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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.

Keywords: anxiety disorders; epidemiology; longitudinal; prospective; retrospective; systematic review

2

1 Introduction

2 Anorexia nervosa is an eating disorder characterised by persistent dietary restriction and an

3 intense fear of weight gain despite maintenance of a low body weight (American Psychiatric

4 Association; APA, 2013). The disorder has the highest mortality rate of any psychiatric

5 disorder (Arcelus, Mitchell, Wales, & Nielsen, 2011) and lasting and aversive implications

6 on physical health (Mehler & Brown, 2015). Recovery rates of established treatments remain

7 below 50% (Brockmeyer, Friederich, & Schmidt, 2018). While there is some evidence to

8 support the efficacy of particular prevention interventions in asymptomatic populations,

9 individuals already displaying symptoms of an eating disorder do not seem to benefit from

10 existing programmes (Le, Barendregt, Hay, & Mihalopoulos, 2017; Watson et al., 2016). The

11 scope for improved prevention and treatment is clear, however achievement of this remains

12 complicated by uncertainty surrounding anorexia nervosa aetiology (Zipfel, Giel, Bulik, Hay,

13 & Schmidt, 2015).

14

15 Existing interventions typically address eating disorder specific cognition (e.g. drives for

16 thinness, heightened valuation of weight and shape) and/or eating behaviour (e.g. dietary

17 restriction) that precede and characterise anorexia nervosa (Jacobi, Hayward, de Zwaan,

18 Kraemer, & Agras, 2004). Augmenting existing interventions with modules that target other

19 factors identified as playing a causal role in anorexia nervosa development and/or

20 maintenance could be highly beneficial. Clinical observations support high levels of anxiety

21 generally in individuals with anorexia nervosa. Subsequently, a number of theoretical

22 accounts of anorexia nervosa propose anxiety *unrelated* to eating and weight-gain, from this

23 point referred to as anxiety, to be causal in anorexia nervosa development. Specifically, it has

24 been proposed that the restrictive eating, and focus on food intake and weight, that

25 characterises anorexia nervosa may reduce anxiety in individuals who develop anorexia

3

1   nervosa, encouraging continuation of dietary restriction, and to increasingly extreme degrees

2   (e.g. (Haynos & Fruzzetti, 2011; Lloyd, Frampton, Verplanken, & Haase, 2017; Kaye, 2008;

3   Nunn, Frampton, & Lask, 2012; Pallister & Waller, 2008)). The majority of anxiety disorders

4   typically emerge in childhood and early adolescence (Bandelow & Michaelis, 2015; Lijster et

5   al., 2017), while anorexia nervosa onset is most common during mid-late adolescence

6   (Micali, Hagberg, Petersen, & Treasure, 2013), consistent with the proposed causal role of

7   anxiety in anorexia nervosa pathology.

8

9   One implication of the hypothesis that anxiety causally influences anorexia nervosa

10   pathology is that targeting anxiety in prevention and treatment efforts could be a promising

11   avenue for improving the outcome of current interventions. Evidence for prevention

12   interventions reducing negative affect (depressive and anxious symptomatology) is weak (Le

13   et al., 2017). Whether existing treatment interventions improve anxiety is unclear since this is

14   not typically reported (Kezelman, Touyz, Hunt, & Rhodes, 2015). However, anxiety remains

15   elevated upon recovery in anorexia nervosa (Holtkamp, Muller, Heussen, Remschmidt, &

16   Herpertz-Dahlmann, 2005; Kaye et al., 2004), suggesting anxiety may not be sufficiently

17   addressed within anorexia nervosa treatment.

18

19   There are few, if any, reported trials of adjunctive therapies designed specifically to reduce

20   anxiety within the context of anorexia nervosa interventions. Without such data,

21   observational studies allow for initial tests of the hypothesis that anxiety plays a causal role in

22   the development and maintenance of anorexia nervosa. Associations between anxiety and

23   anorexia nervosa are reliably reported in cross-sectional studies. Trait anxiety is greater in

24   anorexia nervosa as compared to HC (e.g. (Schneier et al., 2016; Schulze, Calame, Keller, &

25   Mehler-Wex, 2009)). Anxiety disorder pathology and the prevalence of anxiety disorder

1   diagnoses are also elevated amongst anorexia nervosa as compared to HC (Kerr-Gaffney,

2   Harrison, & Tchanturia, 2018; Sternheim, Startup, & Schmidt, 2015; Swinbourne & Touyz,

3   2007). Existing findings support a role for anxiety in anorexia nervosa maintenance as well.

4   When studies have compared individuals who have recovered from anorexia nervosa to those

5   who have not, anxiety and anxiety disorder pathology is elevated in the latter group (Kaye et

6   al., 2004; Toner, Garfinkel, & Garner, 1988; Zerwas et al., 2013).

7

8   Correlation is not causation however, and alternative explanations for the pattern of findings

9   summarised exist. Cross-sectional research is particularly vulnerable to bias by reverse

10   causation, and it is possible the observed associations reflect that physical, psychological and

11   social consequences of anorexia nervosa behaviour result in heightened anxiety. Longitudinal

12   studies assess whether an exposure of interest (in this case anxiety) predicts the later

13   occurrence of a given outcome (i.e. anorexia nervosa), to establish the temporal nature of

14   association, thus allowing for stronger inferences concerning causality as compared to cross-

15   sectional research. The current systematic review gathers longitudinal studies that have

16   assessed whether stable anxiety phenotypes (i.e. trait anxiety and anxiety disorder pathology)

17   predict subsequent anorexia nervosa onset or anorexia nervosa recovery. It is hoped that this

18   process will help to outline the possible role of anxiety in anorexia nervosa, which may

19   inform future research and clinical practice. The review is completed in accordance with a

20   published protocol (see (Lloyd, Haase, & Verplanken, 2018)).

21

22   **Methods**

23

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.

Eligibility criteria

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

[INSERT TABLE 1 APPROXIMATELY HERE]

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).

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 CEF 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.

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.

Risk of Bias and Quality Assessment

Risk of bias was assessed using the Newcastle Ottawa Scale (NOS; (Wells et al., 2000)) 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 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.

Results

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 Figure 1.

[INSERT FIGURE 1 APPROXIMATELY HERE]

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.

Study characteristics

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

1   [INSERT TABLE 2 APPROXIMATELY HERE]

2

3   Of the seven studies probing the role of anxiety phenotypes in anorexia nervosa development,

4   four considered childhood anxiety, and three considered anxiety disorder diagnoses. The

5   single study probing the role of anxiety in anorexia nervosa recovery assessed the association

6   between non-specific anxiety disorder symptoms, as opposed to particular anxiety disorder

7   pathology, and anorexia nervosa.

8

9   Of the eight included studies, five detailed the best (fully adjusted) effect estimates for

10   associations of interest, and these five studies all assessed the predictive effect of anxiety on

11   anorexia nervosa development. Notably, one further study provided estimates for the

12   unadjusted analysis assessing the association between anxiety and anorexia nervosa onset

13   (Kim, Lim, & Treasure, 2011). Another study (Meier et al., 2015) provided estimates

14   pertaining to the predictive effect of anxiety disorders present in the period prior to anorexia

15   nervosa onset, including those anxiety disorders emerging in the year before anorexia nervosa

16   onset. The study indicated that associations did not qualitatively differ when anxiety

17   disorders diagnosed in the year prior to anorexia nervosa development were excluded from

18   the analysis, but sensitivity analysis estimates were not available.

19

20   Ideally a meta-analysis would have been completed, however various issues (aside from

21   missing data) prevented pooling effect estimates across studies. First, while all cohort studies

22   treated anxiety as the independent variable and anorexia nervosa as the dependent variable,

23   this was not the case for case-control studies. As such, available effect estimates are not even

24   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.

Qualitative Synthesis

Anxiety and anorexia nervosa development

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 &

Gibbon, 2004) or the Eating Disorder Examination (Cooper & 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, Heo, Kang, Song, & Treasure, 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, Welch, Doll, Davies, & O'Connor, 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; Kim et al., 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 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 anorexia nervosa, however anxiety was not independently

associated with anorexia nervosa: the relationship disappeared when covariates (including

interpersonal factors and visuoperceptual ability) were added to the prediction model. The

fourth study (Machado et al., 2016) observed an increased proportion of individuals with

anorexia nervosa reporting childhood anxiety as compared to HC, while a reduced proportion

of anorexia nervosa reported anxiety compared to a bulimia nervosa (BN) comparison group.

There was no difference in the proportion of 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.

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, Silgado, & Lewinsohn, 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, Puig-Antich, Chambers, Tabrizi, & Johnson, 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 Longitudinal Interval Follow-Up Evaluation (Keller et al., 1987), and the SCID for DSM-IV disorders (First & 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.

Anxiety and anorexia nervosa maintenance

The single study probing the association between anxiety and recovery from anorexia

nervosa (Rigaud, Pennacchio, Bizeul, Reveillard, & Verges, 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/m^2; 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.

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

1 inflate effect estimates as well as reduce sensitivity to a true association (Greenland,

2 Mansournia, & Altman, 2016; King & Zeng, 2001). While the record linkage study is not

3 subject to this limitation, anxiety disorder and anorexia nervosa diagnoses were identified

4 only when specialist psychiatric treatment was sought. This approach will have resulted in

5 under identification of diagnoses (e.g. when psychiatric disorders were treated within general

6 practice settings), with such measurement error introducing bias into estimates of association.

7 The follow-up periods of prospective studies did not always encompass the entire period of

8 peak anorexia nervosa onset (i.e. age 14-19 (Micali et al., 2013)), which will also have

9 complicated the detection of true associations. Consistency across findings indicates a higher

10 quality of the body of evidence (Guyatt et al., 2008), and was lacking – even when

11 considering findings of prospective and case-control studies separately. That there was a

12 single study assessing the role of anxiety in anorexia nervosa recovery suggests evidence

13 concerning this outcome is weak.

14

Discussion

16
17 The purpose of this systematic review was to identify longitudinal studies probing the

18 association of anxiety with either anorexia nervosa development or recovery. A small number

19 of eligible studies were identified. Findings of retrospective case-control studies generally

20 supported individuals with anorexia nervosa being more likely to report childhood anxiety

21 than HC. Evidence from two prospective cohort studies and the single prospective population

22 registry study did not support specific anxiety disorders explaining unique variation in

23 anorexia nervosa risk. Findings of the population registry study did however support the

24 presence of any anxiety disorder (i.e. pathology common across the anxiety disorders)

25 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; Kim et al., 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, Sullivan, Fear, & Joyce, 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 & 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 & 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, Holmes, & Davey Smith, 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, Sallis, Haase, Verplanken, & Munafo, 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, Tchetgen Tchetgen, & Cohen, 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 & 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, Quadflieg, & Hedlund, 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; Lavender et al., 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 are best able to demonstrate causal relationships.

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, Portnoff, McCurdy-McKinnon, & Feusner, 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.

Conflict of Interest Statement

There are no conflicts of interest to disclose.

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1 **Tables**

2

3 Table 1. Screening Criteria

4

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 Individuals in anorexia nervosa sample must have met or have previously met full diagnostic criteria for anorexia nervosa
Exposure	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

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

6

Table 2. Characteristics of Studies Included in the Review

	Studies assessing association between anxiety and anorexia nervosa onset (outcome = anorexia nervosa diagnosis)										
Design	Study Country	Participants Gender	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]
Retrospective case-control	Kim et al. 2010 Korea	52 Korean AN Female	Specialist ED service	Childhood (prior to emergence of ED symptoms)	16.6 (2.7)	General anxiety (at school, outside of school and in total)	Childhood RFQ	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]
		42 British AN Female	Eating Disorder Research Unit volunteer database	NA	17.8 (3.2)						
		108 Koran HC Female	Community		20.5 (2.4)						
	Kim et al. 2011 Korea/ UK	22 AN (68% AN-R) Female	NR	Childhood (prior to emergence of ED symptoms) NA	15.6 (1.5)	General anxiety	Childhood RFQ	SCID for DSM-IV (Korean version)	Participants matched on general intelligence and years of education. Analyses adjusted for	No association between anxiety and AN	NR
		28 BN			20.4 (2.7)						

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								childhood risk factors (parent attitudes to weight/shape, social support, perfectionism, eating behaviour), visuospatial ability		
	Female									
	26 HC			21.4 (2.8)						
	Female									
Machado et al. 2015 Portugal	98 AN (64.2% AN-R)	Specialist ED service	Childhood (prior to emergence of ED symptoms)	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]
	Female									
	79 BN	Specialist ED service	NA	21.2 (2.2)						
	Female									
	68 Psychiatric Controls	Treatment setting		21.0 (2.6)						
	Female									
	86 HC	Schools and universities		20.8 (2.6)						
	Female									
Taborelli et al. 2013 UK/ Spain/	94 AN	Treatment centres and volunteer databases	Childhood (prior to emergence of ED symptoms)	18.4 (2.2)	Separation anxiety	ORFI	EDE diagnostic items	AN and HC participants (siblings) matched on gender and	Childhood anxiety predicts AN	9.00 [1.20,71.00]
	Female									
	63 BN			19.7 (1.9)						

|	Study/Country	N/Sex	Setting	Age/Timing		Exposure	Exposure measurement	Outcome measurement	Adjustment	Conclusion	Estimate [CI]
Prospective cohort	Slovenia/Austria	Female 157 HC (siblings of cases) Female	NA	NA	22.4 (4.2)				background factors		
	Buckner et al. 2010 United States	841 Mixed (59% Female)	Nine high schools	Mean:16.6 years (SD = 1.2) 13.5 years	NR	Panic Disorder diagnosis (DSM-IV)	K-SADS epidemiologic version and K-SADS present episode version	Longitudinal Interval Follow-up Evaluation and SCID-for DSM-IV non-patient version	Analyses adjusted for age, sex, MDD, OCD, other anxiety disorders	No association between specific anxiety disorders and AN	0 [0.00,0.00]
						Overanxious Disorder diagnosis (DSM-IV)					0 [0.00,0.00]
						Separation Anxiety Disorder diagnosis (DSM-IV)					0 [0.00,0.00]
						Simple Phobia diagnosis (DSM-IV)					0 [0.00,0.00]
						Social Anxiety Disorder diagnosis (DSM-IV)					0 [0.00,0.00]
	Meier et al. 2015 Denmark	1664876 Mixed	Danish Population Registry	At least one year prior to AN diagnosis	NR	Agoraphobia diagnosis (ICD-10)	Medical record: specialist treatment for given anxiety	Medical record: specialist treatment for AN recorded	Analyses adjusted for calendar year, age, sex, age-sex interaction, place of birth,	No association between specific anxiety	NR
						Generalized Anxiety Disorder					

			18 years		diagnosis (ICD-10)	disorder recorded			maternal age, paternal age, psychiatric family history, hospital contact due to any other anxiety/stress disorder or OCD	disorders and AN	
					Panic Disorder diagnosis (ICD-10)						
					Social Anxiety Disorder diagnosis (ICD-10)						
					Specific Phobia diagnosis (ICD-10)						
Ranta et al. 2017 Finland	3278 Mixed (56.4% female)	Regional high schools	Mean:15.5 years (SD = 0.4)* 2 years	NR	Social Phobia diagnosis (DSM-IV)	SPIN	Self-report questionnaire probing eating behaviour, weight concerns and amenorrhea	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]	

Studies assessing association between anxiety and anorexia nervosa recovery (outcome = recovery from anorexia nervosa)

Design	Study	Participants	Recruitment source	Age at anxiety assessment	BMI at AN assessment Mean (SD)	Exposure (s)	Exposure measure	Outcome measure	Statistical Adjustment/ Matching	Finding	Best Estimate OR [95% CI]
	Country	Gender		Follow-up period							
Prospective Cohort	Rigaud et al. 2011	484 AN (71.7% AN-R)	Specialist inpatient ED service	Mean: 22.8 years (SD = 4.4)	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)		13 years							

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.

Figures
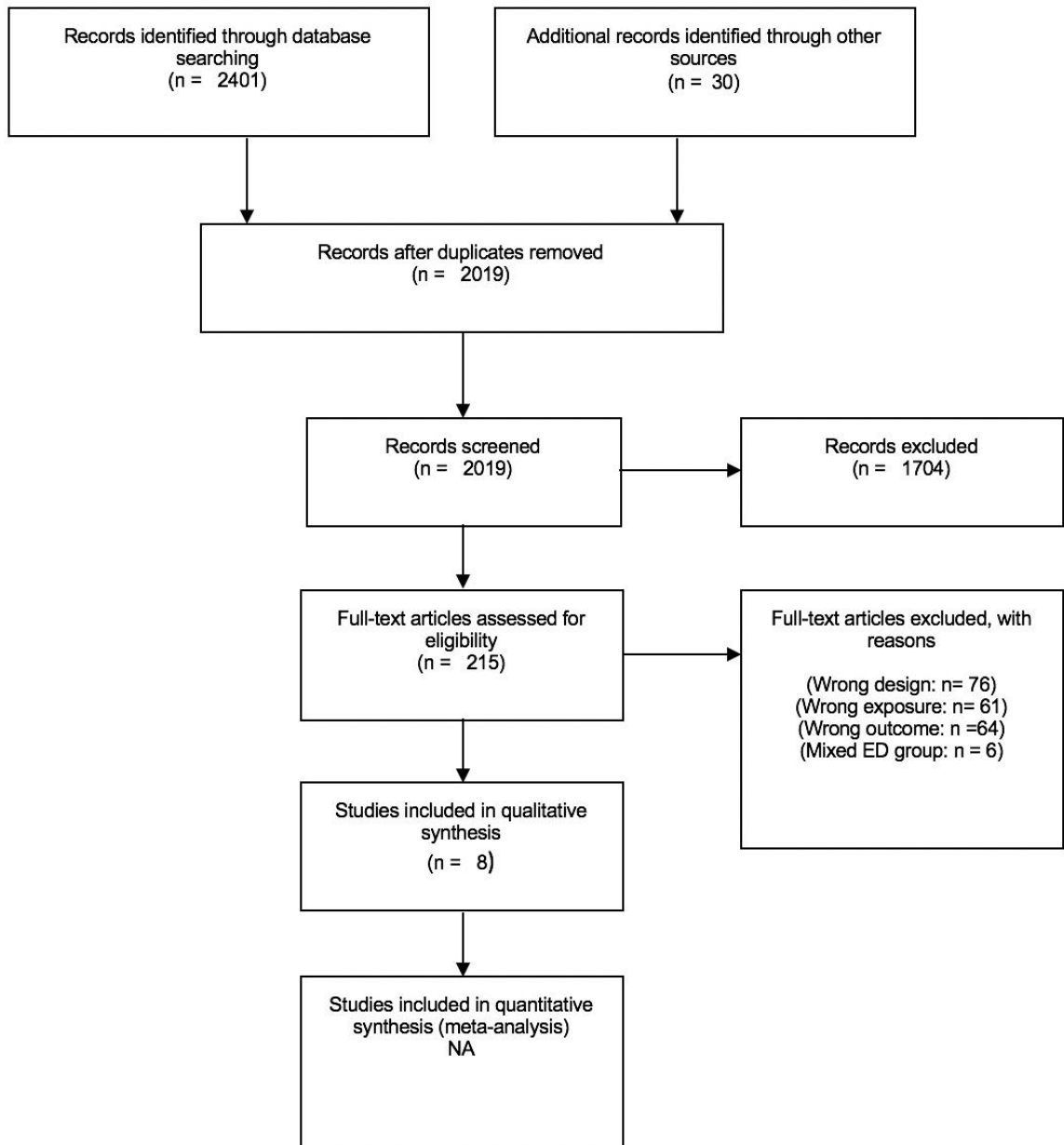
Figure 1. PRISMA flow diagram to show study selection process