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ORIGINAL PAPER

Psychiatric comorbidity as a risk factor for mortality in people with anorexia nervosa

Hubertus Himmerich[1,2] · Matthew Hotopf[1,2] · Hitesh Shetty[2] · Ulrike Schmidt[1,2] · Janet Treasure[1,2] · Richard D. Hayes[1] · Robert Stewart[1,2] · Chin-Kuo Chang[1,2,3]

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Abstract
Anorexia nervosa (AN) is found associated with increased mortality. Frequent comorbidities of AN include substance use disorders (SUD), affective disorders (AD) and personality disorders (PD). We investigated the influence of these psychiatric comorbidities on all-cause mortality with demographic and socioeconomic factors considered as confounders in the observation window between January 2007 and March 2016 for 1970 people with AN, using data from the case register of the South London and Maudsley (SLaM) NHS Foundation Trust, an almost monopoly-secondary mental healthcare service provider in southeast London. We retrieved data from its Clinical Records Interactive Search (CRIS) system as data source. Mortality was ascertained through nationwide tracing by the UK Office for National Statistics (ONS) linked to CRIS database on a monthly basis. A total of 43 people with AN died during the observation period. Standardized Mortality Ratio (SMR) with England and Wales population in 2012 as standard population for our study cohort was 5.21 (95% CI 3.77, 7.02). In univariate analyses, the comorbidity of SUD or PD was found to significantly increase the relative risks of mortality (HRs = 3.10, 95% CI 1.21, 7.92; and 2.58, 95% CI 1.23, 5.40, respectively). After adjustment for demographic and socioeconomic covariates as confounders, moderately but not significantly elevated risks were identified for SUD (adjusted HR = 1.39, 95% CI 0.53, 3.65) and PD (adjusted HR = 1.58, 95% CI 0.70, 3.56). These results suggest an elevated mortality in people with AN, which might be, at least partially, explained by the existence of the comorbidities SUD or PD.

Keywords Anorexia nervosa · Comorbidities · Affective disorder · Substance use disorder · Personality disorder

Introduction

Anorexia nervosa

Anorexia nervosa (AN) is defined by a significantly low body weight in the context of age, sex, and physical health, intense fear of weight gain and disturbed body perception [1]. The number of people with AN is rising, and the illness is affecting people at an increasingly younger age [2–4]. The prevalence of AN is between less than 1% and 4% among women, with a male:female ratio of approximately 1:10 [5]. The peak age of incidence is between 14 and 17 years old [6].

Mortality for people with AN

Dietary deficit is often accompanied by significant physical health issues, including growth retardation, osteopenia, osteoporosis, amenorrhoea, renal insufficiency, and changes in laboratory parameters, cardiac arrhythmia and disturbances of the thyroid function [7]. The most common causes of death in people with AN are sudden cardiac death associated with ventricular arrhythmias, and suicide [8–10]. Mortality rates are five to six times higher for people with AN than in the general population, and in people aged 15–24 years old,

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✉ Chin-Kuo Chang
ckchang@utaipei.edu.tw

1 Department of Psychological Medicine, King's College London, London, UK

2 South London and Maudsley NHS Foundation Trust, London, UK

3 Department of Health and Welfare, University of Taipei, No. 101, Sec. 2, Jhongcheng Rd, Shilin District, Taipei 111, Taiwan

the mortality risk from AN is higher than for other serious diseases in adolescence, such as asthma or type 1 diabetes [3, 4].

Mental health comorbidities in AN as risk factors for mortality

AN is often accompanied by other mental disorders, including substance use disorders (SUD) [11], affective disorders (AD) [12, 13] and personality disorders (PD) [14]. In the Swedish Twin Registry, people with AN exhibited a significantly increased risk for the use of alcohol and illicit drugs, specifically diet pills and stimulants [11]. Another Swedish study which evaluated data from patients presenting to specialist eating disorder clinics between 2008 and 2012 found that 521 (38.8%) of 1343 patients with AN suffered from AD, principally unipolar depression [12]. A German investigation in female inpatients with AN reported a prevalence of around 30% for one or more comorbid PDs [14]. In this study, comorbid PD was found related to a worse treatment outcome. Potential comorbidities of AN including addiction to alcohol [15, 16] or illicit drugs [17], unipolar depression [18] and PD [19] have been found to be associated with increased mortality. In a recent retrospective Swedish register study investigating mortality in women with AN, SUDs and depression significantly contributed to mortality, but not PDs [20].

Other important risk factors contributing to mortality in people with mental disorders include age, gender, marital status, socioeconomic deprivation and ethnicity [21–27]. However, these risk factor influence mortality in people with physical diseases, too [28–30]. Therefore, they seem to be general factors which modify mortality.

Comparable studies, e.g., Kask et al. [20, 31] only covered patients aged 10–40 years. Therefore, results of these studies may not be generalizable to all age groups. We decided not to set an age limit to achieve a comprehensive epidemiologic view on mortality of patients with AN. Moreover, there are case reports of patients newly diagnosed with AN at the age of 65 or older [32], and a recent study demonstrated that active eating disorders are common amongst women in mid-life, both due to new onset and chronic disorders [33].

General aspects of mortality in patients with mental disorders

When thinking about psychiatric comorbidity as a risk factor for mortality in people with AN, it seems sensible to take some important general aspects of mortality in patients with mental disorders into account. According to a recent systematic review and meta-analysis including 203 eligible articles and representing 29 countries in six continents, mortality is significantly higher among people with mental disorders than among the comparison population. About two-thirds of deaths among people with mental disorders are due to natural, about 18% to unnatural, and the remainder to other or unknown causes. The median years of potential life lost was found to be 10 years, and it was estimated that around 14% of deaths worldwide (8 million deaths each year) are attributable to mental disorders [34]. Important overall risk factors contributing to mortality in patients with mental disorders include sociodemographic variables such as age, gender, ethnicity, unemployment and low educational attainment, physical diseases such as cancer and coronary heart disease, the specific psychiatric diagnosis and additional other psychological and behavioural problems like substance abuse and dependence; unnatural and alcohol-related causes of death seem to play a specific role for increased mortality in younger age groups of people with mental disorders [35–38].

Aim of the study

In this study, we sought to investigate the influence of major psychiatric comorbidities on all-cause mortality in people with AN in a case register for a large secondary mental healthcare service provider in southeast London, UK, with confounding from demographic and socioeconomic factors considered. Our hypothesis for this investigation was that AD, SUD and PD had an independent effect on increased mortality in people with AN.

Methods

Setting and study design

A retrospective cohort study was performed in people with AN. The AN cohort was obtained from the South London and Maudsley NHS Foundation Trust (SLaM) which provides near-monopoly-secondary mental healthcare services to a geographic catchment of about 1.36 million residents in southeast London. SLaM's Eating Disorders Service additionally offers a specialist tertiary service for service users across the UK. Patients included in this study mainly resided in the London boroughs of Lambeth, Croydon, Lewisham, Southwark, Bromley, Bexley and Greenwich. The SLaM National Institute for Health Research Biomedical Research Centre (BRC) supports the infrastructure for research of anonymised electronic clinical records from SLaM's case register, using the BRC's Clinical Record Interactive Search (CRIS) system as data source, established in 2008 [39, 40].

Inclusion criteria and primary exposure

The analyzed cohort was extracted via CRIS, consisting of individuals who had received an International Classification of Diseases (ICD-10) diagnosis [41] of AN (F50.0/F50.1) within or before the observation window from 1 January 2007 to 31 March 2016. Structured information on diagnosis from drop-down fields in the source record was supplemented by information extracted from open-text fields using a bespoke algorithm generated using the Generalised Architecture for Text Engineering (GATE) software [39]. The exposure of interest was a further diagnosis of SUD (F10–F19), AD (F31-33) or PD (F60) at any stage during or before the observation window extracted from CRIS using identical procedures.

Primary outcome

The outcome of this analysis was all-cause mortality occurring from January 2007 to March 2016. Information about each death was collected through nationwide tracing using data from the UK Office for National Statistics (ONS) linked to the SLaM database on a monthly basis. In the UK, all death certifications are linked by NHS number (a unique identifier for each UK NHS service user) to all healthcare providers.

Covariates

Date of birth (for year and month), gender, ethnicity, marital status and residing borough were retrieved from the CRIS database. Age in years was calculated from the individual's first AN diagnosis date in the observation period or on 1 January 2007 if the AN diagnosis preceded the observation period.

Recorded ethnicity was classified into three categories: 'white' (including 'British', 'any other white background' and 'Irish'), 'black' (including 'African', 'any other black background' and 'Caribbean'), and 'others/unknown/mixed'. Recorded marital status was classified into four groups: 'married' (including 'cohabitation', 'married' and 'married/civil partnership'), 'single', 'divorced' (including 'divorced/ civil partnership dissolved', 'separated'), and 'others'. Borough was classified by the subject's residence: Lambeth, Croydon, Lewisham, Southwark, Bromley, Bexley and Greenwich, defined by their primary care trust. Multiple deprivation score is a small-area-level measure of socioeconomic status derived from UK Census data, based on the individual's address closest to the diagnosis of AN in the observation window (or 1 January 2007 for those with an earlier diagnosis of AN), covering the seven components, 'employment', 'income', 'education', 'health', 'barriers to housing and services', 'crime' and 'living environment', with specific weightings. The Index of Multiple Deprivation score is a well-established measure which has been widely used as a regional indicator for socioeconomic status in previous studies [42–44]. The score is then transformed into percentiles (from 1 to 100) with a higher score indicating greater deprivation (and thus lower socioeconomic status in the neighbourhood). In the analysis, deprivation scores were regrouped by tertiles (33.3 percentiles).

Ethical approval

Ethical approval was obtained from the Oxfordshire Research Ethics Committee C for the use of CRIS as a source of data for secondary analysis (reference 08/H0606/71 + 5) including the mortality linkage. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

Standardized Mortality Ratio (SMR) was used for the adjustment of age and gender structure, comparing our study cohort to a standard population for mortality. Observed number of death in the window was treated as the numerator of SMR in the calculation. Age spanning in 5-year age and sex bands were then utilized to define age- and gender-specific groups in our study cohort. Denominator of SMR was the sum of expected numbers for age-and-sex bands derived by the number of people in individual band in our study cohort multiplying its corresponding age- and gender-specific mortality rate in the general population of England and Wales in 2012 according to ONS data. Since the study cohort was followed up for up to 9.25 years but mortality rates for the general population were given for a year only, specific weightings based on the average follow-up period for corresponding age-and-sex bands for the calculation of SMR's denominator were applied.

Descriptive statistics on demographic characteristics and psychiatric comorbidities were first carried out for the study cohort. We then used Cox proportional hazards regression to estimate the effect for each of the variable by hazard ratio (HR) with a 95% confidence interval (CI) on death as the 'event' of interest within the observation window. Beginning of the follow-up period was defined as the start of the observation window (1 January 2007) if the first diagnosis was given before the window, otherwise the beginning was taken as the date of first AN diagnosis given in the window. Multivariate analyses were lastly performed in parallel to estimate the effect of the considered psychiatric comorbidities as major exposure of interest, controlling for confounding of age, sex, ethnicity, borough, marital status and deprivation score. All the statistical analyses were performed

using Stata 12.1 (StataCorp, College Station, Texas, USA) and the statistical significance (alpha level) was set at 0.05.

Results

Descriptive statistics

A total of 1970 individuals diagnosed with AN were identified from the CRIS system. Among them, 1834 were female and 136 were male. The mean age was 24.5 years (standard deviation: 11.3 years; range 8–88 years). Twelve (0.6%) patients with AN were 65 years old or older. More detailed information about age distribution was put in Table 1. During the observation window, 43 of the 1,970 study subjects died. Descriptive statistics are shown in detail in Table 2.

Standardized mortality ratio (SMR)

Age- and gender-SMR for our study cohort was 5.21 (95% CI 3.77, 7.02), with the population of England and Wales in 2012 as standard population according to ONS data on its website.

Univariate analysis by Cox regressions

Cox regressions revealed a significant effect of age, marital status, deprivation score, SUD and PD. Specifically, older age, being separated or divorced, being deprived and suffering from comorbidity of SUD and PD were associated with a higher mortality risk (details shown in Table 2). The mean age of the patients who died in the observation window was 41.03 years old (standard deviation = 18.36 years; ranging from 15 to 86 years old), whereas the mean age of patients who survived was 24.11 years old (standard deviation = 10.79 years; ranging from 8 to 88 years old).

Table 1 Age distribution of study participants ($N = 1970$)

Age group (years)	Frequency	Percent
5–10	4	0.20
10–15	284	14.42
15–20	602	30.56
20–25	375	19.04
25–30	255	12.94
30–35	152	7.72
35–40	100	5.08
40–45	64	3.25
45–50	47	2.39
50–55	33	1.68
55–60	29	1.47
60–65	13	0.66
65–70	4	0.25
70–75	2	0.10
75–80	3	0.15
80–85	0	0.00
85–90	2	0.10

Multivariate analyses by Cox regressions

Controlling for age, sex, ethnicity, the residing borough, marital status and deprivation score as confounders, multivariate analysis outcomes by Cox regression is shown in Table 3. Significance of the comorbidities to mortality in people with AN disappeared, when controlling for potential confounders. However, moderately elevated risks were identified for SUD (adjusted HR = 1.39, 95% CI 0.53, 3.65) and PD (adjusted HR = 1.58, 95% CI 0.70, 3.56). All detailed information regarding multivariate analyses outcomes for AD, SUD and PD as the major exposure of interest was separately presented in Supplementary Tables 1–3.

Discussion

Main findings

In summary, 43 of the 1970 people with AN died during the observation period of more than 9 years. A more than five folds of general mortality was found by age and gender standardization, compared to the general population in England and Wales. Moderately elevated mortality risks were estimated for comorbid SUD and PD with confounders controlled, but not significant because of power issues.

Comparison to previous research

The SMR in our study cohort is comparable to previous studies, reporting that patients with AN have five to six times higher mortality than the general population [3, 4]. However, there are also studies reporting even higher all-cause mortality rates [20, 31], but these studies included inpatients only. One can assume that inpatient status reflects a higher degree of severity.

In a recent meta-analysis of mortality studies in AN [45], age was—apart from the applied diagnostic criteria—the most significant factor influencing mortality. The finding that age and social deprivation significantly influence mortality is also in accordance with Franko et al. [46] who investigated 246 treatment-seeking women with AN or bulimia nervosa longitudinally, among them 136 patients with AN. However, in contrast to Franko et al., we could not replicate their finding of a significant contribution of alcohol abuse to all-cause mortality in AN.

Table 2 Univariate analysis on demographics and clinical characteristics for mortality among people with anorexia nervosa by Cox regressions ($N = 1970$)

Variables	Mean ± SD/numbers (% in column)	Number of deaths (% in row)	Hazard ratio (95% CI)	*p* value
Age (years old)	24.48 ± 11.27	–	1.08 (1.06, 1.10)*	< 0.01
Gender				
Female	1,834 (93.10%)	39 (2.13%)	Ref	
Male	136 (6.90%)	4 (2.94%)	1.33 (0.47, 3.71)	0.59
Marital status				
Single	1,532 (77.77%)	24 (1.57%)	Ref	
Married/partner	175 (8.88%)	6 (3.43%)	2.12 (0.87, 5.19)	0.10
Divorced/separated	43 (2.18%)	3 (6.98%)	3.75 (1.13, 12.48)*	< 0.05
Others	220 (11.17%)	10 (4.55%)	2.35 (1.12, 4.93)*	< 0.05
Borough				
Lambeth	298 (15.13%)	3 (1.01%)	Ref	
Croydon	237 (12.03%)	8 (3.38%)	2.61 (0.69, 9.85)	0.16
Lewisham	217 (11.02)%	4 (1.84%)	1.57 (0.35, 7.03)	0.55
Southwark	219 (11.12%)	7 (3.20%)	2.89 (0.75, 11.17)	0.12
Bromley	253 (12.84)	5 (1.98%)	1.87 (0.45, 7.81)	0.39
Bexley	114 (5.79%)	4 (3.51%)	3.15 (0.71, 14.09)	0.13
Greenwich	103 (5.23%)	2 (1.94%)	1.83 (0.30, 10.93)	0.51
Others	529 (26.85%)	10 (1.89%)	1.72 (0.47, 6.24)	0.41
Ethnicity				
White	1,639 (83.20%)	34 (2.07%)	Ref	
Black	63 (3.20%)	2 (3.17%)	1.27 (0.30, 5.28)	0.74
Others/mixed	268 (13.60%)	7 (2.61%)	1.27 (0.56, 2.87)	0.56
Deprivation Score[a]				
1.14–17.60	644 (32.69%)	10 (1.55%)	Ref	
17.61–29.17	643 (32.64%)	10 (1.56%)	0.92 (0.38, 2.22)	0.86
29.18–100	645 (32.74%)	22 (3.41%)	2.12 (1.01, 4.50)*	< 0.05
Missing/homeless	38 (1.93%)	1 (2.63%)	1.37 (0.17, 10.69)	0.77
SUD				
No	1909 (96.90%)	38 (1.99%)	Ref	< 0.05
Yes	61 (3.10%)	5 (8.20%)	3.10 (1.21, 7.92)*	
AD				
No	1,680 (85.28%)	34 (2.02%)	Ref	0.37
Yes	290 (14.72%)	9 (3.10%)	1.40 (0.67, 2.93)	
PD				
No	1,798 (91.27%)	34 (1.89%)	Ref	< 0.05
Yes	172 (8.73)	9 (5.23%)	2.58 (1.23, 5.40)*	

Higher deprivation scores indicate greater deprivation and thus lower socioeconomic status

SUD substance use disorder, *AD* affective disorder, *PD* personality disorder

*Statistically significant according to a level of significance of 0.05

[a]Further information

Considering sample size, data characteristics and the link between a clinical register and a death register, our study seems to be most comparable to the Swedish register studies where the Swedish Hospital Discharge Register is linked to the Swedish Cause-of-Death Register. The latest comparable Swedish studies investigated mortality in 8,069 female inpatients [20] and 609 males who received hospitalized care for AN [31]. Both studies found that SUD significantly contributed to mortality. These two studies included only patients aged 10—40 years to minimize the risk of incorrect diagnoses [20, 31]. In contrast, our study included patients with AN at all ages. If we look at SUD across the age range, SUD are most prevalent and most important between 10 and 40 years of age [47, 48]. Therefore, results of these two studies by Kask et al. may not be generalizable to all age groups of patients with AN [20, 31]. We decided not to set an age

Table 3 Multivariate analysis on demographics and clinical characteristics for mortality among people with anorexia nervosa by Cox regressions, controlling age, sex, ethnicity, borough, marital status and deprivation score ($N = 1970$)

Comorbidity	Adjusted hazard ratio (95% CI)	*p* value
AD	0.80 (0.36, 1.81)	0.60
SUD	1.39 (0.53, 3.65)	0.50
PD	1.58 (0.70, 3.56)	0.27

SUD substance use disorder, *AD* affective disorder, *PD* personality disorder

limit for inclusion of people in our study for three reasons. First, we sought to achieve a comprehensive epidemiologic view on mortality of patients with AN. One should keep in mind though, while interpreting the results of our study, that a diagnosis of AN did neither require that AN was the leading current diagnosis nor that it was the first episode of AN. Second, current research has highlighted the occurrence of AN in mid-life and older adults [32, 33, 49]. Third, studies in AN have used different upper age limits, for example, 40 years of age [20, 31], even though other studies have shown that in a relevant proportion of people with AN is first diagnosed or first treated after the age of 40 [32, 33]. For that reason, imposing a specific age limit seemed arbitrary.

Moderately elevated mortality risks were identified for SUD and PD in people with AN in our analysis, although not significant. Besides the issue of potentially insufficient statistical power, marital status might work as a critical mediator within the causal pathway between AN and mortality, taking away the effect from AN to mortality in the effect estimation by multivariate analysis. However, when we put marital status away from the final model, the outcomes for PD and SUD comorbidity did not change dramatically. Thus, the possibility of a mediating role for marital status seems limited.

Strengths and limitations

The main strengths of this study were the study design and size of cohort using CRIS as our data source. CRIS is one of the largest collections of secondary and tertiary mental healthcare services. Using this data in a retrospective cohort study, we identified a large number of 1970 patients with AN. However, in the observation period, only 43 patients with AN died, resulting in limited statistical power. The research outcomes of this study might be only generalizable to secondary and tertiary health care settings, but not to people with AN in community. In terms of generalizability, we also should be cautious that diagnoses were coded according to ICD-10 [41] which is still the currently used classification in the UK. Nevertheless, it needs to be mentioned that criteria have slightly changed in DSM-5 [1].

In principle, using data derived from secondary and tertiary mental healthcare services may potentially lead to an overestimation of the effect of a certain disorder on mortality and might compromise generalizability. The potential reasons for this assumption are that some patients with the disorder in question may not be under the care of any health service, and some of those cared for in primary care might not be referred to a specialist service. Thus, those who are referred to a specialist service might be more severely affected than the whole group of patients with this specific disorder.

However, studies which have successfully ascertained prevalence and service use rates in AN are scarce due to the relatively low prevalence of AN compared to other eating disorders. For example, a study by Solmi et al. [50] which examined 1698 individuals between 16 and 90 years of age in southeast London found a point prevalence of eating disorders of 4.4%, but no cases of AN at all. Thus, this study was unable to gauge service use among patient with AN. A US-American study found prevalence rates of AN between 0.03 and 0.39% and service utilization rates of patients with AN between 30 and 100% depending on the ethnicity of patients [51]. For non-Latino white patients with AN service use rates were around 76% [51]. White people are currently the biggest ethnic group in London [52] and in our study sample (see Table 2). Therefore, we can assume a similarly high service use rate for our patients. Nevertheless, we are aware of the ongoing debate whether general practitioners are good or poor at identifying the eating disorders [53].

It is likely that most patients presenting with AN to primary care in the UK are referred on to secondary care, including both general mental health services and specialist eating disorder services [54], because previous [54] and current [55] guidelines of The National Institute for Health and Care Excellence (NICE) in the UK advise general practitioners to refer anyone with a suspected eating disorder to specialist services without delay.

As information about each death was obtained through nationwide tracing using ONS, data on mortality are very reliable. A failure to obtain death data would appear, if people left the country during the observation period and died abroad. Such an event could have led to a failure to register the death of a patient with AN treated in SLaM.

Overall, we think that CRIS data on the diagnosis of AN and on mortality are generalizable because we assume—based on the limited evidence available—that most patients with AN seek medical help and are referred to secondary mental healthcare services [51, 54], and SLaM is an almost monopoly-secondary mental healthcare service provider in southeast London. As we can assume that our data on the diagnosis of AN and on the cases of death are reliable, we think that the obtained SMR for our study cohort of 5.21 is accurate.

Compared to other studies [11–14, 56, 57] we obtained relatively low rates of comorbid SUD, AD and PD in patients with AN. Thus, these disorders may have been underdiagnosed in our study sample, and underdiagnosis could be a source of error. When drawing further conclusions from our data, one must keep in mind that our data on SUD, AD and PD were not collected whilst specifically searching for these diagnoses. Instead, these diagnoses were documented by clinicians when clinically relevant. Therefore, our results cannot be easily compared with studies in which researchers used questionnaires and diagnostic tools to specifically detect SUDs, ADs or PDs.

An important limitation of our investigation is that we were not able to consider the subtypes of AN (binge/purge vs. restrictive), illness severity and duration, the number of hospital admissions during the observation period and the body mass index (BMI) which have all been found to contribute to mortality of people with AN in previous studies [46, 58–60]. As what already mentioned before, we do not know, when the diagnosis was first established in participants of this study.

Future research directions

For this particular project, the date of death, but not the cause of death was available from the ONS. The causes of death could be physical consequences of AN such as ventricular arrhythmias or suicide [8–10]. Future research could shed more light on the specific causes of death as the consequence of AN.

Further studies should also focus on modifiable risk factors for premature death prevention. Given a significant contribution of social deprivation to all-cause mortality, the question arises whether a reduction of mortality can be achieved by interventions intending to tackle social deprivation, such as family therapy, social work, social inclusion therapy and debt advice.

We have found an alarmingly increased mortality in patients with AN compared to the general population in accordance with previous studies [3, 4, 20, 31]. Thus, the question arises, whether the increased mortality can, in principle, be influenced by the available therapies. However, scientific knowledge on long-term treatment outcomes of most of the various psychotherapeutic, refeeding and psychopharmacological approaches in AN is scarce [61, 62], and we know even less about whether these therapies can reduce mortality.

Psychotherapy can have side effects such as the emergence of new symptoms, the deterioration of existing symptoms, dependence and regression, traumatic stress, strains or changes in family or work relations and missing the chance to seek suitable medical treatment [63, 64]. This is interesting considering our findings that being separated or divorced and being deprived in the sense of a lower socioeconomic status contribute to mortality in AN. Thus, future research could investigate whether specific therapies influence the occurrence of additional psychiatric symptoms and risk factors in a favourable or in an unfavourable way.

We can assume a widespread use of medications such as olanzapine during inpatient treatment for AN (for example [65]). Moreover, most patient with AN want and request medication to help with anxiety, sleep problems and pain [66, 67]. However, there is almost no evidence for the effects of pharmacological treatment in AN due to a lack of randomized controlled trials [68] apart from a few studies with promising results such as [69]. The effect of psychopharmacological treatment on mortality is also unknown in AN. Due to potential side effects such as electrolyte imbalances and abnormalities of the heart rhythm [70], mortality might even increase in patients with AN during treatment with these medications.

Taken together, potential future research directions to further explore and complement the findings of the present study include the investigation of the specific causes of death, physical risk factors of mortality in patients with AN and the effects of psychotherapeutic, nutritional and psychopharmacological therapies on mortality.

Author contributions HH, MH, UD, JT, RDH, RS and CKC designed the study. HH, MH, HS, RDH, RS and CKC contributed to the statistical analysis; HH and CKC drafted the manuscript; all authors contributed to the interpretation of the results, revised the first draft of the manuscript and approved its final version.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest relevant to this paper.

References

1. American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, Fifth edn. APA Publishing, Arlington
2. Darby A, Hay P, Mond J, Quirk F, Buttner P, Kennedy L (2009) The rising prevalence of comorbid obesity and eating disorder behaviors from 1995 to 2005. Int J Eat Disord 42:104–108

3. Smink FR, van Hoeken D, Hoek HW (2013) Epidemiology, course, and outcome of eating disorders. Curr Opin Psychiatry 26:543–548
4. Schmidt U, Adan R, Böhm I, Campbell IC, Dingemans A, Ehrlich S, Elzakkers I, Favaro A, Giel K, Harrison A, Himmerich H, Hoek HW, Herpertz-Dahlmann B, Kas MJ, Seitz J, Smeets P, Sternheim L, Tenconi E, van Elburg A, van Furth E, Zipfel S (2016) Eating disorders: the big issue. Lancet Psychiatry 3:313–315
5. Keski-Rahkonen A, Mustelin L (2016) Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. Curr Opin Psychiatry 29:340–345
6. Javaras KN, Runfola CD, Thornton LM, Agerbo E, Birgegård A, Norring C, Yao S, Råstam M, Larsson H, Lichtenstein P, Bulik CM (2015) Sex- and age-specific incidence of healthcare-register-recorded eating disorders in the complete Swedish 1979–2001 birth cohort. Int J Eat Disord 48:1070–1081
7. Himmerich H, Schönknecht P, Heitmann S, Sheldrick AJ (2010) Laboratory parameters and appetite regulators in patients with anorexia nervosa. J Psychiatr Pract 16:82–92
8. Sachs KV, Harnke B, Mehler PS, Krantz MJ (2016) Cardiovascular complications of anorexia nervosa: a systematic review. Int J Eat Disord 49:238–248
9. Steinhausen HC (2002) The outcome of anorexia nervosa in the 20th century. Am J Psychiatry 159:1284–1293
10. Zerwas S, Larsen JT, Petersen L, Thornton LM, Mortensen PB, Bulik CM (2015) The incidence of eating disorders in a Danish register study: associations with suicide risk and mortality. J Psychiatr Res 65:16–22
11. Root TL, Pisetsky EM, Thornton L, Lichtenstein P, Pedersen NL, Bulik CM (2010) Patterns of co-morbidity of eating disorders and substance use in Swedish females. Psychol Med 40:105–115
12. Ulfvebrand S, Birgegård A, Norring C, Högdahl L, von Hausswolff-Juhlin Y (2015) Psychiatric comorbidity in women and men with eating disorders results from a large clinical database. Psychiatry Res 230:294
13. Miniati M, Benvenuti A, Bologna E, Maglio A, Cotugno B, Massimetti G, Calugi S, Mauri M, Dell'Osso L (2018) Mood spectrum comorbidity in patients with anorexia and bulimia nervosa. Eat Weight Disord 23:305–311
14. Link TM, Beermann U, Mestel R, Gander M (2017) Treatment outcome in female in-patients with anorexia nervosa and comorbid personality disorders prevalence—therapy drop out and weight gain. Psychother Psychosom Med Psychol 67:420–430
15. Whitfield JB, Heath AC, Madden PAF, Landers JG, Martin NG (2017) Effects of high alcohol intake, alcohol-related symptoms and smoking on mortality. Addiction 113:158–166
16. Willmore J, Marko TL, Taing D, Sampasa-Kanyinga H (2017) The burden of alcohol-related morbidity and mortality in Ottawa, Canada. PLoS One 12:e0185457
17. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, McLaren J (2011) Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction 106:32–51
18. Ho CSH, Jin A, Nyunt MS, Feng L, Ng TP (2016) Mortality rates in major and subthreshold depression: 10-year follow-up of a Singaporean population cohort of older adults. Postgrad Med 128:642–647
19. Cailhol L, Pelletier É, Rochette L, Laporte L, David P, Villeneuve É, Paris J, Lesage A (2017) Prevalence, mortality, and health care use among patients with cluster b personality disorders clinically diagnosed in quebec: a provincial cohort study, 2001–2012. Can J Psychiatry 62:336–342
20. Kask J, Ekselius L, Brandt L, Kollia N, Ekbom A, Papadopoulos FC (2016) Mortality in women with Anorexia Nervosa: the role of comorbid psychiatric disorders. Psychosom Med 78:910–919
21. Fichter MM, Quadflieg N (2016) Mortality in eating disorders—results of a large prospective clinical longitudinal study. Int J Eat Disord 49:391–401
22. Grigoriev P, Jasilionis D, Stumbrys D, Stankūnienė V, Shkolnikov VM (2017) Individual- and area-level characteristics associated with alcohol-related mortality among adult Lithuanian males: a multilevel analysis based on census-linked data. PLoS One 12:e0181622
23. Lung FW, Liao SC, Wu CY, Lee MB (2017) The effectiveness of suicide prevention programmes: urban and gender disparity in age-specific suicide rates in a Taiwanese population. Public Health 147:136–143
24. Malgaroli M, Galatzer-Levy IR, Bonanno GA (2017) Heterogeneity in trajectories of depression in response to divorce is associated with differential risk for mortality. Clin Psychol Sci 5:843–850
25. Pan YJ, Yeh LL, Chen YC, Kuo KH, Chang CK (2016) Hospital treatment, mortality and healthcare costs in relation to socioeconomic status among people with bipolar affective disorder. BJPsych Open 2:10–17
26. Pikala M, Maniecka-Bryła I (2017) Socioeconomic inequalities in mortality due to all causes in the working age population of Poland in 2002 and 2011. Med Pr 68:771–778
27. Suokas JT, Suvisaari JM, Gissler M, Löfman R, Linna MS, Raevuori A, Haukka J (2013) Mortality in eating disorders: a follow-up study of adult eating disorder patients treated in tertiary care, 1995–2010. Psychiatry Res 210:1101–1106
28. Khashram M, Pitama S, Williman JA, Jones GT, Roake J (2017) Survival disparity following abdominal aortic aneurysm repair highlights inequality in ethnic and socio-economic status. Eur J Vasc Endovasc Surg 54:689–696
29. Stringhini S, Zaninotto P, Kumari M, Kivimäki M, Lassale C, Batty GD (2018) Socio-economic trajectories and cardiovascular disease mortality in older people: the English Longitudinal Study of Ageing. Int J Epidemiol 47:36–46
30. Tabue Teguo M, Simo-Tabue N, Stoykova R, Meillon C, Cogne M, Amiéva H, Dartigues JF (2016) Feelings of loneliness and living alone as predictors of mortality in the elderly: the PAQUID Study. Psychosom Med 78:904–909
31. Kask J, Ramklint M, Kolia N, Panagiotakos D, Ekbom A, Ekselius L, Papadopoulos FC (2017) Anorexia nervosa in males: excess mortality and psychiatric co-morbidity in 609 Swedish in-patients. Psychol Med 47:1489–1499
32. Zayed M, Garry JP (2017) Geriatric Anorexia Nervosa. J Am Board Fam Med 30:666–669
33. Micali N, Martini MG, Thomas JJ, Eddy KT, Kothari R, Russell E, Bulik CM, Treasure J (2017) Lifetime and 12-month prevalence of eating disorders amongst women in mid-life: a population-based study of diagnoses and risk factors. BMC Med 15:12
34. Walker ER, McGee RE, Druss BG (2015) Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 72:334–341
35. Starace F, Mungai F, Baccari F, Galeazzi GM (2018) Excess mortality in people with mental illness: findings from a Northern Italy psychiatric case register. Soc Psychiatry Psychiatr Epidemiol 53:249–257
36. Chang CK, Hayes RD, Broadbent M, Fernandes AC, Lee W, Hotopf M, Stewart R (2010) All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. BMC Psychiatry 10:77
37. Leinonen T, Martikainen P, Laaksonen M, Lahelma E (2014) Excess mortality after disability retirement due to mental disorders: variations by socio-demographic factors and causes of death. Soc Psychiatry Psychiatr Epidemiol 49:639–649

38. De Hert M, Detraux J, Vancampfort D (2018) The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci 20:31–40
39. Perera G, Broadbent M, Callard F, Chang CK, Downs J, Dutta R, Fernandes A, Hayes RD, Henderson M, Jackson R, Jewell A, Kadra G, Little R, Pritchard M, Shetty H, Tulloch A, Stewart R (2016) Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. BMJ Open 6:e008721
40. Stewart R, Soremekun M, Perera G, Broadbent M, Callard F, Denis M, Hotopf M, Thornicroft G, Lovestone S (2009) The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 9:51
41. World Health Organization (2000) Manual of the international statistical classification of diseases and related health problems. WHO, Geneva 10 revision (ICD-10)
42. Chang CK, Hayes RD, Broadbent MT, Hotopf M, Davies E, Møller H, Stewart R (2014) A cohort study on mental disorders, stage of cancer at diagnosis and subsequent survival. BMJ Open 4:e004295
43. Hayes RD, Downs J, Chang CK, Jackson RG, Shetty H, Broadbent M, Hotopf M, Stewart R (2015) The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. Schizophr Bull 41:644–655
44. Su YP, Chang CK, Hayes RD, Perera G, Broadbent M, To D, Hotopf M, Stewart R (2014) Mini-mental state examination as a predictor of mortality among older people referred to secondary mental healthcare. PLoS One 9:e105312
45. Keshaviah A, Edkins K, Hastings ER, Krishna M, Franko DL, Herzog DB, Thomas JJ, Murray HB, Eddy KT (2014) Re-examining premature mortality in anorexia nervosa: a meta-analysis redux. Compr Psychiatry 55:1773–1784
46. Franko DL, Keshaviah A, Eddy KT, Krishna M, Davis MC, Keel PK, Herzog DB (2013) A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. Am J Psychiatry 170:917–925
47. Vasilenko SA, Evans-Polce RJ, Lanza ST (2017) Age trends in rates of substance use disorders across ages 18–90: Differences by gender and race/ethnicity. Drug Alcohol Depend 180:260–264
48. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T (2010) The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PLoS One 10:e0116820
49. Gaudiani JL, Brinton JT, Sabel AL, Rylander M, Catanach B, Mehler PS (2016) Medical outcomes for adults hospitalized with severe anorexia nervosa: an analysis by age group. Int J Eat Disord 49:378–385
50. Solmi F, Hotopf M, Hatch SL, Treasure J, Micali N (2016) Eating disorders in a multi-ethnic inner-city UK sample: prevalence, comorbidity and service use. Soc Psychiatry Psychiatr Epidemiol 51:369–381
51. Marques L, Alegria M, Becker AE, Chen CN, Fang A, Chosak A, Diniz JB (2011) Comparative prevalence, correlates of impairment, and service utilization for eating disorders across US ethnic groups: Implications for reducing ethnic disparities in health care access for eating disorders. Int J Eat Disord 44:412–420
52. Office for National Statistics (2012) Ethnicity and National Identity in England and Wales: 2011. Retrieved August 17, 2018 from https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11
53. Waller G, Micali N, James A (2014) General Practitioners are poor at identifying the eating disorders. Adv Eat Disord 2:146–157
54. National Collaborating Centre for Mental Health (2004) Eating disorders: core interventions in the treatment and management of Anorexia Nervosa, Bulimia Nervosa and related eating disorders. National Institute for Health and Care Excellence, UK
55. National Guideline Alliance (2017) Eating disorders: recognition and treatment. National Institute for Health and Care Excellence, UK
56. Martinussen M, Friborg O, Schmierer P, Kaiser S, Øvergård KT, Neunhoeffer AL, Martinsen EW, Rosenvinge JH (2017) The comorbidity of personality disorders in eating disorders: a meta-analysis. Eat Weight Disord 22:201–209
57. Root TL, Pinheiro AP, Thornton L, Strober M, Fernandez-Aranda F, Brandt H, Crawford S, Fichter MM, Halmi KA, Johnson C, Kaplan AS, Klump KL, La Via M, Mitchell J, Woodside DB, Rotondo A, Berrettini WH, Kaye WH, Bulik CM (2010) Substance use disorders in women with anorexia nervosa. Int J Eat Disord 43:14–21
58. Burns T, Crisp AH (1985) Factors affecting prognosis in male anorexics. J Psychiatr Res 19:323–328
59. Gueguen J, Godart N, Chambry J, Brun-Eberentz A, Foulon C, Divac SM, Guelfi JD, Rouillon F, Falissard B, Huas C (2012) Severe anorexia nervosa in men: comparison with severe AN in women and analysis of mortality. Int J Eat Disord 45:537–545
60. Papadopoulos FC, Ekbom A, Brandt L, Ekselius L (2009) Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br J Psychiatry 194:10–17
61. Herpertz-Dahlmann B, van Elburg A, Castro-Fornieles J, Schmidt U (2015) ESCAP Expert Paper: new developments in the diagnosis and treatment of adolescent anorexia nervosa – a European perspective. Eur Child Adolesc Psychiatry 24:1153–1167
62. Garber AK, Sawyer SM, Golden NH, Guarda AS, Katzman DK, Kohn MR, Le Grange D, Madden S, Whitelaw M, Redgrave GW (2016) A systematic review of approaches to refeeding in patients with anorexia nervosa. Int J Eat Disord 49:293–310
63. Linden M, Schermuly-Haupt ML (2014) Definition, assessment and rate of psychotherapy side effects. World Psychiatry 13:306–309
64. Nomura T (2015) Side effects of rogerian psychotherapy and counseling. Seishin Shinkeigaku Zasshi 117:452–456
65. Himmerich H, Au K, Dornik J, Bentley J, Schmidt U, Treasure J (2017) Olanzapine treatment for patients with Anorexia Nervosa. Can J Psychiatry 62:506–507
66. Himmerich H, Joaquim M, Bentley J, Kan C, Dornik J, Treasure J, Schmidt U (2017) Psychopharmacological options for adult patients with anorexia nervosa: the patients' and carers' perspectives. CNS Spectr, Cambridge
67. Tyrrell-Bunge E, de Carvalho AF, Scott C, Tomlin S, Treasure J, Himmerich H (2018) A three level-intervention to reduce PRN medication on a specialist eating disorders ward for adult female patients with anorexia nervosa. Psychiatr Danub 30:107–108
68. Himmerich H, Treasure J (2018) Psychopharmacological advances in eating disorders. Expert Rev Clin Pharmacol 11:95–108
69. Attia E, Kaplan AS, Walsh BT, Gershkovich M, Yilmaz Z, Musante D, Wang Y (2011) Olanzapine versus placebo for outpatients with anorexia nervosa. Psychol Med 41:2177–2182
70. Orsolini L, Tomasetti C, Valchera A, Vecchiotti R, Matarazzo I, Vellante F, Iasevoli F, Buonaguro EF, Fornaro M, Fiengo AL, Martinotti G, Mazza M, Perna G, Carano A, De Bartolomeis A, Di Giannantonio M, De Berardis D (2016) An update of safety of clinically used atypical antipsychotics. Expert Opin Drug Saf 15:1329–1347