Associations between anxiety and anorexia nervosa: evidence for causality?

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Overview

• Background
• Research findings
  - Systematic review
  - Triangulation study
• Summary & Implications
• Future Directions
• Questions
Anxiety & Anorexia nervosa

• Clinically individuals with AN observed to be highly anxious

• Empirical studies report anxiety disorder prevalence, anxious pathology & trait anxiety to be high in AN populations
  - at time of illness, prior to illness & in recovery (Steinglass et al., 2011)

• Suggests anxiety a stable characteristic of individuals with AN
  - possible role for anxiety in illness development
Anxiety & Anorexia nervosa

• Various models of illness include anxiety as an aetiological factor

• Different mechanisms proposed

  - Anxiety relieved by dietary restriction/focus on food to increase reinforcing effects of AN behaviour (Haynos & Fruzetti, 2011; Kaye et al., 2003; 2008; Nunn et al., 2012; Pallister & Waller, 2008; Scolnick, 2017;)

  - Anxiety affects functioning of brain networks implicated in AN (Strober et al., 2007; Lloyd et al., 2018)
An association, but is it causal?

- Current prevention and treatment typically targets eating disorder specific risk factors (e.g. body dissatisfaction/dieting)

- Understanding whether anxiety causally affects AN risk is relevant for development of prevention and treatment interventions
How strong is evidence for temporality?

• For anxiety to cause AN it must precede it

• There are studies that report greater anxiety to predict subsequent AN (e.g. Kim et al., 2010; Meier et al., 2015)

• Possible small number of positive findings repeatedly cited -other studies may not have found the same thing

• Quality of existing studies unclear
Systematic review

• Aggregates all studies probing longitudinal association between anxiety and AN

• Quality appraisal of studies and overall collection of evidence

• For balanced conclusions based on all available evidence

• To inform research better able to establish causal effects
Method

• Followed a published protocol with any diversions fully justified

Anxiety and the development and maintenance of anorexia nervosa: protocol for a systematic review

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Abstract

Background: Several aetiological models of anorexia nervosa (AN) hold non-eating/weight-gain-related anxiety as a factor relevant to the onset and maintenance of the disorder. Longitudinal studies that allow assessment of this hypothesis have been conducted, however, the evidence has not yet been aggregated in a systematic manner. The proposed study will systematically review articles describing prospective investigations of the relationship between anxiety and AN development or maintenance, with the aim of providing a balanced summary of current understanding and identifying areas for further research.

Methods/design: Electronic databases will be searched for articles investigating the longitudinal influence of non-eating/weight-gain-related anxiety (anxiety disorders and trait anxiety) on the development/maintenance of AN. References of eligible articles will be searched to ensure the identification of all relevant studies. Two independent reviewers will complete the title and abstract, and full-text, screening, with a third independent reviewer resolving any conflicts at each stage. A systematic review will be completed, and the quality of the included studies, as well as the strength of the body of evidence generated, will be assessed and reported.

Discussion: Although there are limitations to the present review, understanding the current evidence for the role of non-eating/weight-gain-related anxiety in AN can direct future research that may ensure accurate aetiological models of AN and effective treatments.

Systematic review registration: The study is registered on PROSPERO under the reference number CRD42017069644

Keywords: Aetiology, Anxiety, Anorexia nervosa: risk factor, Longitudinal studies
Method

• Systematic search: any study probing longitudinal association between stable form of anxiety (i.e. traits/disorders) & subsequent AN onset or recovery

• Two reviewers at each stage of screening process

• Data extraction & quality assessment undertaken by two reviewers

• Qualitative synthesis
Results

Records identified through database searching (n = 2401)

Additional records identified through other sources (n = 31)

Records after duplicates removed (n = 1921)

Records screened (n = 1921)

Full-text articles assessed for eligibility (n = 215)

Records excluded (n = 1706)

Full-text articles excluded, with reasons
(Wrong design: n = 76)
(Wrong exposure: n = 61)
(Wrong outcome: n = 64)
(Mixed ED group: n = 6)

Studies included in qualitative synthesis (n = 8)

Studies included in quantitative synthesis (meta-analysis) NA

Results

• Seven studies assessed predictive effects of anxiety on AN development

• Inconsistent findings
  - 2/4 retrospective studies found strong evidence for association between anxious tendencies and later AN
  - No evidence for independent predictive effects of anxiety disorders on AN development, some evidence that presence of any anxiety disorder may indicate greater AN risk

• Quality assessment suggested quality of individual studies = high

• Quality of body of evidence = low
Conclusion

• Inconsistency in findings and designs make results difficult to interpret

• Studies of different design have probed different exposures
  - Retrospective = anxious tendencies, prospective = anxiety disorders
  - Tendency to be anxious better predictor of AN?
  - But the retrospective studies were more prone to bias by reverse causation & confounding

• Strongest conclusion that may be drawn is the need for further high-quality research in this area
Issue with traditional epidemiologic methods:

CONFOUNDING
Issue with traditional epidemiologic methods:

REVERSE CAUSATION
Triangulation

• Different methods subject to different forms of bias

• If studies of different design converge on same outcome, might be more confident that effects are true
Triangulation study

• Compared findings across two different studies

• Each assessed association of worry & anxiety disorders with AN

• Study 1: Observational longitudinal cohort study

• Study 2: Mendelian Randomization
Mendelian randomization

- Uses genetic variants as proxy variables for exposures of interest (Davey-Smith & Ebrahim, 2003)

- Minimises bias due to confounding and reverse causation
Study 1: Methods

Design
Secondary analysis of longitudinal anxiety & AN data

Participants
All consenting children of Avon Longitudinal Study of Parents and Children (ALSPAC) alive at one year (n=14,899)

Measures
Lifetime AN at 24 – defined using previous criteria (Micali et al., 2015), derived from questionnaire responses, clinical weight & height data, at 4 time-points
Worry at age 10 – assessed using parent-report DAWBA
Anxiety disorder presence at age 10 – assessed using parent-report DAWBA
Study 1: Method

Statistical Analysis
Binary logistic regression to assess prediction of AN by worry and anxiety disorder presence
Unadjusted, adjusted & maximally adjusted analyses
Multiple imputation of missing data
Complete case and maximum available data analyses also completed
## Study 1: Results

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Variable</th>
<th>OR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td>14882</td>
<td>Worry</td>
<td>1.6 [0.93, 2.77]</td>
<td>0.090</td>
</tr>
<tr>
<td></td>
<td>14882</td>
<td>Anxiety disorder</td>
<td>2.85 [1.22, 6.63]</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td>14882</td>
<td>Worry</td>
<td>1.41 [0.78, 2.56]</td>
<td>0.256</td>
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<tr>
<td></td>
<td>14882</td>
<td>Anxiety disorder</td>
<td>3.12 [1.14, 8.55]</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Maximally adjusted</strong></td>
<td>14882</td>
<td>Worry</td>
<td>1.34 [0.74, 2.44]</td>
<td>0.332</td>
</tr>
<tr>
<td></td>
<td>14882</td>
<td>Anxiety disorder</td>
<td>2.87 [1.05, 7.82]</td>
<td>0.039</td>
</tr>
</tbody>
</table>
Conclusion

• Predictive effect of anxiety disorders but not worry on AN risk

• Absence of association between worry and AN surprising given worry component of anxiety disorders
  - explained by measurement error in worry phenotype?

• Possible analyses more sensitive to associations of anxiety disorders
## Study 2: Method

<table>
<thead>
<tr>
<th>Phenotypes &amp; Data Sources</th>
<th>Study</th>
<th>Resource</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worry</td>
<td>Nagel et al., 2018</td>
<td>UK Biobank</td>
<td>348,219</td>
</tr>
<tr>
<td>Anxiety Disorder (Case Control)</td>
<td>Otowa et al., 2016</td>
<td>ANGST</td>
<td>5712 cases 11598 controls</td>
</tr>
<tr>
<td>Anxiety Disorder (Quantitative)</td>
<td>Otowa et al., 2016</td>
<td>ANGST</td>
<td>18186</td>
</tr>
<tr>
<td>Anorexia Nervosa</td>
<td>Duncan et al., 2017</td>
<td>PGC</td>
<td>3495 Cases 10982 Controls</td>
</tr>
</tbody>
</table>
Study 2: Method

• Identified independent single nucleotide polymorphisms (SNPs) associated with exposures of interest at genome-wide significance level

• Estimated causal effect using Wald ratio approach: **SNP effect in outcome/SNP effect in exposure**

• Where multiple SNPs eligible as instruments causal effect estimates combined in inverse-variance weighted (IVW) analysis

• Sensitivity analyses robust to MR assumptions completed
### Study 2: Results

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Method</th>
<th>OR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worry</td>
<td>IVW</td>
<td>2.14 [1.18, 3.90]</td>
<td>0.01</td>
</tr>
<tr>
<td>Worry</td>
<td>MR Egger</td>
<td>0.8 [0.04, 16.57]</td>
<td>0.89</td>
</tr>
<tr>
<td>Worry</td>
<td>Weighted median</td>
<td>2.49 [1.15, 5.41]</td>
<td>0.02</td>
</tr>
<tr>
<td>Worry</td>
<td>Weighted mode</td>
<td>3.08 [0.52, 18.19]</td>
<td>0.22</td>
</tr>
<tr>
<td>Anxiety Disorder Case Control</td>
<td>Wald ratio</td>
<td>1.02 [0.69, 1.50]</td>
<td>0.92</td>
</tr>
<tr>
<td>Anxiety disorder Quantitative</td>
<td>Wald ratio</td>
<td>4.26 [0.49, 36.69]</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Outcomes support causal influence of worry on AN
Study 2: Conclusion

• Findings suggest causal role of worry in AN

• Association between worry and AN supported by other observational research (e.g. Sala et al., 2016; Startup et al., 2013; Schaumberg et al., 2016)

• No evidence for causal influence of genetic liability to anxiety disorders on AN risk

• However relatively weak anxiety disorder instruments = low power and bias towards null
Triangulation

• Findings across study 1 & 2 are not consistent

• Worry causally implicated in AN development

• Prior research suggests role for worry in anxiety disorder development too (e.g. Topper et al., 2010; 2017)

• Possible worry is one factor confounding anxiety disorder and AN association in observational research
Cross-study summary and implications

• Some evidence for longitudinal associations between anxiety disorders and AN

• No strong evidence for causal influence of anxiety disorders on AN development

• Strong evidence for causal influence of worry on AN development

• Highlights importance of study of transdiagnostic factors in AN research & potential utility of transdiagnostic prevention interventions
Future research

• Further probing of causal role of anxiety disorders in AN development

• Randomized trial designs for more robust inferences

• Further study of transdiagnostic processes in AN

• Understand mechanisms underlying causal effects
Questions
References


References


