ORIGINAL ARTICLE

Mortality and care of eating disorders

Giovanni Castellini[1,2] | Saverio Caini[3] | Emanuele Cassioli[1] |
Eleonora Rossi[1] | Giorgia Marchesoni[1] | Francesco Rotella[2] |
Nora De Bonfioli Cavalcabo'[3] | Miriam Fontana[4] | Barbara Mezzani[5] |
Brunetto Alterini[6] | Stefano Lucarelli[7] | Valdo Ricca[1,2]

[1]Psychiatry Unit, Department of Health Sciences, University of Florence, Florence, Italy

[2]Psychiatry Unit, Careggi University Hospital, Florence, Italy

[3]Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy

[4]Clinical Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy

[5]Casa di cura "Villa dei Pini", Florence, Italy

[6]Division of Cardiovascular and Perioperative Medicine, Careggi University Hospital, Florence, Italy

[7]UFS Eating Disorders ASL Toscana Centro, Florence, Italy

Correspondence
Giovanni Castellini, Psychiatry Unit, Department of Health Sciences, University of Florence, Florence, Italy.
Email: giovanni.castellini@unifi.it

Abstract

Introduction: Eating disorders (EDs) are considered serious mental illnesses, with one of the highest lethality among psychiatric disorders, even though the issue of mortality due to these conditions is still controversial. The present study was aimed at comparing the mortality rate in a cohort of ED patients representative of the geographic area with that of the age and gender-matched general population of central Italy.

Methods: Patients were enrolled between 1994 and 2018, among those attending the eating disorders treatment network of the Florence area (EDTN), which is a regional multidisciplinary treatment reference center for EDs covering the clinical population of the metropolitan Florence area (Italy). The life status of participants was determined through linkage with the Regional Mortality Registry.

Results: A total of 1277 individuals with EDs were included, including 368 with Anorexia Nervosa (AN), 312 with Bulimia Nervosa (BN), and 597 individuals with Binge Eating Disorder (BED). Twenty-two patients (1.72%) died, during a median follow-up of 7.4 years. The mortality rates among ED patients did not significantly differ from that of the general population of the same age and sex with a Standardized Mortality Ratio (SMR) of 1.19, 95% CI 0.79–1.81. Only among BN patients, the mortality was significantly increased after 10 years from clinical evaluation (SMR 11.24, 95% CI 3.62–34.84).

Conclusion: The low mortality in EDs, compared to published studies, might be due to the EDTN treatment strategy, based on a large network which makes an integrated multidisciplinary team available for almost all the patients with EDs of the geographical area.

KEYWORDS
anorexia nervosa, binge eating disorder, bulimia nervosa, eating disorders, standardized mortality ratio

1 | INTRODUCTION

Eating disorders (EDs) are considered serious mental illnesses[1] representing an emergency in terms of public health due to the high rate of chronicity, hospitalization, and medical comorbidity. Prevalence in western countries is increasing[2] (especially among young persons),[3] even though the lack of recent reliable epidemiological data in Italy makes it difficult to estimate the real impact of these disorders in this country.[4] It has been estimated that over 3.3 million healthy life years worldwide are lost due to EDs.[5] Compared to other psychiatric conditions, there is an increase in the years lived with disability (YLDs).[5] People with EDs have a worse quality of life, and yearly healthcare costs are 48% higher than in the general population.[5]

Even though EDs are often considered to be among the most serious and potentially lethal mental disorders,[6] the issue of mortality due to these disorders is still controversial. Severe weight loss or malnutrition, electrolyte imbalance, substance abuse, and weight fluctuation can cause widespread damage to organs that may persist over time and be responsible, together with suicide, for premature death, unless the disorders are adequately and continuously managed.[5] Different authors often reported that the mortality rate of EDs—especially when considering Anorexia Nervosa (AN)—is one of the highest among all mental disorders, even though there is extreme heterogeneity in the available information on this topic. Indeed, only a minority of the studies in this field reported standardized mortality ratio (SMR), while most of them calculated death incidence rate (e.g., References [7–9]) or crude mortality rate (CMR), which is the number of deaths within the study population over a specified period.[5] SMR is the ratio of observed deaths in the study population versus that of expected deaths in the population of origin (having the same demographic characteristics e.g. distribution by age and sex), and it is generally preferred for comparison reasons because the CMR is not standardized for age and sex.[3] Nevertheless, SMR varied significantly between studies depending on different countries and study design. SMR has been reported to vary in AN from 2.89[10] to 5.91[11] or even 15.9 in hospitalized populations.[12] As compared to AN, SMR was found to be lower in Bulimia Nervosa (BN) and Binge Eating Disorder (BED), with values ranging from 1.49[6] to 2.71[13] and from 1.50[6] to 3.28,[13] respectively.

Such variability across studies might be accounted for by the adopted methods (e.g. ascertainment rates, sample size, severity of illness, and duration of follow-up), as well as the heterogeneity of treatment protocols. However, it can also be due to the different organization of mental health services across countries. Previous

Significant outcomes

- Twenty-two patients (1.72%) died, during a median follow-up of 7.4 years.
- The mortality rates among ED patients did not significantly differ from that of the general population of the same age and sex with a Standardized Mortality Ratio (SMR) of 1.19, 95% CI 0.79–1.81.
- Only among BN patients, the mortality was significantly increased after 10 years from clinical evaluation (SMR 11.24, 95% CI 3.62–34.84).

Limitations

- The present study did not include patients relying on private care services, therefore the calculated SMRs may not be applicable to this subgroup.
- The SMRs were calculated considering gender, age group, and calendar time; future studies should consider additional factors, such as clinical characteristics, type and duration of treatment.

observations adopted a various range of follow up periods ranging from one[14] up to ten[15] and even 30[16] years. Furthermore, most of these studies included clinical populations, without specifying whether they were representative of the geographical area or, alternatively, represented just a selected sample of a specialized center.

Finally, the heterogeneity of treatment interventions should be taken into consideration. In general, recent findings showed that patients with AN and BN who received inpatient treatment had the highest mortality rates.[3] There is a general agreement that patients with EDs are best treated in specialized care centers, in consideration of the great difficulties and specific challenges that they pose in terms of care and treatment.[17,18] Given the high rates of psychiatric and medical comorbidity, specialized ED care should be delivered through multidisciplinary teams,[19] even though this requisite is rarely fulfilled by standard psychiatric services.[20] Thus, the lack of integration between specialized centers applying the standards of care for EDs and the general psychiatric services where most of the patients with EDs usually seek help is one of the main issues for continuity of care in this field.

From this perspective, the Eating Disorders Treatment Network of the Florence area (EDTN) can be

considered a unique health organization model in the Italian context, due to the great coordination effort between the different nodes of the ED healthcare network. The EDTN is a regional treatment reference center specialized in EDs, including the Local Health Unit "Tuscany Centre" and the Eating Disorders Unit of the Florence University Hospital "Careggi" (the largest hospital in the region). The network for multidisciplinary assessment and treatment of all the subjects suspected to have diagnoses of EDs attending the public services involves various health care professionals (psychiatrists, internal medicine specialists, psychotherapists, and dieticians), providing evidence-based specific treatment, available throughout different levels of care (i.e., outpatient, inpatient medical treatment, residential rehabilitation treatment, and day hospital care). The EDTN is based upon different outpatient and inpatient local services, including a clinical nutrition unit specialized in the management of extremely severe undernutrition and its somatic complications. Intensive medical care is provided to stabilize the patients prior to their being transferred to a tertiary ED program, better described in the method section. This organization also represents a uniqueness in the European context, allowing an integration of the enhanced cognitive behavior (CBT-E) approach for the treatment of EDs with the Italian mental healthcare organization. Indeed, Italy is one of the countries in which the reform of the health system toward community-oriented services has been established in the whole country at once following the psychiatric reform law in 1978.[21] The so-called deinstitutionalization procedure, decreed by the law, implied a sudden shift from hospital-based models of care to community-oriented mental health services, strongly influencing pathways to mental health care.[22,23]

Considering EDs treatment, it can be hypothesized that the abovementioned pathway to care may have exerted significant effects on preventing worse outcomes, with particular attention to mortality. Thus, the main aim of the present study was to compare the mortality rate in a cohort of ED patients, which is representative of the clinical population of the Florence area, with that of the age and gender-matched general population using SMRs. Factors associated with increased mortality during the follow up were also evaluated.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients were recruited from the two main public centers for the treatment of adult patients with EDs in Tuscany,

namely the ED Service of the Local Health Unit "Tuscany Centre", which takes care of the health needs of 1.5 million people (approximately 40% of the regional population), and the Eating Disorders Unit of the Florence University Hospital "Careggi", where patients are referred from all over the Region. Adult patients who performed the first clinical evaluation from the 1st of October 1994 to the 1st of December 2018 were enrolled in this study. All participants provided consent to use their data for research purposes at the time of their first contact with the ED services. The use of these data to conduct the present investigation was approved by the local ethics committee, and it did not require any further contact with the patients, since their life status was determined by linkage with the mortality registry of Tuscany. This approach is part of a routine activity in Italy for retrospective studies using existing data, and abide by all applicable laws and regulations. Of all the patients who were initially evaluated, 40 did not agree to start treatment, and 118 did not provide consent to participate in the study (or withdrew it at a later time).

During the recruitment period, the EDTN took care of numerous patients with EDs regardless of what the diagnosis was according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria of the time. However, for the present study, only patients who retrospectively met the criteria for AN, BN or BED according to the DSM-5 (Fifth Edition) were included in the analyses.

Therefore, the inclusion criteria were as follows: age >18 years; current diagnosis of AN, BN or BED according to the DSM-5,[24] as assessed by a clinical interview. Exclusion criteria were as follows: intellectual disability, illiteracy, current diagnosis of bipolar or psychotic disorder according to the DSM-5[24]; residence outside Tuscany; absence of written informed consent.

2.2 | Treatment

Treatment of EDs in the metropolitan Florence area is based on a third level network including services provided by the University Hospital and the Local Health Unit "Tuscany Centre".

All the included patients received a multidisciplinary treatment tailored to the clinical needs of the individual, in line with the Guidelines of the National Institute for Health and Care Excellence for the management of EDs.[25] In particular, as stated by the principles of precision psychiatry,[26] the EDTN protocol is based on a stepwise approach. The interventions are individualized based on specific psychopathological dimensions (e.g., presence or not of depressive symptoms, post-traumatic

psychopathology and/or severe emotion dysregulation), as well as different degrees of severity of medical conditions (e.g., extreme underweight, electrolyte imbalance) and psychopathological comorbidity (e.g., suicidal ideation or self-injurious behaviors). Patients were first admitted to a clinical visit, where the protocol included a standardized medical, psychopathological, and nutritional assessment performed by an expert psychiatrist of the network and a dietitian. The first assessment included an accurate reconstruction of the anamnesis, a structured clinical interview for DSM diagnoses,[27,28] evaluations of the nutritional status through the determination of anthropometric measures, the estimation of food intake and the collection of biochemical parameters, and the administration of psychometric questionnaires for the evaluation of general and ED-specific psychopathology. Based on the severity of the clinical presentation of the disorder, patients were treated in the context of outpatient visits, Day Hospital, or hospitalization in internal medicine ward. Hospital admission was provided in case of severe malnutrition and/or medical complications. When BMI was below $13 \, kg/m^2$, an initial and cautious refeeding treatment was provided in a medical unit, to stabilize the patient's medical condition before being transferred to a cognitive-behavioral and nutritional treatment. Patients who needed psycho-nutritional rehabilitation in a residential context were hospitalized in the "Villa dei Pini" nursing home. In all treatment settings, patients were provided with regular psychiatric and dietetic evaluations and, when necessary, specialistic medical assessments (e.g., endocrinological or cardiological). Regular monitoring of physical health was performed through the collection of blood samples for the evaluation of routine parameters as well as of the hormonal profile, when necessary. Furthermore, according to the clinical requirements, instrumental examinations were performed, including electrocardiogram, echocardiography, abdominal ultrasound, and bone densitometry. All patients were provided with Cognitive Behavior Therapy (CBT)[29,30] by trained psychiatrists. Pharmacotherapy was provided in case of comorbid psychiatric symptoms. Furthermore, patients with higher levels of impulsivity and emotion dysregulation attended group sessions of Dialectical Behavior Therapy Skills Training,[31] whereas Eye Movement Desensitization and Reprocessing (EMDR) was offered in case of a history of childhood trauma.[32] Finally, psychoeducational groups based on the Maudsley approach[33] were provided for the parents of patients who still lived with their family of origin. The EDTN is illustrated in Figure 1. One of the main strengths of the EDTN is that it provides a long-term continuity in the clinical management of patients across time. Indeed, after discontinuation of the intensive phase of treatment, patients are regularly monitored in their clinical status. This is allowed by a stable bilateral communication (structured regular meetings, telephone, or online contacts) between the University Hospital, the Local Health Unit and localized services and general practitioners (GPs). The coordination with local services and GPs makes it possible to verify the clinical status of patients by means of regular visits, even domiciliary when necessary, thus early intercepting critical conditions and re-exacerbations, even if patients are not compliant with the proposed treatments. Finally, according with the Italian legislation, life-threatening conditions in the absence of illness insight allow clinicians to perform compulsory interventions for short periods of time, which in some cases of severe EDs are important to avoid death.

2.3 | Statistical analysis

The life status of all ED patients was determined through linkage with the Regional Mortality Registry (RMR) of Tuscany, and the cause of death of deceased patients was coded based on the death certificate according to the International Classification of Diseases, 10th edition (ICD-X). Residents outside Tuscany were removed from the database used for the current analysis because their life status could not be determined with certainty. The analysis was conducted by applying the indirect standardization method, using as reference mortality rates those produced by the RMR of Tuscany.

In detail, person-years were computed from the date of the first encounter of the patient with the ED services until the date of death or end of follow-up (December 31st, 2018), whichever came first. The follow-up end date was determined by the fact that, at the time of conducting the analyses, 2018 was the last year for which RMR data was complete. Therefore, subjects visited for the first time in 2019 or in subsequent years were excluded from the current analysis. Gender, age group (5-year interval), and calendar time (1-year interval)-stratified mortality rates were multiplied by the number of person-years accrued during follow-up to obtain the number of expected deaths in the cohort. Thus, the number of expected deaths were obtained based on the mortality rates of the population from which the cohort of ED patients originate (i.e., the population of Tuscany), and not from an external cohort assembled ad hoc or by any other method. Then, SMRs were calculated as the ratio between observed (O) and expected (E) deaths, and their 95% confidence intervals (CI) were obtained by assuming that deaths occurred during follow-up according to a Poisson distribution. In terms of interpretation, a SMR equal to 1.00 (null value) indicates that upon adjusting
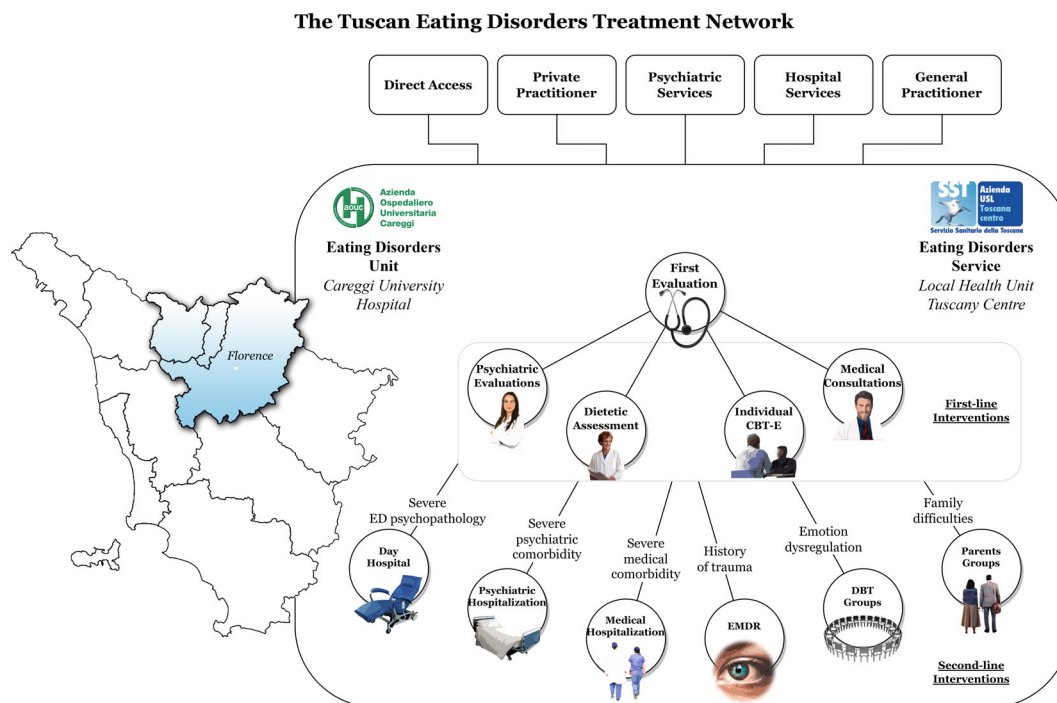
FIGURE 1   Illustration of the Tuscan eating disorders treatment network services

for temporal trends in mortality rates and patients' demographics (sex and age), the mortality among ED patients is the same as that in the reference population (i.e., the general population of Tuscany), while an SMR significantly above (below) 1.00 implies that the mortality among ED patients is higher (lower) than in the reference population. SMRs were calculated for the entire cohort of ED patients and separately among those suffering from AN, BN, or BED. In addition, separate SMRs were calculated for death from all causes, death from diseases of the circulatory system (ICD-X codes I00-I99), and death from neoplasms (ICD-X codes C00-D48). Analyses were conducted using STATA software version 16. All statistical tests were two-sided and were considered as significant when *p* values were below 0.05.

3 | RESULTS

A total of 1277 individuals with EDs were included in the present study, including 368 AN patients (28.8%), 312 BN patients (24.4%), and 597 individuals with BED (46.8%). Considering AN patients, 203 were of the restricting subtype (55.2%), whereas 165 were binge-eating/purging (44.8%). Females accounted for 92.4% of all included patients, and the median age at clinical evaluation was 31.1 years (inter-quartile range [IQR] 21.7–44.9), but demographics varied across ED types: AN and BN patients

were mostly females (97.6% and 97.8%, respectively) and were most frequently seen in their third decade of life (the median age was 22.5 years, IQR 18.7–29.5, for the former, and 26.8 years, IQR 20.8–37.2, for the latter). Instead, males accounted for a larger proportion of BED patients (13.6%), whose median age at clinical evaluation was 43.0 years (IQR 31.3–52.4). The median age of onset was 17.0 years (IQR 15.0–19.0) for AN, 17.0 years (IQR 14.0–19.0) for BN, and 17.5 years (IQR 14.0–29.75) for BED. A total of 483 patients (37.8%) attended Day Hospital services in the initial treatment period, whereas 56 AN patients, 8 BN patients and 3 with BED required hospitalization. The median duration of treatment was 1.8 years (IQR 1.0–3.1), with a median time to recovery of 1.6 years (IQR 1.0–2.8). On average, patients with AN received 42 CBT sessions, whereas BN and BED patients 28.

Twenty-two ED patients (equal to 1.72% of all those included in the analyses) died during follow-up, of whom three AN patients (0.82%), three BN patients (0.96%), and 16 BED patients (2.68%), during a median follow-up of 7.4 years (IQR 2.9–12.0, range <0.1 to 24.2 years) (Table 1). Deaths occurred at the age of 35.3, 56.8, and 64.3 years among AN patients, and at the age of 48.9, 71.5, and 82.2 years among BN patients. For BED patients, the deaths occurred at a median age of 64.3 years (range 40.4–75.5 years). In terms of time elapsed between first clinical evaluation and death, this ranged between 0.4 and 11.6 years for AN patients,

TABLE 1 Cause of deaths of the 22 individuals with eating disorders included in the analyses who died during follow-up

Eating disorder type	Sex	Age at death	Years between clinical evaluation and death	Cause of death (ICD-10 classification)		
				Code(s)	Chapter	Detail
AN	Female	35.3	11.6	T50 + X44	XIX—Injury, poisoning and certain other consequences of external causes	Poisoning by diuretics and other and unspecified drugs, medicaments and biological substances, accidental
	Female	56.8	0.4	C34	II—Neoplasms	Malignant neoplasm of bronchus or lung
	Female	64.3	6.2	E83	IV—Endocrine, nutritional and metabolic diseases	Disorders of mineral metabolism
BN	Female	48.9	10.6	C71	II—Neoplasms	Malignant neoplasm of brain
	Female	71.5	11.8	I26	IX—Diseases of the circulatory system	Pulmonary embolism
	Female	82.2	10.8	C64	II—Neoplasms	Malignant neoplasm of kidney
BED	Female	40.4	0.4	S02 + S14	XIX—Injury, poisoning and certain other consequences of external causes	Fracture of skull and facial bones + Injury of nerves and spinal cord at neck level
	Female	47.1	4.2	C92	II—Neoplasms	Myeloid leukemia
	Female	50.6	7.1	E66	IV—Endocrine, nutritional and metabolic diseases	Obesity
	Female	54.0	8.7	C25	II—Neoplasms	Malignant neoplasm of pancreas
	Female	54.8	1.5	C55	II—Neoplasms	Malignant neoplasm of uterus (part unspecified)
	Female	59.6	11.9	I24	IX—Diseases of the circulatory system	Other acute ischemic heart diseases
	Male	63.9	11.7	I11	IX—Diseases of the circulatory system	Hypertensive heart disease
	Female	64.0	6.4	C19	II—Neoplasms	Malignant neoplasm of rectosigmoid junction
	Female	64.6	9.6	I61	IX—Diseases of the circulatory system	Intracerebral hemorrhage
	Female	66.0	2.8	J42	X—Disease of the respiratory system	Chronic bronchitis, unspecified
	Male	66.3	9.7	I25	IX—Diseases of the circulatory system	Chronic ischemic heart disease
	Female	67.2	7.8	C55	II—Neoplasms	Malignant neoplasm of uterus (part unspecified)
	Female	69.7	8.5	I25	IX—Diseases of the circulatory system	Chronic ischemic heart disease
	Male	69.9	10.5	C18	II—Neoplasms	Malignant neoplasm of colon
	Female	74.7	9.8	C67	II—Neoplasms	Malignant neoplasm of bladder
	Female	75.5	1.5	C25	II—Neoplasms	Malignant neoplasm of pancreas

between 10.6 and 11.8 years for BN patients, and between 0.4 and 11.9 years (median 8.1) for BED patients. Survival curves are reported in Figure 2. The most frequent causes of deaths were neoplasms ($n = 11$, 50% of all observed deaths) and diseases of the circulatory systems ($n = 6$, 27.3%) (Table 1). Two patients died from endocrine, nutritional and metabolic diseases; two from injury or accidental poisoning (of note, none committed suicide), and one from a disease of the respiratory system.
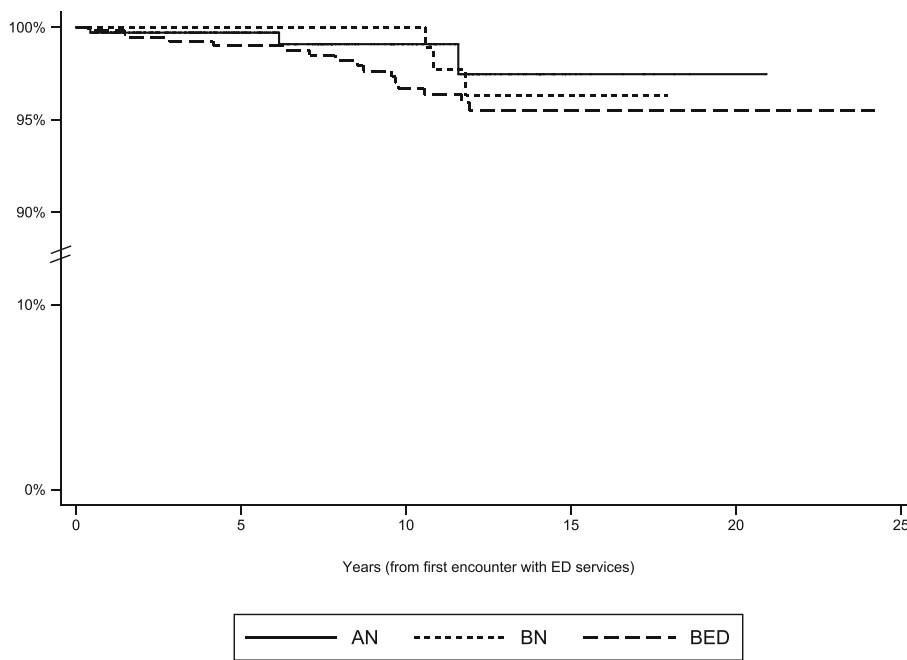
FIGURE 2   Survival curves grouped by diagnosis

TABLE 2   Observed (O) and expected (E) deaths (from any cause, diseases of the circulatory system, and neoplasms), standardized mortality ratio (SMR) and 95% confidence intervals (CI), among eating disorder (ED) patients, overall and by ED type

ED patients	No.	All causes				Diseases of the circulatory system (ICD-X I00-I99)				Neoplasms (ICD-X C00-D48)			
		O	E	SMR	95% CI	O	E	SMR	95% CI	O	E	SMR	95% CI
All	1277	22	18.43	1.19	(0.79–1.81)	6	3.53	1.70	(0.76–3.78)	11	9.66	1.14	(0.63–2.06)
Anorexia nervosa (AN)	368	3	1.20	2.49	(0.80–7.74)	0	0.18	-	-	1	0.59	1.71	(0.24–12.13)
Bulimia nervosa (BN)	312	3	1.45	2.07	(0.67–6.42)	1	0.24	4.09	(0.58–29.04)	2	0.72	2.78	(0.70–11.11)
Binge eating disorder (BED)	597	16	15.78	1.01	(0.62–1.66)	5	3.10	1.61	(0.67–3.87)	8	8.36	0.96	(0.48–1.91)

The all-cause mortality rates among ED patients did not significantly differ from that of the general population of the same age and sex (Table 2): the SMR was 1.19 (95% CI 0.79–1.81), originating from 22 observed versus 18.43 expected deaths. Upon stratifying by ED type, there were suggestive increases in all-cause mortality among both AN and BN patients, which failed, however, to achieve statistical significance, possibly because of the limited numbers of observed deaths (n = 3 for each of the two ED types). Namely, the SMR was 2.49 among AN patient (95% CI 0.80–7.74), and 2.07 among BN patients (95% CI 0.67–6.42). Instead, no evidence of an increase in mortality rates emerged among BED patients: the SMR was 1.01 (95% CI 0.62–1.66; 16 observed vs. 15.78 expected deaths). The risk of dying from diseases of the circulatory system was increased by 70% compared to the general population, although not significantly (95% CI 0.76–3.78), while the number of deaths by neoplasms did not substantially differ from what was expected based on cause-specific reference rates (11 observed deaths vs. 9.66 expected, SMR 1.14, 95% CI 0.63–2.06) (Table 2).

The analyses stratified by decade of age (30–39.9, 40–49.9, 50–59.9, and ≥60 years; no deaths were observed before the age of 30, Table 3) and by years from the time of clinical evaluation (0–4.9, 5.0–9.9, ≥10.0 years, Table 4) did not suggest the presence of any temporal trend among both AN and BED patients (although stratified analyses were possibly underpowered among the former because of the low-absolute number of observed deaths). Among BN patients, however, the SMR was significantly increased after the age of 60 years (SMR 4.22, 95% CI 1.06–16.88, 2 observed deaths vs. 0.47 expected)

TABLE 3 Observed (O) and expected (E) deaths (by any cause), standardized mortality ratio (SMR) and 95% confidence intervals (CI), among eating disorder (ED) patients, overall and by ED type, stratified by age group

ED patients	No.	30–39.9 years of age				40–49.9 years of age				50–59.9 years of age				≥60 years of age			
		O	E	SMR	95% CI	O	E	SMR	95% CI	O	E	SMR	95% CI	O	E	SMR	95% CI
All	1277	1	0.74	1.36	(0.19–9.62)	3	1.82	1.64	(0.53–5.10)	5	3.80	1.31	(0.55–3.16)	13	11.60	1.12	(0.65–1.93)
Anorexia nervosa (AN)	368	1	0.20	4.94	(0.70–35.07)	0	0.22	-	-	1	0.20	5.12	(0.72–36.33)	1	0.38	2.61	(0.37–18.50)
Bulimia nervosa (BN)	312	0	0.24	-	-	1	0.33	2.99	(0.42–21.25)	0	0.26	-	-	2	0.47	4.22	(1.06–16.88)
Binge eating disorder (BED)	597	0	0.30	-	-	2	1.27	1.57	(0.39–6.29)	4	3.35	1.19	(0.45–3.18)	10	10.74	0.93	(0.50–1.73)

TABLE 4 Observed (O) and expected (E) deaths (by any cause), standardized mortality ratio (SMR) and 95% confidence intervals (CI), among eating disorder (ED) patients, overall and by ED type, stratified by time since clinical evaluation

ED patients	No.	0–4.9 years from evaluation				5–9.9 years from evaluation				≥10 years from evaluation			
		O	E	SMR	95% CI	O	E	SMR	95% CI	O	E	SMR	95% CI
All	1277	6	6.27	0.96	(0.43–2.13)	9	7.21	1.25	(0.65–2.40)	7	4.94	1.42	(0.67–2.97)
Anorexia nervosa (AN)	368	1	0.54	1.83	(0.26–13.03)	1	0.47	2.12	(0.30–15.06)	1	0.19	5.36	(0.75–38.05)
Bulimia nervosa (BN)	312	0	0.61	0.00	-	0	0.57	-	-	3	0.27	11.24	(3.62–34.84)
Binge eating disorder (BED)	597	5	5.12	0.98	(0.41–2.35)	8	6.17	1.30	(0.65–2.59)	3	4.49	0.67	(0.22–2.07)

and after 10 years from clinical evaluation (SMR 11.24, 95% CI 3.62–34.84, 3 observed deaths vs. 0.27 expected), showing how an excess in mortality rates among these patients started to become relevant in our study population only after several years had elapsed from disease onset, that is, not before late adulthood.

4 | DISCUSSION

This is the first study that evaluated the SMR of the principal EDs diagnoses in a representative cohort of the clinical population of an Italian region. Its strengths included the large representative sample, the long duration of follow-up, the careful assessment of diagnoses and outcomes, and the uniformity of the treatment approach in the whole sample.

Overall, the SMR (2.49) derived from the present study for patients with AN was similar to the one obtained by Winkler et al. (2.37),[10] but quite reduced as compared to those obtained from almost all the similar recent studies in this field: for example, 4.37 for Franko et al.,[34] 10.6 for Huas et al.,[35] 5.21 for Himmerich et al.[36] On the contrary, SMR for BN (2.07) was comparable to previous observations: 2.33 for Franko et al.,[34] 2.37 for Winkler et al.,[10] 2.52 for Himmerich et al.,[36] and greater only as compared to Keel et al., who reported that BN patients had no increased risk of death.[37] Instead, no evidence of an increase in mortality rates emerged among BED patients, with SMR estimated as 1.01 (95% CI 0.62–1.66).

The reduced SMR in AN as compared with other studies was a quite surprising result, given that the considered sample also included severe patients reporting clinical characteristics commonly associated with increased mortality ratio, such as very low BMI, frequent purging behaviors and psychiatric comorbidity.[38] A meta-analysis by Arcelus et al.[39] reported an SMR of 5.9 (95% CI 4.2–8.3) for patients with AN and an SMR of 1.9 (95% CI 1.4–2.6) for patients with BN. SMR significantly increased when stratifying for different clinical settings, reaching 15.9 (95% CI 11.6–21.4) for inpatients with AN and (complications of) severe malnutrition,[12] and 4.7 adjusted hazard ratio mortality risk in a 12-year follow-up study in hospitalized patients with BN.[8] Other studies including hospitalized patients reported quite higher SMR as compared to what was found in the present study: Auger et al. reported an SMR of 9.01,[40] Huas et al. reported an SMR of 10.6, 10 years after hospitalization in a tertiary psychiatric department specialized in ED,[35] Rosling et al. reported an SMR of 11.7,[41] and Guinhut et al. reported an SMR of 15.9.[12] All these studies reported data regarding cohorts of very severe patients. However, it is important to note that the present study also included a cohort of severe patients who underwent several lifetime hospitalizations.

No suicide death was detected in the present sample across the follow-up period, in contrast with previous observations,[10,34,42] and with a recent meta-analysis, which found that persons with EDs were 7 for BN and 31 for AN times more likely to die by suicide than the comparable general population.[43]

Several explanations can be suggested for differences in the SMRs between studies. First of all, the composition of the sample should be taken into account, as a large proportion of previous studies included only inpatient subjects.[10] Furthermore, heterogeneity of follow-up periods among participants might partially explain the different SMR as compared to previous investigations. Accordingly, some previous long time longitudinal observations demonstrated that the number of deaths increased with increasing duration of follow-up.[44] However, it is unclear whether the risk of death remained stable during follow-up, as both Lowe et al. and Fichter et al. detected most of the recorded deaths earlier in the follow-up period,[45,46] suggesting that deaths directly associated with EDs might depend on critical medical conditions intervening in the early phases of the illness. On the other hand, especially in patients with BN, SMR increased for other causes of death with a longer duration of illness, according to Franko et al. findings,[34] suggesting that chronicity is a crucial factor in premature death for causes not directly correlated with illness.

Even though the reduced number of deaths of the present study made it difficult to estimate associations with specific variables, age was the most significant factor influencing mortality, according with previous observations.[34,42,47] Furthermore, according to Guinhut et al.,[12] one of the most relevant predictors of death was the discontinuation of treatment after hospitalization. Indeed, the striking difference in SMR could be partly attributable to the organizational changes in treatment, like what others have suggested.[35,48] For example, Crisp et al.[48] found 1.4 SMR in a cohort of EDs patients, and they suggested that the presence of the specialist unit was accountable for the lower SMR. Also Lindblad et al.[49] study supported these findings, with a decreased mortality when comparing two cohorts a decade apart (SMR 7.7 vs. 2.9). In the latter cohort, specialized units were established in Sweden, and the authors presumed this to be the main cause of the decreased mortality.[49] The authors hypothesized that this decrease was due to increased awareness and improved care. Indeed, the distinctiveness of the Italian pathways to care for help-seeking behavior of people with chronic illnesses[18] might be the explanation of different mortality rates between Italian and other European countries.[22,23] The Italian psychiatric context may represent a "special one" since the 1978 psychiatric

reform law may have exerted significant effects on psychiatric care in general and, in particular, for ED care.[18]

It is important to note that the treatment strategy in the Florence area is not based on long-term hospitalization, in line with the observation that specialized outpatient units (in which evidence-based approaches are routinely used with a multidisciplinary approach) are to be considered the preferred treatment setting for EDs, in terms of clinical outcomes, consistency of care, and cost reduction.[50] Indeed, the strength of the Florence organization is based on a large network which makes an integrated multidisciplinary team available for almost all the patients with EDs of the geographical area. Furthermore, the protocol of intervention is based on the homogeneous adoption of CBT-E in all the Florence clinical setting, while it has been reported[51] that in some Italian settings, a multidisciplinary team was used in less than 20% of patients, supporting evidence of a poor level of organization and co-operation between members of the different specialities involved, without an adequate implementation of standardized protocols.[51]

The exclusion from the analyses of patients who resided outside Tuscany at the time of recruitment, or whose residence changed during the follow-up, represents a limitation of the present study. It is not possible to know whether the 158 patients who declined treatment or refused to participate in the study would have influenced the results (e.g., if they were, on average, more severely ill). Moreover, the present study was somewhat underpowered to detect late/very late increases in SMR (i.e., increases in SMR that occur 15 or more years after clinical evaluation); an update of this analysis in 5–10 years (when a larger proportion of patients will have had a sufficiently long observation time) will be able to provide further insight into the topic.

It is important to note that patients included in the present study were selected using DSM-5 criteria, which were retrospectively applied based on clinical records reviews. This has led to the inclusion of patients who, at the time of the first evaluation (before 2013), fell into the category then called EDs not otherwise specified (EDNOS) in the DSM-IV. Several clinical and epidemiological studies showed that DSM-5 criteria are more inclusive than those of DSM-IV, expanding the AN and especially BN and BED diagnoses, and maintaining EDNOS as a truly residual category.[52–57] However, previous observations seem to demonstrate that the adoption of DSM-5 criteria did not determine a substantial change of the EDs pictures, in terms of recovery and relapses rates, diagnostic instability, and main factors associated with the different outcomes.[52,58] Furthermore, the choice of DSM-5 criteria made it possible to offer data updated to modern standards, and more easily comparable with respect to the literature published in the last decade.

To conclude, as a partial explanation for the low SMR of the present study the continuity in the health care program of patients with EDs in the Florence clinical setting deserves attention. Indeed, a high frequency and prolonged team monitoring, management, and multidisciplinary care of these patients after discharge from the hospital is provided for all patients with EDs. Furthermore, the EDTN represents a unique setting for the treatment of EDs, in terms of integration between specialized centers, mental health professionals, general practitioners, and residential structures of the mental health care system. This model of organization allows intensive and continuous health care management—not limited to the inpatient intervention—which is supposed to represent an efficacious approach for preventing lethal outcomes in EDs.

4.1 | Future directions

Even though an adequate health care organization for EDs might be partially responsible for reduced SMR, several interventions should be considered in order to improve the overall quality of treatments. In particular, the reduction of the interval between onset and first access to multi-dimensional intervention seems to be one of the most important outcome modifiers suggested by the literature.[59–63] This aim could be achieved by means of a better definition of pathways to care, in particular enhancing the interaction between EDs and mental health services and general practitioners, who should be more involved in the first steps of EDs psychopathological assessment.

CONFLICT OF INTEREST
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee (Comitato Etico Regione Toscana, sezione Area Vasta Centro). Informed consent was obtained from all individual participants included in the study.

ORCID

Emanuele Cassioli https://orcid.org/0000-0003-3623-7096

Eleonora Rossi https://orcid.org/0000-0003-4755-3879

REFERENCES

1. Klump KL, Bulik CM, Kaye WH, Treasure J, Tyson E. Academy for eating disorders position paper: eating disorders are serious mental illnesses. *Int J Eat Disord*. 2009;42(2):97-103. doi:10.1002/eat.20589

2. Nagl M, Jacobi C, Paul M, et al. Prevalence, incidence, and natural course of anorexia and bulimia nervosa among adolescents and young adults. *Eur Child Adolesc Psychiatry*. 2016;25(8):903-918. doi:10.1007/s00787-015-0808-z

3. van Eeden AE, van Hoeken D, Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. *Curr Opin Psychiatry*. 2021;34(6):515-524. doi:10.1097/YCO.0000000000000739

4. Preti A, de Girolamo G, Vilagut G, et al. The epidemiology of eating disorders in six European countries: results of the ESEMeD-WMH project. *J Psychiatr Res*. 2009;43(14):1125-1132. doi:10.1016/j.jpsychires.2009.04.003

5. van Hoeken D, Hoek HW. Review of the burden of eating disorders: mortality, disability, costs, quality of life, and family burden. *Curr Opin Psychiatry*. 2020;33(6):521-527. doi:10.1097/YCO.0000000000000641

6. Fichter MM, Quadflieg N. Mortality in eating disorders—results of a large prospective clinical longitudinal study. *Int J Eat Disord*. 2016;49(4):391-401. doi:10.1002/eat.22501

7. Edakubo S, Fushimi K. Mortality and risk assessment for anorexia nervosa in acute-care hospitals: a nationwide administrative database analysis. *BMC Psychiatry*. 2020;20(1):19. doi:10.1186/s12888-020-2433-8

8. Tith RM, Paradis G, Potter BJ, et al. Association of bulimia nervosa with long-term risk of cardiovascular disease and mortality among women. *JAMA Psychiat*. 2020;77(1):44-51. doi:10.1001/jamapsychiatry.2019.2914

9. Fichter MM, Quadflieg N, Crosby RD, Koch S. Long-term outcome of anorexia nervosa: results from a large clinical longitudinal study. *Int J Eat Disord*. 2017;50(9):1018-1030. doi:10.1002/eat.22736

10. Winkler LA-D, Bilenberg N, Hørder K, Støving RK. Does specialization of treatment influence mortality in eating disorders?—a comparison of two retrospective cohorts. *Psychiatry Res*. 2015;230(2):165-171. doi:10.1016/j.psychres.2015.08.032

11. Quadflieg N, Strobel C, Naab S, Voderholzer U, Fichter MM. Mortality in males treated for an eating disorder—a large prospective study. *Int J Eat Disord*. 2019;52(12):1365-1369. doi:10.1002/eat.23135

12. Guinhut M, Godart N, Benadjaoud M, Melchior J, Hanachi M. Five-year mortality of severely malnourished patients with chronic anorexia nervosa admitted to a medical unit. *Acta Psychiatr Scand*. 2021;143(2):130-140. doi:10.1111/acps.13261

13. Suokas JT, Suvisaari JM, Gissler M, et al. Mortality in eating disorders: a follow-up study of adult eating disorder patients treated in tertiary care, 1995–2010. *Psychiatry Res*. 2013;210(3):1101-1106. doi:10.1016/j.psychres.2013.07.042

14. Hoang U, Goldacre M, James A. Mortality following hospital discharge with a diagnosis of eating disorder: national record linkage study, England, 2001-2009. *Int J Eat Disord*. 2014;47(5):507-515. doi:10.1002/eat.22249

15. Fichter MM, Naab S, Voderholzer U, Quadflieg N. Mortality in males as compared to females treated for an eating disorder: a large prospective controlled study. *Eat Weight Disord—Stud Anorexia, Bulim Obes*. 2021;26(5):1627-1637. doi:10.1007/s40519-020-00960-1

16. Dobrescu SR, Dinkler L, Gillberg C, Råstam M, Gillberg C, Wentz E. Anorexia nervosa: 30-year outcome. *Br J Psychiatry*. 2020;216(2):97-104. doi:10.1192/bjp.2019.113

17. Halmi KA. Salient components of a comprehensive service for eating disorders. *World Psychiatry*. 2009;8(3):150-155. doi:10.1002/j.2051-5545.2009.tb00235.x

18. Volpe U, Fiorillo A, Luciano M, et al. Pathways to mental health care in Italy: results from a multicenter study. *Int J Soc Psychiatry*. 2014;60(5):508-513. doi:10.1177/0020764013501648

19. Volpe U, Monteleone AM, Ricca V, et al. Pathways to specialist care for eating disorders: an Italian multicentre study. *Eur Eat Disord Rev*. 2019;27(3):274-282. doi:10.1002/erv.2669

20. Treasure J, Claudino AM, Zucker N. Eating disorders. *Lancet*. 2010;375(9714):583-593. doi:10.1016/S0140-6736(09)61748-7

21. Piccinelli M, Politi P, Barale F. Focus on psychiatry in Italy. *Br J Psychiatry*. 2002;181(6):538-544. doi:10.1192/bjp.181.6.538

22. De Girolamo G, Bassi M, Neri G, Ruggeri M, Santone G, Picardi A. The current state of mental health care in Italy: problems, perspectives, and lessons to learn. *Eur Arch Psychiatry Clin Neurosci*. 2007;257(2):83-91. doi:10.1007/S00406-006-0695-X

23. Luciano M, Sampogna G, del Vecchio V, et al. The family in Italy: cultural changes and implications for treatment. *Int Rev Psychiatry*. 2012;24(2):149-156. doi:10.3109/09540261.2012.656306

24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596

25. National Institute for Health and Care Excellence. Eating disorders: recognition and treatment (NICE guideline [NG69]); 2020. Accessed October 15, 2021. https://www.nice.org.uk/guidance/ng69

26. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of "precision psychiatry". *BMC Med*. 2017;15(1):1-7. doi:10.1186/S12916-017-0849-X/FIGURES/1

27. Kübler U. Structured clinical interview for DSM-IV (SCID). *Encyclopedia of Behavioral Medicine*. Springer; 2013:1919-1920. doi:10.1007/978-1-4419-1005-9_66

28. First MB, Williams JBW, Karg RS, Spitzer RL. *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. American Psychiatric Association; 2016.

29. Fairburn CG. A cognitive behavioural approach to the treatment of bulimia. *Psychol Med*. 1981;11(4):707-711. doi:10.1017/S0033291700041209

30. Fairburn CG. *Cognitive Behavior Therapy and Eating Disorders*. Guilford Press; 2008.

31. Linehan MM. Dialectical behavior therapy for borderline personality disorder. Theory and method. *Bulletin of the Menninger Clinic*. 1987;51(3):261-276.

32. Shapiro F. Eye movement desensitization and reprocessing (EMDR) therapy: basic principles, Protocols, and Procedures. 2018. doi:10.4324/9781315268286-4

33. Treasure J, Nazar BP. Interventions for the carers of patients with eating disorders. *Curr Psychiatry Rep*. 2016;18(2):16. doi:10.1007/s11920-015-0652-3

34. Franko DL, Keshaviah A, Eddy KT, et al. A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. *Am J Psychiatry*. 2013;170(8):917-925. doi:10.1176/appi.ajp.2013.12070868

35. Huas C, Caille A, Godart N, et al. Factors predictive of ten-year mortality in severe anorexia nervosa patients. *Acta Psychiatr Scand*. 2011;123(1):62-70. doi:10.1111/j.1600-0447.2010.01627.x

36. Himmerich H, Hotopf M, Shetty H, et al. Psychiatric comorbidity as a risk factor for the mortality of people with bulimia nervosa. *Soc Psychiatry Psychiatr Epidemiol*. 2019;54(7):813-821. doi:10.1007/s00127-019-01667-0

37. Keel PK, Dorer DJ, Eddy KT, Franko D, Charatan DL, Herzog DB. Predictors of mortality in eating disorders. *Arch Gen Psychiatry*. 2003;60(2):179. doi:10.1001/archpsyc.60.2.179

38. Kask J, Ekselius L, Brandt L, Kollia N, Ekbom A, Papadopoulos FC. Mortality in women with anorexia nervosa: the role of comorbid psychiatric disorders. *Psychosom Med*. 2016;78(8):910-919. doi:10.1097/PSY.0000000000000342

39. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. *Arch Gen Psychiatry*. 2011;68(7):724-731. doi:10.1001/archgenpsychiatry.2011.74

40. Auger N, Potter BJ, Ukah UV, et al. Anorexia nervosa and the long-term risk of mortality in women. *World Psychiatry*. 2021;20(3):448-449. doi:10.1002/wps.20904

41. Rosling AM, Sparén P, Norring C, von Knorring A-L. Mortality of eating disorders: a follow-up study of treatment in a specialist unit 1974-2000. *Int J Eat Disord*. 2011;44(4):304-310. doi:10.1002/eat.20827

42. Himmerich H, Hotopf M, Shetty H, et al. Psychiatric comorbidity as a risk factor for mortality in people with anorexia nervosa. *Eur Arch Psychiatry Clin Neurosci*. 2019;269(3):351-359. doi:10.1007/s00406-018-0937-8

43. Preti A, Rocchi MBL, Sisti D, Camboni MV, Miotto P. A comprehensive meta-analysis of the risk of suicide in eating disorders. *Acta Psychiatr Scand*. 2011;124(1):6-17. doi:10.1111/j.1600-0447.2010.01641.x

44. Ratnasuriya RH, Eisler I, Szmukler GI, Russell GFM. Anorexia nervosa: outcome and prognostic factors after 20 years. *Br J Psychiatry*. 1991;158(April):495-502. doi:10.1192/bjp.158.4.495

45. Fichter MM, Quadflieg N, Hedlund S. Twelve-year course and outcome predictors of anorexia nervosa. *Int J Eat Disord*. 2006;39(2):87-100. doi:10.1002/eat.20215

46. Löwe B, Zipfel S, Buchholz C, Dupont Y, Reas DL, Herzog W. Long-term outcome of anorexia nervosa in a prospective 21-year follow-up study. *Psychol Med*. 2001;31(5):881-890. doi:10.1017/S003329170100407X

47. Keshaviah A, Edkins K, Hastings ER, et al. Re-examining premature mortality in anorexia nervosa: a meta-analysis redux. *Compr Psychiatry*. 2014;55(8):1773-1784. doi:10.1016/j.comppsych.2014.07.017

48. Crisp AH, Callender JS, Halek C, Hsu LKG. Long-term mortality in anorexia nervosa. *Br J Psychiatry*. 1992;161(1):104-107. doi:10.1192/bjp.161.1.104

49. Lindblad F, Lindberg L, Hjern A. Improved survival in adolescent patients with anorexia nervosa: a comparison of two Swedish National Cohorts of female inpatients. *Am J Psychiatry*. 2006;163(8):1433-1435. doi:10.1176/ajp.2006.163.8.1433

50. House J, Schmidt U, Craig M, et al. Comparison of specialist and nonspecialist care pathways for adolescents with anorexia nervosa and related eating disorders. *Int J Eat Disord*. 2012;45(8):949-956. doi:10.1002/eat.22065

51. Sukkar SG, Foppiani L, Campostano A. Management and treatment of eating disorders in an Italian region. *Eat Weight Disord Stud Anorexia Bulim Obes*. 2005;10(3):204-209. doi:10.1007/BF03327548

52. Castellini G, Lo Sauro C, Mannucci E, et al. Diagnostic crossover and outcome predictors in eating disorders according to DSM-IV and DSM-V proposed criteria: a 6-year follow-up study. *Psychosom Med*. 2011;73(3):270-279. doi:10.1097/PSY.0b013e31820a1838

53. Allen KL, Byrne SM, Oddy WH, Crosby RD. DSM–IV–TR and DSM-5 eating disorders in adolescents: prevalence, stability, and psychosocial correlates in a population-based sample of male and female adolescents. *J Abnorm Psychol*. 2013;122(3):720-732. doi:10.1037/a0034004

54. Birgegård A, Norring C, Clinton D. DSM-IV versus DSM-5: implementation of proposed DSM-5 criteria in a large naturalistic database. *Int J Eat Disord*. 2012;45(3):353-361. doi:10.1002/eat.20968

55. Machado PPP, Gonçalves S, Hoek HW. DSM-5 reduces the proportion of ednos cases: evidence from community samples. *Int J Eat Disord*. 2013;46(1):60-65. doi:10.1002/eat.22040

56. Mitchell JE, Crosby RD, Wonderlich SA, et al. Latent profile analysis of a cohort of patients with eating disorders not otherwise specified. *Int J Eat Disord*. 2007;40(S3):S95-S98. doi:10.1002/eat.20459

57. Walsh BT, Sysko R. Broad categories for the diagnosis of eating disorders (BCD-ED): an alternative system for classification. *Int J Eat Disord*. 2009;42(8):754-764. doi:10.1002/eat.20722

58. Keel PK, Brown TA, Holm-Denoma J, Bodell LP. Comparison of DSM-IV versus proposed DSM-5 diagnostic criteria for eating disorders: reduction of eating disorder not otherwise specified and validity. *Int J Eat Disord*. 2011;44(6):553-560. doi:10.1002/eat.20892

59. Steinhausen H-C. The outcome of anorexia nervosa in the 20th century. *Am J Psychiatry*. 2002;159(8):1284-1293. doi:10.1176/appi.ajp.159.8.1284

60. Fairburn CG. Risk factors for bulimia nervosa. *Arch Gen Psychiatry*. 1997;54(6):509. doi:10.1001/archpsyc.1997.01830180015003

61. Lewinsohn PM, Striegel-Moore RH, Seeley JR. Epidemiology and natural course of eating disorders in young women from adolescence to young adulthood. *J Am Acad Child Adolesc Psychiatry*. 2000;39(10):1284-1292. doi:10.1097/00004583-200010000-00016

62. Currin L, Schmidt U, Treasure J, Jick H. Time trends in eating disorder incidence. *Br J Psychiatry*. 2005;186(2):132-135. doi:10.1192/bjp.186.2.132

63. McClelland J, Hodsoll J, Brown A, et al. A pilot evaluation of a novel First episode and rapid early intervention service for eating disorders (FREED). *Eur Eat Disord Rev*. 2018;26(2):129-140. doi:10.1002/erv.2579