was not possible. However, the studies selected in this meta-analysis allow examination of the influence of weight and age at presentation on the SMR. One study included in the meta-analysis²² found that when SMR is used as an index of mortality, an inverse trend seems to occur, namely, higher SMR with lower weight at presentation. In view of this, some studies have suggested low BMI on assessment as a predictor of death. However, meta-regression analysis of the studies did not show a significant correlation between mortality and BMI on assessment. Because age at presentation is known, this point frequently is used as a proxy variable for age at illness onset. Age at onset is difficult to determine with any precision in most cases. Most of the studies included in this meta-analysis indicated effect of age at presentation, which

for most studies was a highly significant effect. Most studies report too few deaths in the younger age groups and too many deaths in those presenting for treatment at age 20 years or older. A clear pattern can be observed across ages: an SMR of approximately 3 in the youngest, approximately 10 in those aged 15 to 19 years, close to 18 in those aged 20 to 29 years, and approximately 6 in those who present for treatment at age 30 years or older.^{19,47,55,56}

LIMITATIONS AND FUTURE STUDIES

This analysis has a number of limitations. Notably, we relied on the quality and nonrepetition of primary publications. We sought to ensure data integrity by excluding small studies with less than 1 year of follow-up and fewer than 15 patients. The possibility exists of counting some individuals twice, especially when several related publications are derived from 1 group. We attempted to deal with duplicate data from the same authors by excluding studies in which the population characteristics were nearly identical to those already entered. The study is limited by the number of available published data for these diagnoses, and although these were reasonably robust for AN, fewer were available for the other diagnoses. Through the years, investigators used many diagnostic and outcome assessment measures; these measures reflected numerous definitions (ie, diagnoses) of illness. The lack of consistency of measures makes comparisons across studies difficult. Consolidation of measures, standardized definitions, and reporting guidelines are critical to the further advancement of the field. In addition, although we have used the values published in the relevant studies, it is possible that not all deaths reported were due to the eating disorder itself because comorbid physical conditions were not reported. Despite the number of studies examined, it is impossible to conclude whether patient death is a direct result of eating disorders. Future studies only will be able to investigate cause and predictive factors of death in patients with eating disorders by developing large national or international databases containing information that should include psychiatric and physical comorbidity, drug and alcohol abuse, and personality factors, as well as the psychopathologic features of eating disorders. The study showed that mortality rates in individuals with eating disorders are high not only for those with AN but also for those with EDNOS and BN, which highlights the seriousness of these conditions. Future, robust studies should inform physicians of the predictive factors associated with mortality rate in patients with EDNOS and BN; so far, late presentation of AN appears to be the only clear predictor of death among these disorders.^{55,56}

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