Relapse in anorexia nervosa: a systematic review and meta-analysis

Tamara Berends[a], *Nynke Boonstra*[b], *and Annemarie van Elburg*[a,c,d]

Purpose of review
Relapse is common in patients with anorexia nervosa. The aim of this study is to systematically review the existing literature on relapse in anorexia nervosa.

Recent findings
A systematic literature search was conducted in PubMed, PsychInfo and CINAHL published up to April 2018. Of the 1527 studies screened, 16 studies were included in the present review.

Summary
This analysis shows that, of the patients included in this review, 31% relapsed after treatment. The highest risk of relapse is during the first year after discharge and this risk continues for up to 2 years. An overview was made of all factors significantly associated with a higher risk of relapse, resulting in the following four clusters: eating disorder variables, comorbidity symptoms, process treatment variables and demographic variables. Future research on relapse prevention is necessary to further unravel the mechanisms that might lead to relapse.

Keywords
anorexia nervosa, predictors, rate, relapse, risk factors, timing

INTRODUCTION

Anorexia nervosa is a severe mental disorder with a lifetime prevalence among women of 2–4% [1], whereas the prevalence among men is 10 times lower [2]. High mortality rates of 5% are reported [3]. The overall incidence rate has remained stable over the past decades (i.e. 6.0 per 100 000 population), and the age-specific incidence is highest in the age group 15–19 years [4]. It is estimated that 46% of the patients completely recover from anorexia nervosa, 34% improve partially with residual symptoms of anorexia nervosa and 20% develop a chronic course of the disorder [5].

Evidence-based clinical guidelines represent an important step towards dissemination and implementations of evidence-based treatments into clinical practice. Despite advances in clinical research on eating disorders, a growing body of literature demonstrates that individuals with eating disorders often do not receive an evidence-based treatment for their disorder [6▪]. In leading guidelines in the field of eating disorders [7▪,8,9▪], consensus exists that relapse of an eating disorder is a common phenomenon and relapse prevention is essential. However, a major problem is the lack of structured methods for relapse prevention to support professionals in clinical practice. Thus, there is a need for the development of sound, scientifically based interventions that contribute to relapse prevention in this patient group.

In a 2017 review on relapse, remission and recovery in anorexia nervosa, Khalsa *et al.* [10▪▪] provided a summary of the different definitions used and concluded that there is limited consensus about these definitions [11▪]. They proposed a set of standardized criteria for relapse, recovery and remission for anorexia nervosa, which is internally consistent and can facilitate longitudinal assessment by clinicians and researchers. Apart from the required use of unambiguous definitions, future intervention programmes on relapse prevention should be based

[a]Altrecht Eating Disorders Rintveld, Zeist, [b]NHL Stenden University of Applied Science, Research Group Care and Innovation in Psychiatry, Leeuwarden, [c]Utrecht Research Group Eating Disorders and [d]Department of Social Sciences, Utrecht University, Utrecht, The Netherlands

Correspondence to Tamara Berends, RN/MSc, Wenshoek 4, 3705 WE Zeist, The Netherlands. Tel: +31 6 18879895; e-mail: t.berends@altrecht.nl

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KEY POINTS

- The overall estimated rate of relapse in anorexia nervosa is 31%, irrespective of age.
- As relapse in anorexia nervosa occurs mainly in the first year and up to 2 years posttreatment, relapse prevention interventions during this period are essential.
- Factors associated with relapse can be divided into four main clusters: eating disorder factors, comorbid factors, treatment factors and demographic factors.
- Definitions of remission, recovery and relapse for anorexia nervosa should be unified as proposed by Khalsa *et al*.
- The Guideline 'Relapse Prevention Anorexia Nervosa' provides a structured method for relapse prevention.

on existing scientific evidence, in particular with respect to rates of relapse (in different subpopulations), timing of relapse and factors associated with relapse. With this knowledge, preventive strategies can be deployed at the right time and after appropriate treatment duration, with a focus on high-risk patient groups.

The present study aims to review the available scientific evidence on these topics, that is relapse rate, timing and factors associated with relapse in anorexia nervosa. This overview of knowledge can form the basis for the development and testing of future relapse prevention programmes for patients with anorexia nervosa, and, thereby, contribute to better recovery and improved quality of life in patients treated for anorexia nervosa.

MATERIALS AND METHODS

Literature search

This systematic review using the PRISMA guidelines was conducted in 2016 and updated in March 2018 to include latest published articles. Relevant articles were identified through a search in the following electronic databases of PubMed, PsychINFO and CINAHL, which was performed in close collaboration with an experienced librarian. Databases were searched combining the terms 'Anorexia Nervosa' with 'Relapse', as well as their relevant synonyms.

Data extractions and quality assessment

Figure 1 presents the selection procedure. English language articles focusing on anorexia nervosa with relapse as a primary outcome, measured using a clear definition, were considered for inclusion. After removing duplicates, the remaining articles were screened independently by two researchers based on title and abstract. Any disagreement between the reviewers was resolved through discussion. All disagreements were related to the decision as to whether the inclusion criteria were applicable. For example, an article based on outcome mentioned relapse but did not present a clear definition of relapse. In such cases, the first author (TB) read the full text, after which follow-up discussion took place until consensus was reached. Papers fulfilling the inclusion criteria were considered for full-text review.

Excluded from this review were studies with a sample size, n less than 40, studies combining patients with anorexia nervosa and bulimia nervosa, and studies using the same/duplicate study sample. The remaining studies were included in the qualitative analysis.

The standard quality assessment criteria for evaluating primary research articles from a variety of fields, as described by Kmet *et al*. [12], were used to assess the methodological quality of the individual articles, using a standardized approach.

Statistical analyses

Rate of relapse

Assuming that the estimates differed between populations in the different studies, as well as the definitions and instruments used, a random effects model was used for meta-analysis. A meta-regression was performed to examine the influence of the mean age of participants on event rate magnitude. When results are compared in a meta-analysis, ideally, the studies are uniform in their use of protocols. However, as this was not the case for the present meta-analysis, study heterogeneity was examined and reported using the Q and I^2 statistic [13]. The I^2 ranges from 0% (no observed heterogeneity) to 100% (high heterogeneity). Also, because publication bias can be a problem with meta-analyses, Egger's test was applied to identify such bias [14]. All analyses were conducted using comprehensive meta-analysis [15]. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity.

Factors associated with relapse

The factors associated with relapse were extracted from each study and the list of factors was categorized into specific clusters, independently, by two researchers. Finally, through discussion, consensus on the clusters was reached.

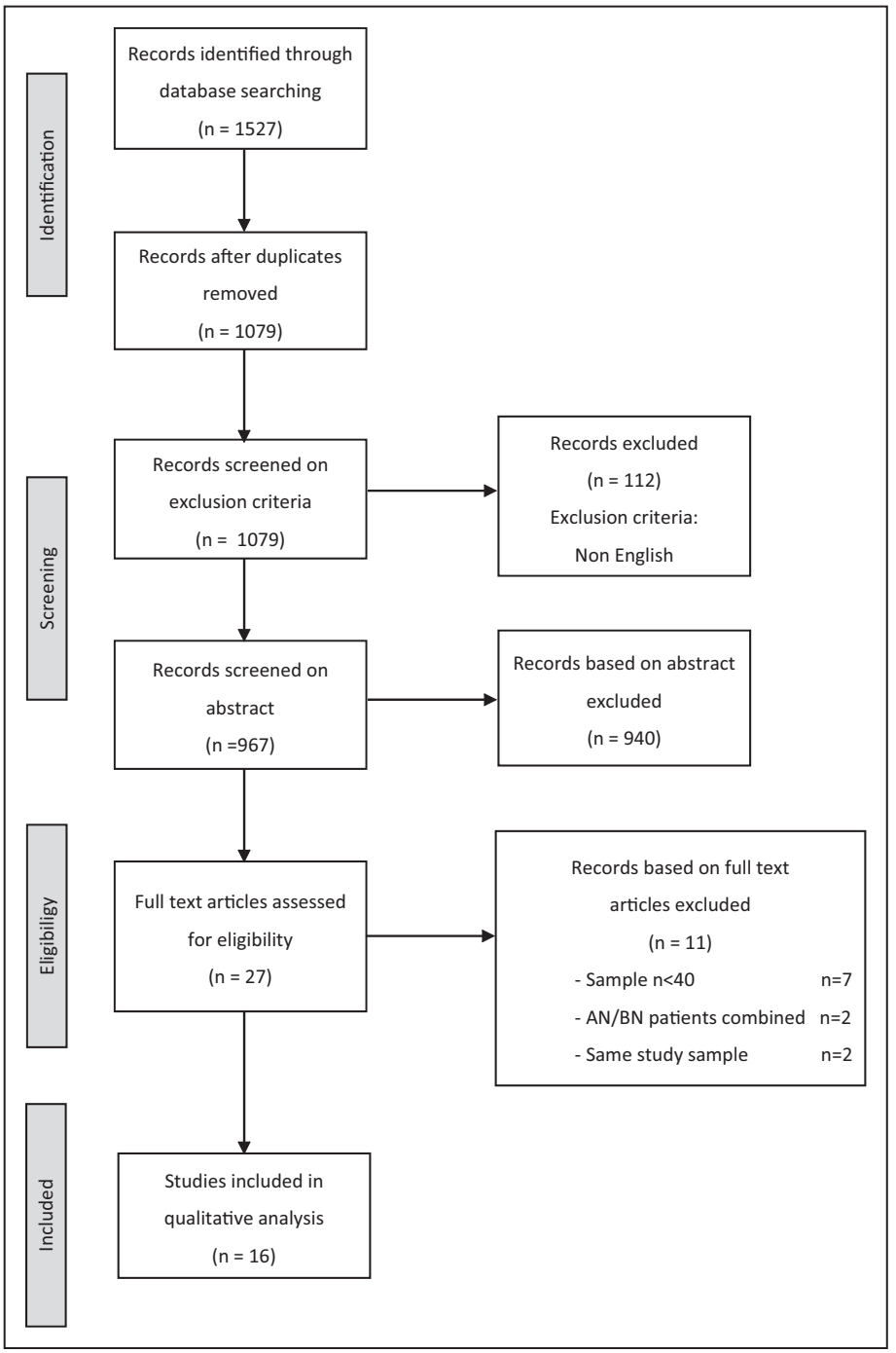

FIGURE 1. PRISMA flowchart, inclusion process.

RESULTS

The initial search yielded 1527 articles (Fig. 1); of these, 448 duplicates and 112 non-English language studies were excluded. After two independent reviewers had screened the remaining 967 abstracts, 27 articles remained after screening on title and abstract. After careful review, 16 articles [16▪,17▪,18–31] were included in the present qualitative analyses.

Sample

Sample characteristics of all included studies are presented in Table 1. All studies examined the rate of relapse in patients with anorexia nervosa and were included in the meta-analyses. Eight studies presented the period of occurrence of relapse and the period of the highest risk of relapse [17▪,18,19,22,26,27,29,30]; eight studies also presented the factors associated with relapse

Table 1. Overview of the included studies ($n = 16$)

Reference[a]	Study design	N[b]	Mean age (SD) in years	Mean follow-up duration (SD) in months	Definition of recovery	Definition of relapse	Relapse rate (n)	Relapse range in months	Highest-risk of relapse in months	Factors associated with relapse
Avnon *et al.* [16▪] ISR	Cohort study	44	14.9 (SD = 1.87)	12	Weight restoration; the patient is discharged from hospital when they attain their target weight set by a dietician	Rehospitalization after discharge. Exacerbation of eating disorder symptoms.	34% ($n = 15$)	1–12	N.R.	Weight restoration curves characterized by high negative cubic variation (NCV) rates, that is by sudden drops in weight, are associated with a greater risk for rehospitalization $P < 0.05$
Berends *et al.* [17▪] NLD	Cohort study	83	17.9 (SD = 4.45)	18 (SD = 4.39)	Participants had successfully completed their treatment, were weight restored with a normal (SD) BMI based on their age and height.	Full relapse: BMI <18.5 for adults, and SD BMI <-1 for adolescents, together with full recurrence of the core diagnostic symptoms of AN according to DSM-IV criteria. Partial relapse: the re-occurrence of one or more core diagnostic symptoms of AN, after a previous positive response to treatment (If during the partial relapse a longer intensification of 3 months of the program was needed it was classified as full relapse).	10.8% ($n = 9$) full relapse 19.3% ($n = 16$) partial relapse	1–18	4–16	Longer duration of treatment $P = 0.007$ Type of treatment (in- and outpatient higher risk vs. only outpatient) $P = 0.039$ Higher age $P = 0.034$
Carter *et al.* [18] CAN	Survival analysis	51	26.9 (SD = 9.0)	15.6 (SD = 4.5)	Participants that were weight restored to a BMI of at least 20.	If the participants' BMI dropped below 17.5 for a period of at least 3 consecutive months over the follow-up period or when binge eating and/or purging at least weekly for a 3-month period.	35% ($n = 18$)	4–17	6–17	History of suicide attempts $P = 0.028$ Previous specialized treatment for the eating disorder $P = 0.05$ Presence of higher washing compulsions on PI subscales post treatment $P = 0.038$ Presence of higher rumination posttreatment on PI subscales $P = 0.030$ Insufficient change in problem avoidance scores on the CSI from admission to discharge $P = 0.034$ High-level exercise during first 3 months after discharge $P = 0.027$
Carter *et al.* [19] CAN	Longitudinal prospective design	100	25.4 (SD = 7.7)	12	Participants who successfully completed the treatment programme. Weight restored to a BMI 20 for 2 weeks, not more than one binge-purge episode during 28 days at the end of treatment.	BMI ≤17.5 for 3 consecutive months or at least one episode of BP behaviour per week for 3 consecutive months during 1-year follow-up.	41% ($n = 41$)	2–12	4–9	BP subtype of AN $P = 0.001$ Presence of a history of childhood physical abuse at admission $P = 0.034$ Higher scores on EDE-Q eating concern at admission $P = 0.028$ Higher scores on PI Checking behaviour subscale at admission $P = 0.002$ Decrease in level of motivation from pre-treatment to 4 weeks $P = 0.010$ Pre–post increase on EDE-Q Shape Concern $P = 0.027$ Pre–post increase on EDE-Q Weight Concern $P = 0.048$ Pre–post decrease on the Rosenberg Self-Esteem Scale $P = 0.044$ Lower motivation to recover at discharge $P = 0.005$ Higher EDE fear of weight gain scores at discharge $P = 0.043$
Castellini *et al.* [20] ITA	Longitudinal prospective design	165	27.2 (SD = 9.1)	72	Participants were considered recovered when at T3 they did not fulfil the DSM-IV of DSM-5 criteria for any ED.	The return to a full syndromal or EDNOS criteria after a period of remission.	26% ($n = 43$)	N.R.	N.R.	N.R.

Table 1 (*Continued*)

Reference[a]	Study design	N[b]	Mean age (SD) in years	Mean follow-up duration (SD) in months	Definition of recovery	Definition of relapse	Relapse rate (*n*)	Relapse range in months	Highest-risk of relapse in months	Factors associated with relapse
Deter and Herzog[21] (DEU)	Longitudinal prospective design	84	20.7 (SD = 6.0)	142	Using the Morgan–Russel General Outcome Categories; poor, intermediate and good: Authors used the term improvement when a patient's condition was rated 'good' during one of the years after first presentation. The term permanent recovery when the patient was assessed as 'good' and remained so.	If the condition was 'good' and afterwards was again assessed as 'intermediate' or 'poor'	20% (*n* = 17)	N.R.	N.R.	N.R.
Eckert *et al.* [22] (USA)	Follow-up study	66	20.0 (SD = 5.2)	115	Weight within 15% of ideal weight, clinical menses and no significant disturbance in eating or weight control behaviour of body image disturbance.	First weight loss below normal (-15% of average body weight) at any time after the index hospitalisation.	55% (*n* = 34)	1–96	1–12	N.R.
Eddy *et al.* [23] (USA)	Longitudinal prospective design	136	20.8	96	Full recovery defined as the absence of symptomatology (PSR 1, 2) or presence of minimal symptomatology for at least 8 consecutive weeks. Partial recovery defined as a reduction of symptomatology (PSR 3, 4) to less than full criteria for a period of at least 8 consecutive weeks.	Relapse defined as the return of full criteria symptomatology (PSR = 5, 6) for at least 1 week following a period of full recovery.	57% (*n* = 78)	N.R.	N.R.	N.R.
van Elburg *et al.* [24] (NLD)	Controlled clinical trial, no randomization used	69	15.4	12	Recovery defined as a MROAS score: good and the sdBMI above -1 and the presence of a regular menstrual cycle.	Patients were considered relapsed when their MROAS score dropped from good to intermediate or poor, when the sdBMI dropped below -1 after initial recovery or discontinuation of a regular menstrual cycle.	17% (*n* = 12)	N.R.	N.R.	N.R.
Helverskov *et al.* [25] (DNK)	Naturalistic design	58	22 (SD = 6.5)	30	Full remission defined as the absence of all symptoms or the presence of only residual symptoms for at least 12 consecutive weeks (PSR 1, 2) Partial remission defined as a reduction of symptoms to a subdiagnostic level for at least 12 consecutive weeks (PSR 3)	(PSR 4 = EDNOS, PSR 5, 6 = full syndrome AN or BN)	19% (*n* = 11)	N.R.	N.R.	N.R.
Herzog *et al.* [26] (USA)	Longitudinal prospective design	136	24.8 (SD = 6.7)	90	Partial recovery defined as a reduction of symptoms to less than full criteria for at least 8 consecutive weeks (PSR 3, 4) Full recovery defined as the absence of symptoms or the presence of only residual symptoms for at least 8 consecutive weeks (PSR 1, 2)	Relapse defined as the return of full criteria symptoms (PSR of 5 or 6) for at least 8 weeks following a state of full recovery	40% (*n* = 18) of *n* = 46 (fully recovered AN patients)	1–47	1–23	There were no significant predictors of relapse from full recovery in the total sample.
Isager *et al.* [27] (DNK)	Historic-prospective naturalistic design	120	16.6	150	Only patients who experience remission during therapeutic contact are included in the analysis.	Relapse defined as when the patient, within a 1-year period, loses 15% or more of the weight acquired during the course of treatment. Using weight curves.	26% (*n* = 31)	0–168	1–12	Relapse was twice as high after short-term (less than a year) therapeutic contact as after longer contact (1 year or more). $P < 0.05$

Table 1 (*Continued*)

Reference[a]	Study design	N[b]	Mean age (SD) in years	Mean follow-up duration (SD) in months	Definition of recovery	Definition of relapse	Relapse rate (*n*)	Relapse range in months	Highest-risk of relapse in months	Factors associated with relapse
Keel *et al.* [28] (USA)	Longitudinal prospective design	42	Median age 20.7	103	Remission defined as having a period of 8 consecutive weeks in which no or minimal symptoms of the syndrome were present (Psychiatric Status Rating Scale score 1 or 2) MacArthur guidelines.	Relapse represented a return of full syndromal criteria after a period of remission for AN (Psychiatric Status Rating Scale score 5 or 6)	36% ($n=15$)	N.R.	N.R.	Misperception of body $P=0.0002$ Fear of gaining weight or becoming fat $P=0.006$ Worse psychosocial function $P<0.01$ Concern about weight or shape $P<0.02$ Global assessment of functioning Scale score $P<0.02$ Higher age $P<0.04$ Increased individual psychotherapy $P<0.04$
Richard *et al.* [29] (DEU)	Longitudinal prospective naturalistic design	135	24.8 (SD = 5.6)	30	Recovery and remission require a symptom-free status for a period of time (12 months recovery, 2 months full remission) Partial remission defined as a subclinical symptomatic status, where symptoms are less severe but have not improved enough for a symptom-free status.	Relapse defined as returning to full symptomatic status after partial or full remission.	33% ($n=44$)	1–20	1–7	Time (after end treatment) was related to rate of relapse, indicating a decrease in the risk of relapse with every month after end of treatment $P<0.05$ Low desired weight was associated with a higher risk of relapse $P<0.05$ Long duration of illness was associated with higher risk of relapse $P<0.05$ Low severity of eating disorder symptoms were associated with a higher risk of relapse (EDI) $P<0.05$ Additional psychiatric treatment $P<0.1$ Additional medical treatment. $P<0.05$ Specialization was identified as a risk factor, that is those patients treated in specialized hospitals showed a lower risk of relapse than those treated in other hospitals. $P<0.05$
Strober *et al.* [30] (USA)	Naturalistic, longitudinal prospective design	95	Range: 12–17 years, 11 months	129	Full recovery refers to patients who have been free of all criterion symptoms of anorexia nervosa for not less than 8 consecutive weeks. Partial recovery is used to denote the attainment of good outcome per Morgan and Russel criteria, for at least 8 consecutive weeks.	Postdischarge relapse: a drop in body weight to $\leq$ 85% of average, occurring prior to the point at which a patient meets criteria for partial recovery. Post-recovery relapse: when patients had a prospectively observed exacerbation of illness following either partial recovery or full recovery. For patients having a relapse following full recovery, the new illness was further categorized as subsyndromal if the patient had reappearance of psychological symptoms but remained at least 85% of average body weight, and syndromal if weight fell below this criterion.	29.5% ($n=28$)	1–58	1–12	Final outcome status (chronic course vs. partial or full recovery) was a significant predictor of earlier time to postdischarge relapse $P=0.027$
Walsh *et al.* [31] (USA) (CAN)	Randomized controlled trial	93	23 (SD = 4.6)	12	Successfully treated and BMI at least 19 and maintained for 2 weeks	BMI $\leq$ 16.5 for 2 consecutive weeks, severe medical complications, a risk for suicide or developed another severe psychiatric disorder requiring treatment.	28% $n=26$	N.R.	N.R.	N.R.

AN, anorexia nervosa; BP subtype, Binge Purge subtype; CSI, Coping Strategies Inventory; ED, eating disorder; EDE-Q, Eating Disorder Examination-Questionnaire; EDI, Eating Disorder Inventory; EDNOS, Eating Disorder Not Otherwise Specified; MROAS, Morgan and Russel Outcome Assessment Schedule; N.R., not reported; PI subscale, Padua Inventory subscale; PSR, Psychiatric Status Rating; sdBMI, standard deviation BMI.
[a]ISO codes of representative countries (International Organization for Standardization).
[b]*N* = Sample size, patients with anorexia nervosa.

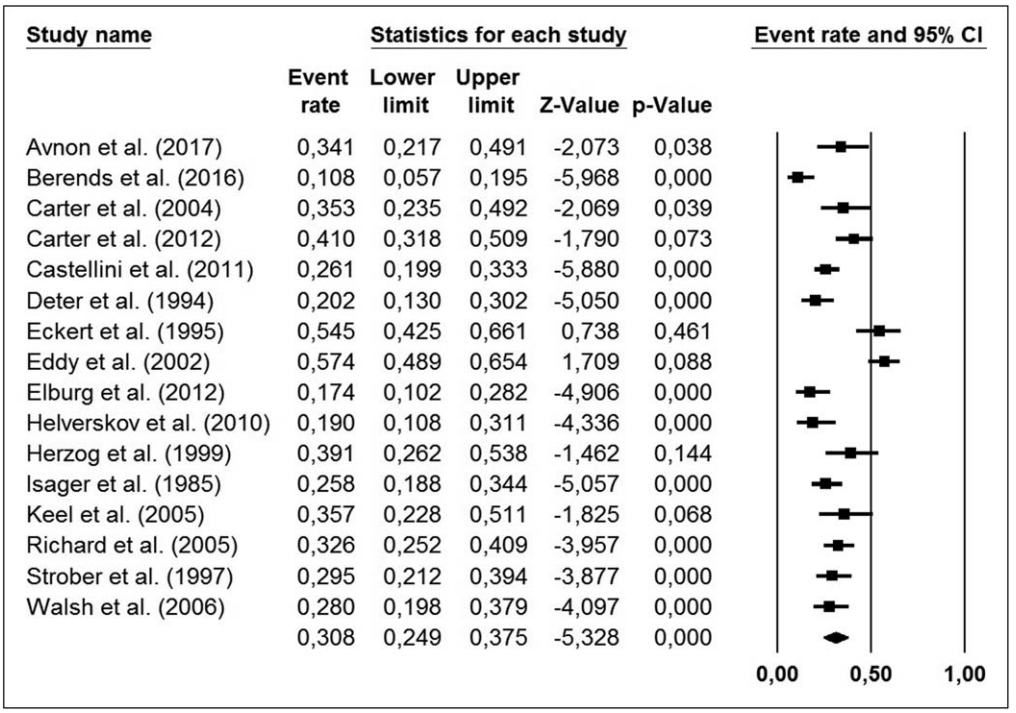

FIGURE 2. Forest plot of the meta-analysis of rate of relapse.

[17▪,18,19,21,27–30]. The (mean) age of all participants ranged from 15.4 to 26.9 years. Studies were conducted in the USA [22,23,26,28,30,31], Canada [18,19,31] Denmark [25,27], Germany [21,29], the Netherlands [17▪,24], Italy [20] and Israel [16▪].

Rate of relapse

Figure 2 is a forest plot of the meta-analysis. The summary statistic shows that the overall estimated event rate equals 30.8% [confidence interval (CI) 24.9–37.5%, $P < 0.001$]. There was considerable heterogeneity between the studies [$Q(15) = 92.15$, $P < 0.001$, $I^2 = 84\%$]. Meta regression shows that the mean age of participants had no influence on the magnitude of the event rate ($\beta = 0.02$, $P = 0.30$). For this analysis, the study of Strober *et al.* [30] was excluded because no mean age of participants was available. The Egger's test revealed a marginal indication of publication bias ($P = 0.097$). The nature of this bias is difficult to confirm because a relatively large proportion of the studies (i.e. six out of 16) fall outside the CI around the estimated effect, given the standard error on the ordinate axis. There seems to be a counterintuitive tendency for studies with low (logit) event rates to be published when there is low precision (or small sample size, indicated by a higher standard error), while higher (logit) event rates are more likely to be published when precision is higher.

Timing of relapse

Nine of the 16 studies reported the period of occurrence of relapse, with substantial variability in the duration of follow-up. Studies with a longer duration of follow-up, ranging from a (mean) follow-up of 30 to 265 months [22,26,27,29,30], reported an occurrence of relapse ranging from 1 to 168 months. Studies with a shorter duration of follow-up, ranging from a (mean) follow-up of 12 to 18 months, reported an occurrence of relapse ranging from 1 to 18 months [16▪,17▪,18,19]. However, in studies with both a shorter *and* longer follow-up, the highest risk of relapse was reported in the first year after discharge from treatment [19,22,27,29,30]; moreover, some studies reported a high risk of relapse through to the second year after discharge, that is at 16 [17▪], 17 [18] and 23 months [26].

Factors associated with relapse

Eight studies reported significant factors associated with relapse [16▪,17▪,18,19,27–30]. As there was substantial variability on the procedures and instruments used to identify factors associated with relapse, there was also substantial variability in the factors found, which complicates the present analysis. Factors significantly associated with relapse were selected and, after consensus was reached, divided into four main clusters (Table 2): eating disorder variables, comorbidity symptoms,

Table 2. Factors associated with relapse

Eating disorder variables	Measure moment/timing of risk	*P*	References
Increase on EDE-Q Shape Concern	Pre-posttreatment	0.027	Carter *et al.* [19]
Increase on EDE-Q Weight Concern	Pre-posttreatment	0.048	Carter *et al.* [19]
Concern about weight or shape	After remission	0.02	Keel *et al.* [28]
Fear of gaining weight or becoming fat	After remission	0.006	Keel *et al.* [28]
Higher EDE fear of weight gain scores	At discharge	0.043	Carter *et al.* [19]
Low desired weight	N.R.	<0.05	Richard *et al.* [29]
Misperception of body	After remission	0.0002	Keel *et al.* [28]
Higher scores on EDE-Q eating concern	At admission	0.028	Carter *et al.* [19]
Weight restoration curves characterised by high NCV, that is by sudden drops in weight	During treatment	<0.05	Avnon *et al.* [16▪]
BP subtype of AN	At admission	0.001	Carter *et al.* [19]
High-level exercise	During first 3 months after discharge	0.027	Carter *et al.* [18]
Low severity of eating disorder symptoms (EDI)	N.R.	<0.05	Richard *et al.* [29]
Comorbidity symptoms			
Higher scores on PI Checking behaviour subscale	At admission	0.002	Carter *et al.* [19]
Higher discharge scores on Washing compulsions (PI scale)	Posttreatment	0.038	Carter *et al.* [18]
Higher discharge scores on Rumination (PI scale)	Posttreatment	0.030	Carter *et al.* [18]
Insufficient change in problem avoidance scores (CSI)	Pre-posttreatment	0.034	Carter *et al.* [18]
Decrease in level of motivation	Pre-treatment to 4 weeks	0.010	Carter *et al.* [19]
Lower motivation to recover	At discharge	0.005	Carter *et al.* [19]
Decrease on the Rosenberg Self-Esteem Scale	Pre-posttreatment	0.044	Carter *et al.* [19]
Worse psychosocial function	After remission	0.01	Keel *et al.* [28]
History of childhood physical abuse	At admission	0.034	Carter *et al.* [19]
History of suicide attempts	At admission	0.028	Carter *et al.* [18]
Worse global assessment of functioning scale scores	After remission	0.02	Keel *et al.* [28]
Process treatment variables			
Longer duration of treatment	At start aftercare programme	0.007	Berends *et al.* [17▪]
Type of treatment (in- and outpatient higher risk vs. only outpatient)	Treatment process	0.039	Berends *et al.* [17▪]
Previous specialized treatment for eating disorder	At admission	0.05	Carter *et al.* [18]
Relapse twice as high after short-term (less than a year) therapeutic contact as after longer contact (1 year or more)	Treatment process	<0.05	Isager *et al.* [27]
Increased individual psychotherapy	After remission	0.04	Keel *et al.* [28]
Additional psychiatric treatment	During follow-up	<0.1	Richard *et al.* [29]
Additional medical treatment	During follow-up	<0.05	Richard *et al.* [29]
Treatment in a nonspecialized hospital	Treatment process	<0.05	Richard *et al.* [29]
Demographic variables			
Higher age	After remission	0.04	Keel *et al.* [28]
	At start aftercare programme	0.034	Berends *et al.* [17▪]
Long duration of illness	N.R.	<0.05	Richard *et al.* [29]
Final outcome status (chronic course vs. partial or full recovery)	Postdischarge	0.027	Strober *et al.* [30]

AN, anorexia nervosa; BP subtype, Binge Purge subtype; CSI, Coping Strategies Inventory, N.R., not reported; EDE-Q, Eating Disorder Examination-Questionnaire; EDI, Eating Disorder Inventory; NCV, negative cubic variation; PI subscale, Padua Inventory subscale.

process treatment variables and demographic variables.

DISCUSSION

This review summarizes the outcomes of 16 studies by examining the rate, timing and factors associated with relapse in anorexia nervosa.

Rate of relapse

Of all patients included in these studies, the overall estimated rate of relapse was 31%. This result was irrespective of the mean age of participants, implying that younger patients with anorexia nervosa are at the same risk of relapse as older patients. Although the definitions of recovery and relapse used in the studies were divergent, in all definitions, some similarities were present. For example, all studies defining recovery used weight restoration as a measuring point, with the lowest measuring point of weight within 15% of ideal body weight. Also, all studies used a decrease in weight to define relapse, with the measuring point a BMI less than 18.5 or −15% of average body weight. Nine studies included the recurrence of eating disorder symptoms in their definition of relapse [16▪,17▪,20,23,25,26,28–30].

Timing of relapse

The highest risk of relapse occurred during the first year after discharge; however, it appeared that this risk could continue for up to 2 years. During this period, patients should be guided and supported with a personalized relapse prevention strategy. Currently, the leading protocols for the treatment of anorexia nervosa are the Maudsley Model of Anorexia Treatment in Adults (MANTRA) [32], Specialist Supportive Clinical Management (SSCM) [33], Cognitive Behavioral Therapy-Enhanced (CBT-E) [34] and Family-Based Treatment (FBT) [35]. The MANTRA and the SSCM protocol have a 4-month follow-up, CBT-E has a 5-month follow-up and the last phase of the FBT protocol insists on three completing sessions during 3 months without any follow-up. Although all these protocols address the importance of relapse, their follow-up might be too short when considering the length of the period of highest risk of relapse, that is up to 2 years.

We support the recommendation of Khalsa *et al.* [10▪▪] to standardize definitions of relapse, remission and recovery, and suggest that relapse prevention strategies should already start with achieving partial remission: defined by Khalsa *et al.* [10▪▪] as BMI 18.5 or 85% ideal body weight, fear of gaining weight or disturbance in body image present, no restricting, binging or purging, scores on the Eating Disorder Examination (EDE) within 2 SD of normal and duration 1 month [10▪▪]. Patients should receive relapse prevention interventions for up to 2 years after discharge but, preferably, until achieving full recovery: defined by Khalsa *et al.* [10▪▪] as BMI more than 20 or 90% of ideal body weight, no significant fear of gaining weight or disturbance in body image, no restricting, binging or purging, EDE within 1 SD or normal, duration 12 months [10▪▪].

Factors associated with relapse

An overview is presented of all factors significantly associated with a higher risk of relapse, which led to the formation of the following clusters: eating disorder variables, comorbidity symptoms, process treatment variables and demographic variables. A limitation is that there was substantial variability in the factors associated with relapse, due to the different procedures and instruments used in the studies to identify predictors of relapse.

Within the cluster of eating disorder variables, those related to weight and shape concern were prominent because six of the 12 factors mentioned in this cluster referred to these topics. At all stages of treatment, these cognitive distortions should be targeted and, at the end of treatment, patients should be informed (by means of objective measurements) to what extent these variables might still be present. Khalsa *et al.* [10▪▪] suggest that the EDE [36] should be used to unambiguously determine the definitions of remission and recovery. In addition, the outcome of the EDE scores could be used in relapse prevention programmes to inform patients and to personalize relapse prevention plans.

Within the cluster of comorbidity variables, obsessions and compulsions were present; this makes patients with AN more susceptible to relapse. Teaching patients appropriate coping mechanisms, and how to deal with problems related to their self-esteem, psychosocial functioning and level of motivation, should also be important elements of treatment and relapse prevention programmes. The treatment variables, together with the demographic variables, show that patients needing a longer duration of treatment or more intensive treatment are at a higher risk of relapse, and older patients with a longer duration of illness are also at a higher risk of relapse.

As the range of factors associated with relapse is wide, extensive screening is required during treatment to determine the presence of relevant factors. With this knowledge, the relapse prevention plans can be personalized. We suggest that patients be consistently, but low frequently, monitored throughout the high-risk period after discharge.

Relapse prevention strategies

Overall, few relapse prevention strategies for anorexia nervosa have been extensively researched. Some strategies focus on relapse prevention during treatment: for example, internet-based relapse prevention by Fichter *et al*. [37], the use of Relapse Management Cards by Page *et al*. [38] and the Recovery Record application by Tregarthen and Argue (www.recoveryrecord.eu) [39]. The Guideline Relapse Prevention (GRP) developed by Berends *et al*. [40] focuses on relapse prevention at the end of treatment (www.relapse-an.com); this guideline provides a structured method to set up a personalized relapse prevention plan, focuses on self-management and provides a low-frequency checking system during at least 18 months up to 5 years. Patients and family members were generally satisfied with the support provided by the GRP, which contributed significantly to a better understanding of the personal process of relapse [41▪]. An earlier cohort study on working with the GRP found a relapse rate of 11% [17▪].

Future research

Additional research on relapse prevention is necessary to further unravel the mechanisms related to relapse. Preferably, these should be longitudinal studies with a follow-up of at least 24 months and including data on the rate of relapse using the definitions proposed by Khalsa *et al*. [10▪▪]. To identify factors of relapse, instruments used should include (at least) the four clusters identified here (i.e. eating disorder variables, comorbidity factors, process treatment variables and demographic variables) in order to develop a standardized prognostic model.

CONCLUSION

On the basis of 16 studies, this review shows that one-third of the patients with anorexia nervosa relapse. Because the greatest risk of relapse is within the first 2 years after discharge, personalized relapse prevention interventions should be applied during this period. A pattern emerged between the severity of the eating disorder and comorbid symptoms, and the level of risk of relapse. Moreover, as the risk of relapse increases with longer duration of illness and longer period of treatment, apart from good relapse prevention, early adequate treatment is required to improve the chance of recovery.

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Conflicts of interest

There are no conflicts of interest.

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This qualitative study explores by in-depth interviews how patients and their parents experience working with the guideline relapse prevention. It also describes the factors that support or hinder successful application of the guideline