



A systematic review of studies probing longitudinal associations between anxiety and anorexia nervosa



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ABSTRACT

The current study aimed to establish whether anxiety predicts subsequent anorexia nervosa onset and maintenance. A systematic review of longitudinal studies assessing the association between stable anxiety exposures (e.g. trait anxiety/anxiety disorder pathology) and anorexia nervosa development or maintenance was undertaken. Eight studies met inclusion criteria. Seven probed the association between anxiety and anorexia nervosa onset, and one assessed the association between anxiety and anorexia nervosa maintenance. Individuals with anorexia nervosa were more likely to report childhood anxiety compared to healthy individuals, but whether childhood anxiety explains unique variance in anorexia nervosa development is unclear. Current evidence does not support longitudinal associations between specific anxiety disorders (independently of other anxiety disorders) and subsequent anorexia nervosa onset, however anxiety disorder diagnosis in general may predict increased anorexia nervosa risk. The single study probing the association between anxiety and anorexia nervosa maintenance did not find evidence supporting a relationship. The quality of individual studies was fair to high, however the body of evidence was of low quality. Further research that minimises bias, allowing for strong conclusions concerning longitudinal associations between anxiety and subsequent anorexia nervosa outcomes, is required to inform anorexia nervosa aetiology. This in turn may promote improved prevention and treatment.

1. Introduction

Anorexia nervosa is an eating disorder characterised by persistent dietary restriction and an intense fear of weight gain despite maintenance of a low body weight (American Psychiatric Association; APA, 2013). The disorder has the highest mortality rate of any psychiatric disorder (Arcelus et al., 2011) and lasting and aversive implications on physical health (Mehler and Brown, 2015). Recovery rates of established treatments remain below 50% (Brockmeyer et al., 2018). While there is some evidence to support the efficacy of particular prevention interventions in asymptomatic populations, individuals already displaying symptoms of an eating disorder do not seem to benefit from existing programmes (Le et al., 2017; Watson et al., 2016). The scope for improved prevention and treatment is clear, however achievement of this remains complicated by uncertainty surrounding anorexia nervosa aetiology (Zipfel et al., 2015).

Existing interventions typically address eating disorder specific cognition (e.g. drives for thinness, heightened valuation of weight and shape) and/or eating behaviour (e.g. dietary restriction) that precede

and characterise anorexia nervosa (Jacobi et al., 2004). Augmenting existing interventions with modules that target other factors identified as playing a causal role in anorexia nervosa development and/or maintenance could be highly beneficial. Clinical observations support high levels of anxiety generally in individuals with anorexia nervosa. Subsequently, a number of theoretical accounts of anorexia nervosa propose anxiety *unrelated* to eating and weight-gain, from this point referred to as anxiety, to be causal in anorexia nervosa development. Specifically, it has been proposed that the restrictive eating, and focus on food intake and weight, that characterises anorexia nervosa may reduce anxiety in individuals who develop anorexia nervosa, encouraging continuation of dietary restriction, and to increasingly extreme degrees (e.g. (Haynos and Fruzzetti, 2011; Lloyd et al., 2017; Kaye, 2008; Nunn et al., 2012; Pallister and Waller, 2008)). The majority of anxiety disorders typically emerge in childhood and early adolescence (Bandelow and Michaelis, 2015; Lijster et al., 2017), while anorexia nervosa onset is most common during mid-late adolescence (Micali et al., 2013), consistent with the proposed causal role of anxiety in anorexia nervosa pathology.

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One implication of the hypothesis that anxiety causally influences anorexia nervosa pathology is that targeting anxiety in prevention and treatment efforts could be a promising avenue for improving the outcome of current interventions. Evidence for prevention interventions reducing negative affect (depressive and anxious symptomatology) is weak (Le et al., 2017). Whether existing treatment interventions improve anxiety is unclear since this is not typically reported (Kezelman et al., 2015). However, anxiety remains elevated upon recovery in anorexia nervosa (Holtkamp et al., 2005; Kaye et al., 2004), suggesting anxiety may not be sufficiently addressed within anorexia nervosa treatment.

There are few, if any, reported trials of adjunctive therapies designed specifically to reduce anxiety within the context of anorexia nervosa interventions. Without such data, observational studies allow for initial tests of the hypothesis that anxiety plays a causal role in the development and maintenance of anorexia nervosa. Associations between anxiety and anorexia nervosa are reliably reported in cross-sectional studies. Trait anxiety is greater in anorexia nervosa as compared to HC (e.g. (Schneier et al., 2016; Schulze et al., 2009)). Anxiety disorder pathology and the prevalence of anxiety disorder diagnoses are also elevated amongst individuals with anorexia nervosa as compared to HC (Kerr-Gaffney et al., 2018; Sternheim et al., 2015; Swinbourne and Touyz, 2007). Existing findings support a role for anxiety in anorexia nervosa maintenance as well. When studies have compared individuals who have recovered from anorexia nervosa to those who have not, anxiety and anxiety disorder pathology is elevated in the latter group (Kaye et al., 2004; Toner et al., 1988; Zerwas et al., 2013).

Correlation is not causation however, and alternative explanations for the pattern of findings summarised exist. Cross-sectional research is particularly vulnerable to bias by reverse causation, and it is possible the observed associations reflect that physical, psychological and social consequences of anorexia nervosa behaviour result in heightened anxiety. Longitudinal studies assess whether an exposure of interest (in this case anxiety) predicts the later occurrence of a given outcome (i.e. anorexia nervosa), to establish the temporal nature of association, thus allowing for stronger inferences concerning causality as compared to cross-sectional research. The current systematic review gathers longitudinal studies that have assessed whether stable anxiety phenotypes (i.e. trait anxiety and anxiety disorder pathology) predict subsequent anorexia nervosa onset or anorexia nervosa recovery. It is hoped that this process will help to outline the possible role of anxiety in anorexia nervosa, which may inform future research and clinical practice. The review is completed in accordance with a published protocol (see (Lloyd et al., 2018)).

2. Methods

2.1. Search strategy

Medline and PsychInfo were searched using the Ovid Interface and the search strategy detailed in Supplementary File 1 for studies published prior to 16th August 2018. The search strategy was developed by ECL following multiple preliminary searches. To capture all relevant studies, the strategy was amended (with search criteria broadened) from that detailed in the published protocol.

2.2. Eligibility criteria

The eligibility criteria for studies of the current review are detailed in Table 1.

Obsessive-compulsive disorder (OCD) and Posttraumatic stress disorder (PTSD) symptoms or diagnosis were not eligible exposures given OCD and PTSD are no longer classified as anxiety disorders (APA, 2013). Studies solely assessing associations between OCD/PTSD psychopathology and anorexia nervosa outcomes were therefore not included in the current review.

Additional inclusion/exclusion criteria varied according to whether studies were probing the role of anxiety in the development of, or recovery from, anorexia nervosa. Studies assessing the role of anxiety in anorexia nervosa onset must have included a healthy control group (i.e. alternative eating disorder or psychiatric control group was not sufficient), however this was not required for studies probing the role of anxiety in anorexia nervosa recovery. Studies assessing the role of anxiety in recovery from anorexia nervosa must have provided a definition of recovery to be eligible.

The application of timing criteria in risk factor studies assessing the role of anxiety in anorexia nervosa development was lenient. Included retrospective studies probed anxiety in the entire childhood period prior to anorexia nervosa symptom onset, potentially capturing anxiety in the year preceding anorexia nervosa onset. These studies were included since the purpose of our timing eligibility criteria was to mitigate bias due to reverse causality, and the studies each took steps to minimise this same bias while capturing anxiety that preceded anorexia nervosa (i.e. the exposure of interest).

2.3. Data collection

ECL and an independent reviewer separately screened the titles and abstracts of studies retrieved from database searches. Full texts of eligible studies were retrieved via institutional membership permissions, and independently screened by ECL and CF for inclusion in the review. An additional reviewer (BV) resolved discrepancies at both stages. References of eligible studies were screened to identify additional studies for inclusion in the review; no further studies were identified.

2.4. Data extraction and synthesis

Tailored data extraction forms were used to extract relevant information as per the study protocol (Lloyd et al., 2018), by two independent reviewers (ECL and AMH). All reported estimates of association were extracted, with the most adjusted estimate deemed the best one. Where data/study information of interest was missing, authors were contacted in attempts to retrieve it.

Studies were grouped according to whether they assessed the role of anxiety in anorexia nervosa onset or recovery, and according to the type of anxiety assessed (i.e. trait anxiety/anxious tendencies or anxiety disorder pathology). A qualitative synthesis of study findings was then completed.

2.5. Risk of bias and quality assessment

Risk of bias was assessed using the Newcastle Ottawa Scale (NOS; (Wells et al., 2001)) by two independent reviewers (ECL and AMH). Use of this quality assessment instrument reflects a diversion from the protocol (Lloyd et al., 2018), and is justified given the suitability of the NOS for both case-control and cohort studies. The scale assesses study quality across three domains. Studies may be awarded a single star for 'Selection' and 'Exposure/Outcome' items, and a maximum of two stars for 'Comparability'. The cohort study rating scale was modified slightly, with the follow-up interval item removed given review inclusion criteria specified an interval of one year between anxiety exposure and subsequent anorexia nervosa outcome assessment. As such, case-control studies could receive a maximum rating of nine stars, while cohort studies could achieve scores of up to eight stars.

To aid evaluation of the strength of the body of evidence included in the review, we provide a qualitative summary of the risk of bias, as well as finding inconsistency, across studies.

Table 1
Screening Criteria.

| Domain | Criteria |
|----------------------|--|
| Research question | Studies must have intended to evaluate the longitudinal association between anxiety and later anorexia nervosa onset or recovery |
| Design | Retrospective and prospective cohort and case-control studies |
| Participants | Human |
| Exposure | Individuals in anorexia nervosa sample must have met or have previously met full diagnostic criteria for anorexia nervosa Symptoms or diagnosis of any anxiety disorder (excluding OCD or PTSD) Trait anxiety/Anxious tendencies |
| Exposure measurement | Anxiety exposure must have been assessed with validated measure |
| Outcomes | Anorexia nervosa onset Anorexia nervosa recovery |
| Timing | The anorexia nervosa outcome is measured at least one year following the anxiety exposure |
| Language | English |
| Publication type | Article published in peer-reviewed journal |

OCD: Obsessive-compulsive disorder; PTSD: Posttraumatic stress disorder.

3. Results

3.1. Study selection

Following deduplication, 1921 studies were identified from literature searches, 215 of which were included in the full-text screen. Eight studies were subsequently deemed eligible for inclusion in the review. The screening process is detailed further in Fig. 1.

Seven studies assessed the longitudinal association between anxiety and anorexia nervosa onset, and only one study probed the association of anxiety with later recovery from anorexia nervosa. A number of studies considered anxiety within a cluster of more general psychological or psychiatric symptoms, for example probing associations between negative affect/psychiatric comorbidity and anorexia nervosa outcomes. These studies were excluded, since inclusion criteria specified that only investigations of the association between anxiety-specific exposures and anorexia nervosa were eligible. This inclusion criterion was applied to promote straightforward interpretation of the collection of evidence, however it is noted that this contributed to the small number of studies included in the present review. For the same reason of seeking to aid interpretation, of the studies probing associations between anxiety and anorexia nervosa maintenance only those that focused on recovery from anorexia nervosa were included. This decision also reduced the number of eligible studies given other outcomes (e.g. relapse, remission) have been studied to inform the relevance of particular exposures to anorexia nervosa maintenance.

3.2. Study characteristics

Details of the studies included in the present review are available in Table 2.

Of the seven studies probing the role of anxiety phenotypes in anorexia nervosa development, four considered childhood anxiety, and three considered anxiety disorder diagnoses. The single study probing the role of anxiety in anorexia nervosa recovery assessed the association between non-specific anxiety disorder symptoms, as opposed to particular anxiety disorder pathology, and anorexia nervosa.

Of the eight included studies, five detailed the best (fully adjusted) effect estimates for associations of interest, and these five studies all assessed the predictive effect of anxiety on anorexia nervosa development. Notably, one further study provided estimates for the unadjusted analysis assessing the association between anxiety and anorexia nervosa onset (Kim et al., 2011). Another study (Meier et al., 2015) provided estimates pertaining to the predictive effect of anxiety disorders present in the period prior to anorexia nervosa onset, including those anxiety disorders emerging in the year before anorexia nervosa onset. The study indicated that associations did not qualitatively differ when anxiety disorders diagnosed in the year prior to anorexia nervosa development were excluded from the analysis, but sensitivity analysis

estimates were not available.

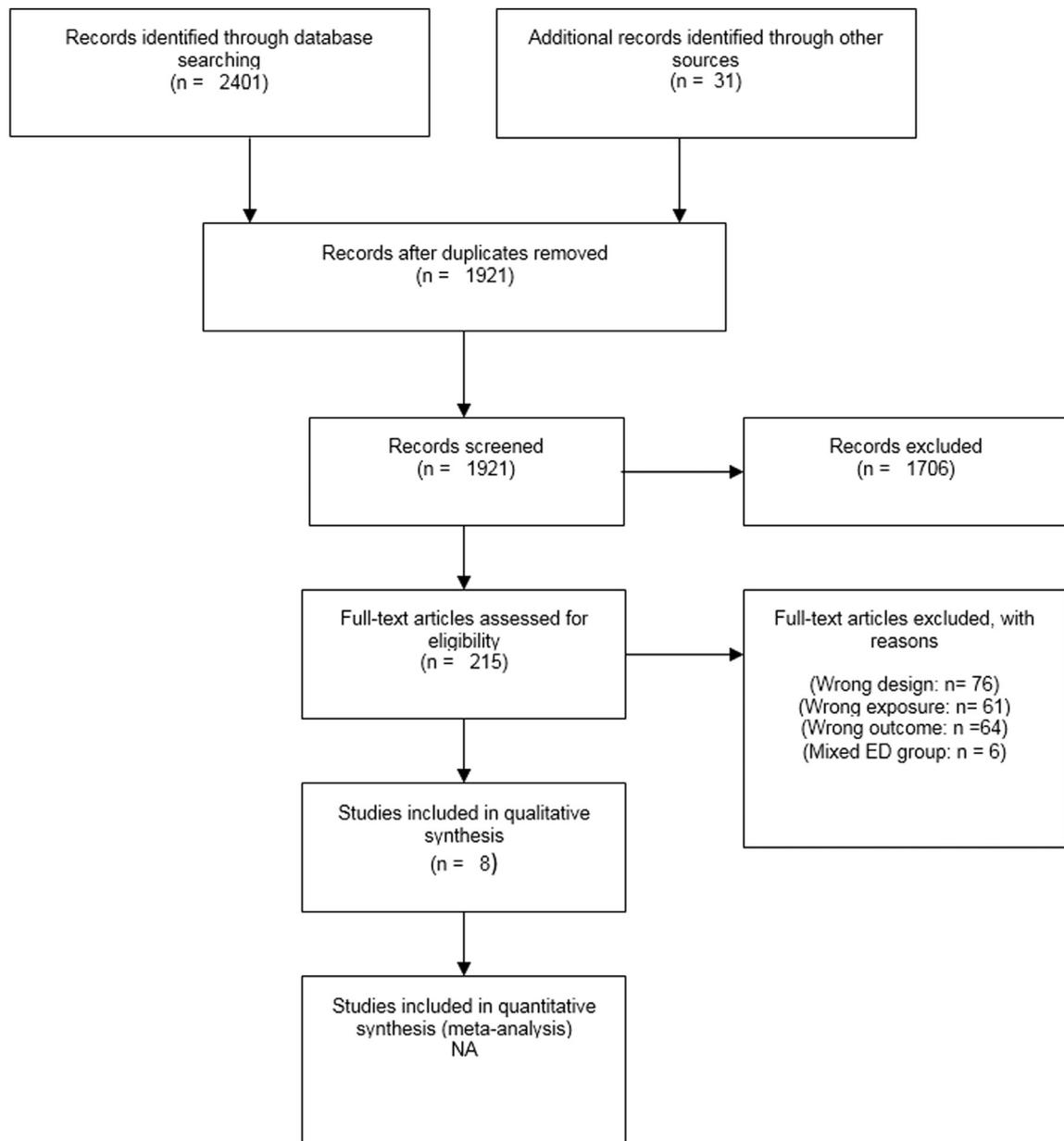
Ideally a meta-analysis would have been completed, however various issues (aside from missing data) prevented pooling effect estimates across studies. First, while all cohort studies treated anxiety as the independent variable and anorexia nervosa as the dependent variable, this was not the case for case-control studies. As such, available effect estimates are not even theoretically comparable across all studies. In addition, anxiety exposures differed markedly between studies and were measured on different scales, which makes meaningful interpretation of a pooled effect challenging.

3.3. Qualitative synthesis

3.3.1. Anxiety and anorexia nervosa development

3.3.1.1. Childhood anxiety. All studies assessing the role of childhood anxiety in anorexia nervosa development were of retrospective case-control design. Studies used diagnostic items from structured clinical interviews, either the Structured Clinical Interview for DSM-IV disorders (SCID) (First and Gibbon, 2004) or the Eating Disorder Examination (Cooper and Fairburn, 1987), to establish anorexia nervosa status. HC were excluded if they had experienced lifetime clinically significant eating disorder pathology. To address the research question of whether individuals with anorexia nervosa were more likely to be anxious during childhood than HC, all participants completed assessments developed to identify risk factors for anorexia nervosa onset. In two studies (Machado et al., 2016; Taborelli et al., 2013) a semi-structured interview, the Oxford Risk Factor Interview (Fairburn et al., 1998), was administered. The other two studies (Kim et al., 2010; Kim et al., 2011) assessed childhood experiences by way of a self-report questionnaire compiled by the authors. Both childhood risk factor measures are reported to have acceptable psychometric properties (Fairburn et al., 1997; Kim et al., 2011), however assessment of childhood anxiety generally consists of a single question. In all studies anorexia nervosa participants were asked explicitly to focus on the childhood period prior to emergence of their first anorexia nervosa symptom when responding to questions.

One study found that individuals with anorexia nervosa were more likely to experience separation anxiety than their healthy sisters, who comprised the control group (Taborelli et al., 2013). Two studies (Kim et al., 2010, 2011) may have included an overlapping sample; it was not possible to verify whether this was the case. Of these two studies, one reported greater childhood anxiety in anorexia nervosa individuals relative to HC – both in and outside of school (Kim et al., 2010). The other study (Kim et al., 2011) found evidence consistent with elevated childhood anxiety in individuals with anorexia nervosa, however anxiety was not independently associated with anorexia nervosa: the relationship disappeared when covariates (including interpersonal factors and visuo-perceptual ability) were added to the prediction model. The fourth study (Machado et al., 2016) observed an increased proportion



Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Fig. 1. PRISMA flow diagram to show study selection process.

of individuals with anorexia nervosa reporting childhood anxiety as compared to HC, while a reduced proportion of those with anorexia nervosa reported anxiety compared to a bulimia nervosa (BN) comparison group. There was no difference in the proportion of individuals with anorexia nervosa and individuals of a psychiatric control group (individuals with anxiety and depressive disorders) reporting childhood anxiety, and statistical analyses did not provide strong evidence for an association between childhood anxiety and group membership.

Across the collection of retrospective findings there is evidence to support individuals with anorexia nervosa being more likely to recall anxiety in childhood as compared to HC. However, whether childhood anxiety is able to explain unique variation in anorexia nervosa development is unclear from the existing body of research.

3.3.1.2. Anxiety disorders. All three studies assessing the predictive effect of anxiety disorders on anorexia nervosa onset were prospective

in design. One study assessed whether social anxiety disorder at age 15, measured using a validated self-report instrument, the 17-item Social Phobia Inventory (Connor et al., 2000), predicted lifetime anorexia nervosa two years later, and found no evidence to support an association (Ranta et al., 2017). Lifetime anorexia nervosa was assessed using a self-report questionnaire, and recorded if individuals reported an episode in which they had engaged in dieting behaviour, and experienced weight-concerns as well as amenorrhea during this episode. Notably a BMI criterion was not applied. A further cohort study (Buckner et al., 2010) assessed associations of panic disorder, overanxious disorder, separation anxiety disorder, simple phobia, and social phobia (measured at age 16), with lifetime anorexia nervosa at age 30. Lifetime anxiety disorders were assessed with epidemiologic (Orvaschel et al., 1982) and clinical versions of the Kiddie-Schedule for Affective Disorders and Schizophrenia. The anorexia nervosa outcome was determined using a combination of structured interviews: the

Table 2
Characteristics of Studies Included in the Review.

| Design | Study | Participants | Recruitment source | Age at anxiety assessment | Follow-up period | BMI at AN assessment Mean (SD) | Exposure (s) | Exposure measure | Outcome measure | Statistical Adjustment/ Matching | Finding | Best Estimate OR [95% CI] |
|---|------------------------|--|---|---|------------------|--------------------------------|---|------------------|----------------------------------|---|---|---|
| Studies assessing association between anxiety and anorexia nervosa onset (outcome = anorexia nervosa diagnosis) | | | | | | | | | | | | |
| Retrospective case-control | Kim et al., 2010 | 52 Korean AN | Specialist ED service | Childhood (prior to emergence of ED symptoms) | Childhood | 16.6 (2.7) | General anxiety (at school, outside of school and in total) | Childhood RFO | EDE and EDE-Q diagnostic items | Korean AN and HC matched on current age (analyses compare these two groups) | Childhood anxiety (all types) predicts AN | Anxiety at school: 2.1 [1.45,3.04] Anxiety outside of school: 2.07 [1.38,3.10] Total anxiety: 1.66 [1.31,2.10] |
| | Korea | Female 42 British AN | Eating Disorder Research Unit volunteer database | NA | NA | 17.8 (3.2) | | | | | | |
| | | Female 108 Koran HC | Community | | | 20.5 (2.4) | | | | | | |
| | Kim et al., 2011 | Female 22 AN (68% AN-R) | NR | Childhood (prior to emergence of ED symptoms) | Childhood | 15.6 (1.5) | General anxiety | Childhood RFO | SCID for DSM-IV (Korean version) | Participants matched on general intelligence and years of education. Analyses adjusted for childhood risk factors (parent attitudes to weight/shape, social support, perfectionism, eating behaviour), visuospatial ability | No association between anxiety and AN | NR |
| | Korea/UK | Female 28 BN Female 26 HC Female 98 AN (64.2% AN-R) | NA | 20.4 (2.7) 21.4 (2.8) | | | | | | | | |
| | Machado et al. 2015 | Female 79 BN | Specialist ED service | Childhood (prior to emergence of ED symptoms) | Childhood | 15.1 (1.6) | General anxiety | ORFI | EDE and EDE-Q | Participants matched on current age and SES | No association between anxiety and AN | 1.16 [0.41,3.28] |
| | Portugal | Female 68 Psychiatric Controls Female 86 HC | Specialist ED service Treatment setting | NA | NA | 21.2 (2.2) 21.0 (2.6) | | | | | | |
| | Taborelli et al., 2013 | Female 94 AN | Schools and universities Treatment centres and volunteer databases | Childhood (prior to emergence of ED symptoms) | Childhood | 18.4 (2.2) | Separation anxiety | ORFI | EDE diagnostic items | AN and HC participants (siblings) matched on gender and background factors | Childhood anxiety predicts AN | 9.00 [1.20,71.00] |

(continued on next page)

Table 2 (continued)

| Design | Study | Participants | Recruitment source | Age at anxiety assessment | Mean (SD) | BMI at AN assessment | Exposure (s) | Exposure measure | Outcome measure | Statistical Adjustment/ Matching | Finding | Best Estimate OR [95% CI] |
|--------------------|---------------------|----------------------|---------------------------------|------------------------------|-----------|---------------------------|----------------------------------|------------------|---|---|---|---------------------------|
| | Ranta et al., 2017 | 3278 | Regional high schools | Mean: 15.5 years (SD = 0.4)* | NR | NR | Social Phobia diagnosis (DSM-IV) | SPIN | Self-report questionnaire probing eating behaviour, weight concerns and amenorrhoea | Analyses adjusted for family relocation, parent unemployment, baseline depression (BDI scores), baseline AN | No association between social anxiety disorder and AN | 0.5 [0.10, 3.10] |
| | Finland | Mixed (56.4% female) | | 2 years | | | | | | | | |
| Design | Study | Participants | Recruitment source | Age at anxiety assessment | Mean (SD) | BMI at AN assessment | Exposure (s) | Exposure measure | Outcome measure | Statistical Adjustment/ Matching | Finding | Best Estimate OR [95% CI] |
| Prospective Cohort | Rigaud et al., 2011 | 484 AN (71.7% AN-R) | Specialist inpatient ED service | Mean: 22.8 years (SD = 4.4) | 13 years | 12.8 (1.6) at study onset | General anxiety | HAM-A | Questionnaire including items from EDE, EDI and Morgan-Russell outcome assessment | None | Anxiety does not predict recovery | NR |
| | France | Mixed (95.5% female) | | | | | | | | | | |

AN: anorexia nervosa; BDI: Beck Depression Inventory Short Version; BMI: body mass index; ED: eating disorder; EDE: Eating Disorder Examination; EDE-Q: Eating Disorder Examination Questionnaire version; EDI: Eating Disorder Inventory; HAM-A: Hamilton Rating Scale for Anxiety; K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; ORFI: Oxford Risk Factor Questionnaire; RFQ: Risk Factor Questionnaire; SCID: Structured Clinical Interview for DSM-IV; SES: socioeconomic status; SPIN: Social Phobia Inventory. Best estimate is the fully adjusted estimate of association.

Longitudinal Interval Follow-Up Evaluation (Keller et al., 1987), and the SCID for DSM-IV disorders (First and Gibbon, 2004) non-patient version. Analyses were adjusted for all other anxiety disorders, as well as depression and OCD. None of the anxiety disorders explained unique variance in subsequent anorexia nervosa onset. In both prospective cohort studies described the anorexia nervosa outcome was extremely rare.

A further study (Meier et al., 2015) completed in a childhood cohort adopted a population register linkage approach to identify all individuals who received specialist psychiatric treatment across a 23 year period. Generalized anxiety disorder (GAD) and social phobia diagnoses were associated with increased likelihood of later anorexia nervosa in analyses adjusted for a range of potential confounders including age, sex, and family psychiatric history. When hospital contact for other psychiatric disorders (not including anxiety/stress disorders or OCD) was added to statistical models, evidence for social phobia (though not GAD) predicting increased risk of anorexia nervosa remained. The presence of any anxiety disorder (or OCD/PTSD diagnosis) also predicted increased risk of subsequent anorexia nervosa diagnosis in adjusted analyses. There was no strong evidence to support a unique predictive effect of any single anxiety disorder when analyses were adjusted for hospital contact due to other anxiety disorders/PTSD/OCD.

The prospective studies do not provide evidence to support a specific anxiety disorder diagnosis predicting anorexia nervosa development independently of other anxiety disorders and OCD/PTSD. However, findings of one large study (Meier et al., 2015) suggest that the presence of any anxiety disorder (i.e. collapsing across diagnostic categories) predicts anorexia nervosa onset.

3.3.2. Anxiety and anorexia nervosa maintenance

The single study probing the association between anxiety and recovery from anorexia nervosa (Rigaud et al., 2011) found no evidence to support anxiety symptoms at the end of index hospitalization predicting recovery 13 years later. Participants fulfilled DSM-IV criteria for anorexia nervosa at the start of the study, and anxiety was assessed with the Hamilton Anxiety Scale (Hamilton, 1959). Recovery was assessed by way of self-report questionnaire, and defined by: maintenance of BMI between 18.5 and 25 kg/m²; absence of excessive exercise; and normal eating behaviour (i.e. regular and appropriate food intake, absence of fear of food/obsessive behaviour concerning eating or weight-monitoring, ability to eat with others). This study did observe relapse (a reduction of 1.5 BMI points in the context of a high drive for thinness) at the two-year follow-up to be more likely in individuals with high levels of anxiety at the end of hospitalisation.

Evidence from a single study is not consistent with anxiety symptoms predicting recovery from anorexia nervosa. However, whether this finding is robust is unclear, as is whether different types of anxiety show different associations with anorexia nervosa recovery.

3.4. Quality assessment

Outcomes of the study quality assessment are detailed fully in Supplementary File 2. The quality of individual studies ranged from fair to high, and each of the studies adopted methods designed to minimise bias. Cohort studies generally obtained higher scores, and these studies typically included representative populations, used robust methods to assess exposures and outcomes, and adjusted for various covariates in the analysis. Case-control studies used convenience sampling methods to recruit participants, and did not blind assessors to case status when evaluating whether the anxiety exposure was present. Although cases and controls were matched to some extent, this was fairly limited, which also contributed to the lower quality rating of case-control studies, as compared to those of cohort design.

The quality across the body of research was evaluated in the context of the scope of the review. That is, the collection of evidence was not downgraded for being observational in nature, given the particular aim

of aggregating longitudinal studies. Nonetheless, across included studies assessing the association between anxiety and anorexia nervosa onset, the quality was considered low. Retrospective studies are limited by their reliance on accurate recall, and resulting conclusions are invalidated when this assumption is violated. Furthermore, anxiety was generally assessed with a single question in retrospective studies, reducing the sensitivity and specificity of assessment. The prospective cohort studies were limited by the rarity of anxiety disorder exposures and anorexia nervosa outcome, which can inflate effect estimates as well as reduce sensitivity to a true association (Greenland et al., 2016; King and Zeng, 2001). While the record linkage study is not subject to this limitation, anxiety disorder and anorexia nervosa diagnoses were identified only when specialist psychiatric treatment was sought. This approach will have resulted in under identification of diagnoses (e.g. when psychiatric disorders were treated within general practice settings), with such measurement error introducing bias into estimates of association. The follow-up periods of prospective studies did not always encompass the entire period of peak anorexia nervosa onset (i.e. age 14–19 (Micali et al., 2013)), which will also have complicated the detection of true associations. Consistency across findings indicates a higher quality of the body of evidence (Guyatt et al., 2008), and was lacking – even when considering findings of prospective and case-control studies separately. That there was a single study assessing the role of anxiety in anorexia nervosa recovery suggests evidence concerning this outcome is weak.

4. Discussion

The purpose of this systematic review was to identify longitudinal studies probing the association of anxiety with either anorexia nervosa development or recovery. A small number of eligible studies were identified. Findings of retrospective case-control studies generally supported individuals with anorexia nervosa being more likely to report childhood anxiety than HC. Evidence from two prospective cohort studies and the single prospective population registry study did not support specific anxiety disorders explaining unique variation in anorexia nervosa risk. Findings of the population registry study did however support the presence of any anxiety disorder (i.e. pathology common across the anxiety disorders) predicting subsequent anorexia nervosa development. The high risk of bias, and inconsistency, across the collection of findings resulted in a weak body of evidence concerning the role of anxiety in anorexia nervosa onset. The single eligible study assessing the association between anxiety and later anorexia nervosa recovery did not produce evidence that supported an association. However, strong conclusions cannot be made on the basis of findings from one study. Thus, while there is not robust evidence for an association between anxiety and anorexia nervosa onset or maintenance, this does not necessarily reflect the absence of a meaningful relationship.

The case-control and cohort studies probing the role of anxiety in anorexia nervosa onset considered different anxiety exposures, however findings across the study design categories may actually point towards the same conclusion. The presence of any anxiety disorder predicting increased risk for anorexia nervosa, while specific anxiety disorder diagnoses had no unique explanatory power (Buckner et al., 2010; Meier et al., 2015), suggests anxiety (regardless of its particular focus) is associated with subsequent anorexia nervosa. This interpretation is consistent with the association between general childhood anxiety and anorexia nervosa in retrospective studies (Kim et al., 2010, 2011; Taborelli et al., 2013). It is also consistent with the high comorbidity between various anxiety disorders and anorexia nervosa – with the anxiety disorders reported to almost always precede anorexia nervosa onset (Bulik et al., 1997; Kaye et al., 2004).

Confidence in anxiety predicting increased risk of later anorexia nervosa is complicated by the vulnerability of studies included in the review to various sources of bias. In the retrospective case-control

studies, the order of anxiety and anorexia nervosa onset may have been confused, such that findings of anxiety being associated with increased risk of anorexia nervosa actually reflect the reverse direction of association. Alternatively, individuals with anorexia nervosa may have mistakenly reported greater anxiety in childhood, or prior to anorexia nervosa onset, in attempts to explain illness development. Inaccuracies in memory recall are well known, and pose serious threats to the validity of retrospective study findings (Kopec and Esdaile, 1990). Case-control studies also accounted for relatively few plausible confounders in the study design, which may have inflated effect estimates. Indeed, the statistical evidence for associations did weaken upon greater adjustment in these studies (Kim et al., 2011). However, it is possible for anxiety to universally precede anorexia nervosa, and even to be causally relevant to the onset of the disorder, while other anorexia nervosa-specific risk factors explain a greater proportion of unique variation in onset. The prospective studies were also subject to limitations. The inclusion of PTSD/OCD within the any anxiety disorder category in the population registry study may have led to inaccurate conclusions over the predictive effect of DSM-5 anxiety disorders. On the other-hand, sample size and measurement issues likely reduced sensitivity to true associations between specific anxiety disorders and anorexia nervosa.

To clarify the potential role of anxiety in anorexia nervosa onset, further high-quality research that minimises the risk of biased conclusions is required. Future observational studies should control for potential confounders in the study design as far as possible. Novel methods that minimise bias due to confounding can assess the robustness of findings from longitudinal research. Mendelian randomization (MR) (Davey Smith and Ebrahim, 2003) is a method that uses genetic variants to instrument an exposure, minimising bias due to confounding and reverse causation (for an overview see (Davies et al., 2018)). MR analyses have produced evidence consistent with a causal influence of genetic liability to worry, though not anxiety disorders, on anorexia nervosa development (Lloyd et al., 2018). Further investigation using different anxiety exposures, participant populations, and specific MR methods is encouraged. To assess whether a longitudinal association is likely to be spurious, future studies might include supplementary control analyses whereby the relationship (that cannot plausibly be causal) of a third factor with exposure or outcome is assessed (see (Lipsitch et al., 2010)).

Future prospective studies should include a sufficient number of participants (and particularly cases) for adequate power to detect associations between anxiety exposures and anorexia nervosa. Use of population registry datasets, and selection of cohorts based on anorexia nervosa risk or anxiety status, is particularly recommended. Future studies should also aim to minimise measurement error in anxiety and anorexia nervosa assessment as far as possible. Meta-analysis of longitudinal findings is not indicated on the basis of existing data. Obtaining a pooled estimate of association and an indication of variability in effect estimates across studies would inform the strength of evidence concerning the potential role of anxiety in anorexia nervosa. To facilitate future meta-analyses, studies probing the association between anxiety and subsequent anorexia nervosa outcomes should assess associations from the direction of exposure to outcome, and report fully adjusted effect estimates.

Future research might also directly assess differential associations of different anxiety exposures (i.e. specific anxiety disorder diagnoses versus transdiagnostic components common to anxiety disorders) with anorexia nervosa pathology. While anxiety disorder diagnoses and dimensional anxiety constructs are overlapping phenotypes, variation in their independent/unique associations with anorexia nervosa could inform mechanisms of association. For example, should a general tendency to experience anxiety explain associations between anxiety disorders and anorexia nervosa, this might suggest that anxiety disorders are only related to anorexia nervosa insofar as they signal a propensity to develop concerns typical of anorexia nervosa. In contrast, should anxiety disorder presence better predict anorexia nervosa onset as

compared to anxious tendencies, this might support anorexia nervosa cognition and behaviour having favourable effects on anxiety disorder pathology (e.g. (Kaye, 2008; Lloyd et al., 2017; Nunn et al., 2012; Pallister and Waller, 2008)). Exploration of factors moderating the effects of anxiety on anorexia nervosa risk might also help to elucidate pathways of association. Probing the interaction between restrictive eating and anxiety disorder presence in the prediction of anorexia nervosa onset could indicate whether anorexia nervosa behaviour likely functions to mitigate fears particular to anxiety disorders.

Outcomes of the present review also highlight the need for further studies investigating the role of anxiety in anorexia nervosa recovery. This is particularly so given longitudinal studies considering alternative anorexia nervosa maintenance outcomes have produced conflicting findings. For example, greater trait anxiety predicted reduced likelihood of anorexia nervosa remission (Yackobovitch-Gavan et al., 2009), yet in a separate study general anxiety symptoms were not associated with likelihood of anorexia nervosa diagnosis at follow-up (Fichter et al., 2006). Notably the definitions of anorexia nervosa maintenance outcomes in these other studies overlap with each other and with the definition of recovery in the included study. Therefore, differences in exact outcome cannot necessarily explain finding disparity. The follow-up period of the included anorexia nervosa recovery study was thirteen years; future studies might consider shorter follow-up periods to avoid masking important proximal predictive effects of anxiety. While out of scope for the current review (see (Lloyd et al., 2018)), we note that studying anorexia nervosa behaviour in relation to both trait and state forms of anxiety could be highly informative for understanding how anxiety may maintain anorexia nervosa pathology (e.g. (Lavender et al., 2013, 2016)).

The limited confidence that can be placed in findings of the present review prevents outcomes informing aetiological models of anorexia nervosa, and intervention practice. However, by identifying the need for further research concerning the role of anxiety in anorexia nervosa pathology, and posing directions for future research, we may indirectly promote a better understanding. This in turn may inform the utility of addressing anxiety, or processes underlying anxiety, in both anorexia nervosa prevention and treatment, for improved intervention outcomes. Ideally future studies will include those of experimental or trial design that minimise the risk of confounding to provide the best test of causality.

This review adhered to a published protocol (Lloyd et al., 2018), with transparent reporting and justification of any diversions ensuring integrity of the research. The inclusion of studies investigating the influence of a variety of anxiety phenotypes allowed for comparison between these phenotypes in terms of their associations with anorexia nervosa. This approach promotes the development of novel and testable hypotheses that may be addressed within future research.

The review has important limitations. The focus on recovery as the specific maintenance outcome was implemented to promote homogeneity of included studies. The distinction between different outcomes of anorexia nervosa (i.e. recovery, relapse, remission, disorder absence) in current research is to some extent false however, given the absence of consistent operationalisations of these terms (Khalsa et al., 2017). As such, informative evidence may have been missed. Despite the absence of meta-analytic estimates, we intended to evaluate the strength of the body of evidence generated by the review using a modified version of the Grading of Assessment, Development and Evaluation (GRADE) system (Guyatt et al., 2008). This could have further informed the quality of evidence collected in the course of the review. However, marked differences in the design of studies assessing the role of anxiety in anorexia nervosa onset, and inclusion of only one study considering anorexia nervosa recovery, prevented GRADE evaluation being a meaningful exercise.

To conclude, the evidence aggregated within the review has provided an important basis for future research, however it is not sufficient for robust evaluation of whether anxiety exposures are longitudinally

associated with anorexia nervosa development or maintenance. The review unequivocally establishes the need for further research in this area, ideally within studies of trial as well as observational design, to in turn inform anorexia nervosa prevention and treatment. Future investigations should seek to adopt methods that minimise potential biases, and that may inform pathways of association.

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Conflict of interest statement

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Supplementary materials

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