

Associations between anxiety and anorexia nervosa: evidence for causality?



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 & Fruzzetti, 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

PROTOCOL

Open Access



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.

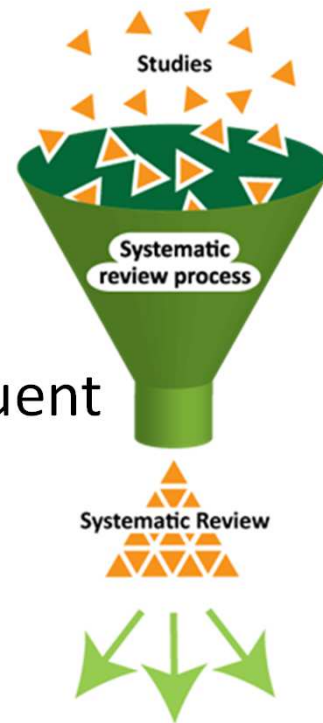
Discussion: Although there are limitations to the present review, understanding the current evidence for the role of non-eating/weight-gain-related anxiety in AN can direct future research that may ensure accurate aetiological models of AN and effective treatments.

Systematic review registration: The study is registered on PROSPERO under the reference number [CRD42017069644](https://doi.org/10.1111/CRD4.2017069644)

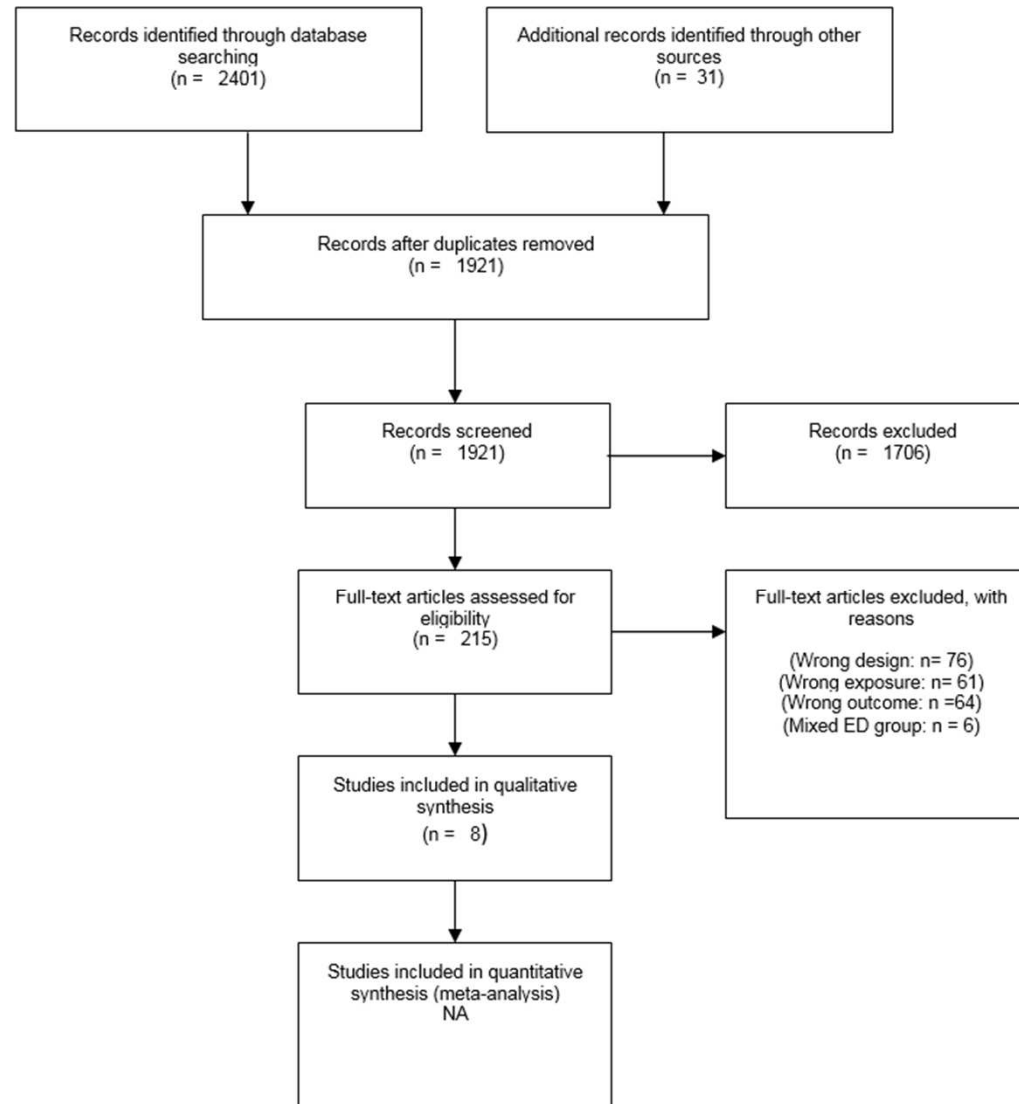
Keywords: Aetiology, Anxiety, Anorexia nervosa: risk factor, Longitudinal studies

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

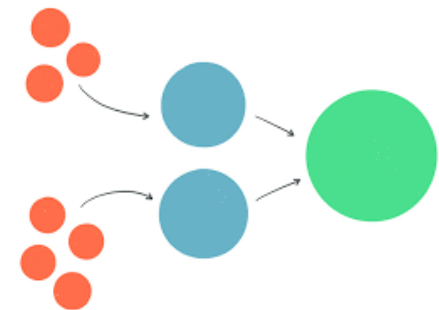


Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

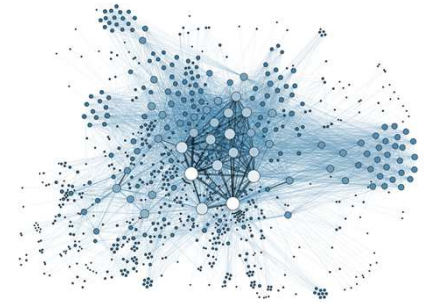


Results

- 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



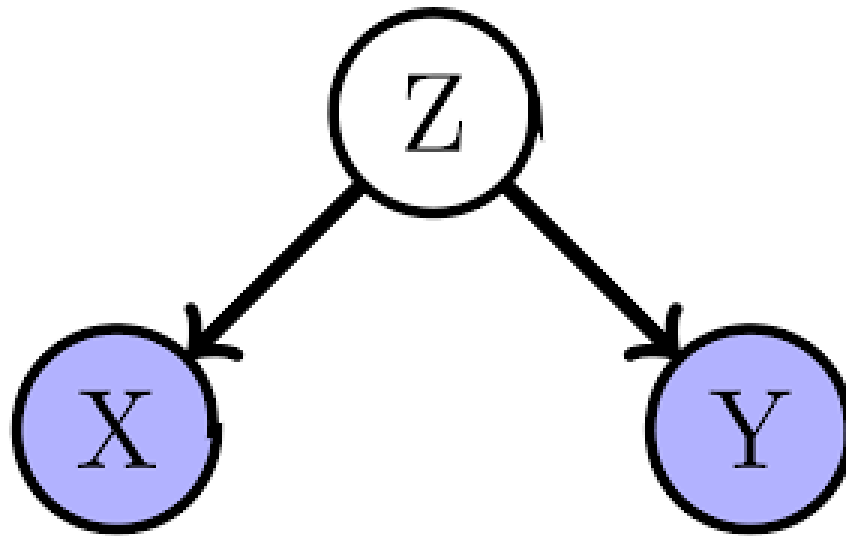
Conclusion



- 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

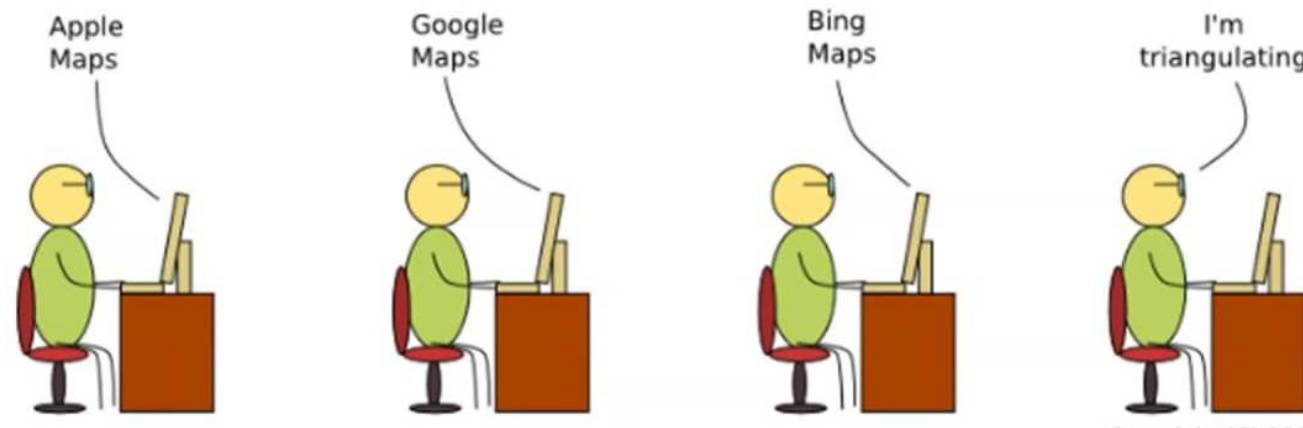
Issue with traditional epidemiologic methods:



REVERSE CAUSATION

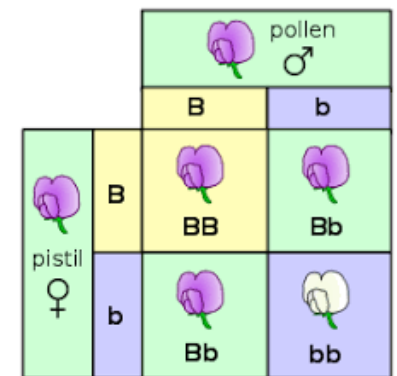
Triangulation

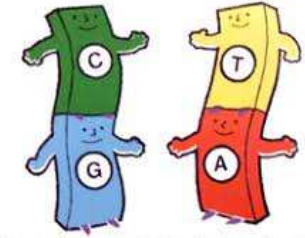
- Different methods subject to different forms of bias
- If studies of different design converge on same outcome, might be more confident that effects are true



Triangulation study

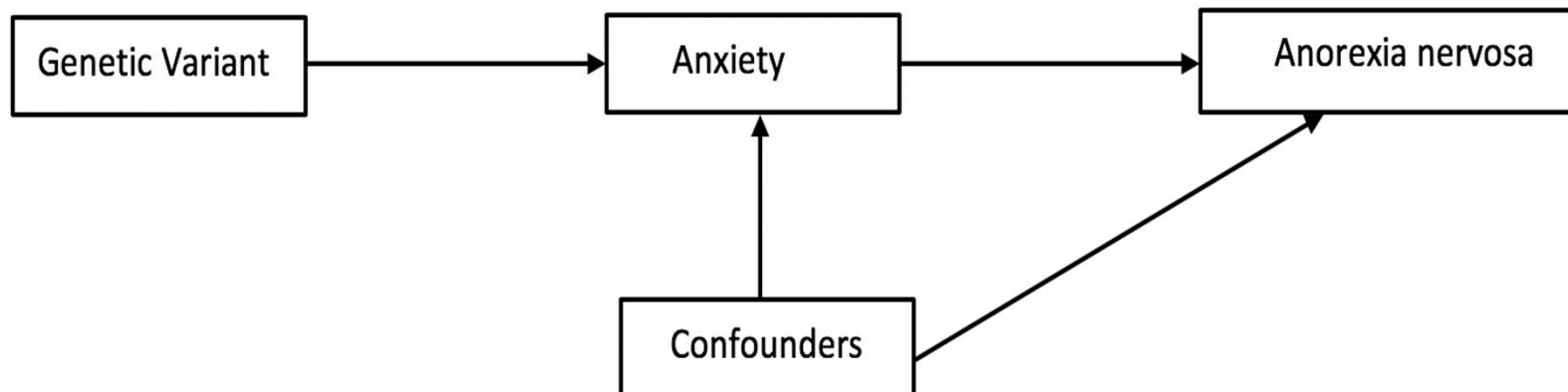
- Compared findings across two different studies
- Each assessed association of worry & anxiety disorders with AN
- Study 1: Observational longitudinal cohort study
- Study 2: Mendelian Randomization

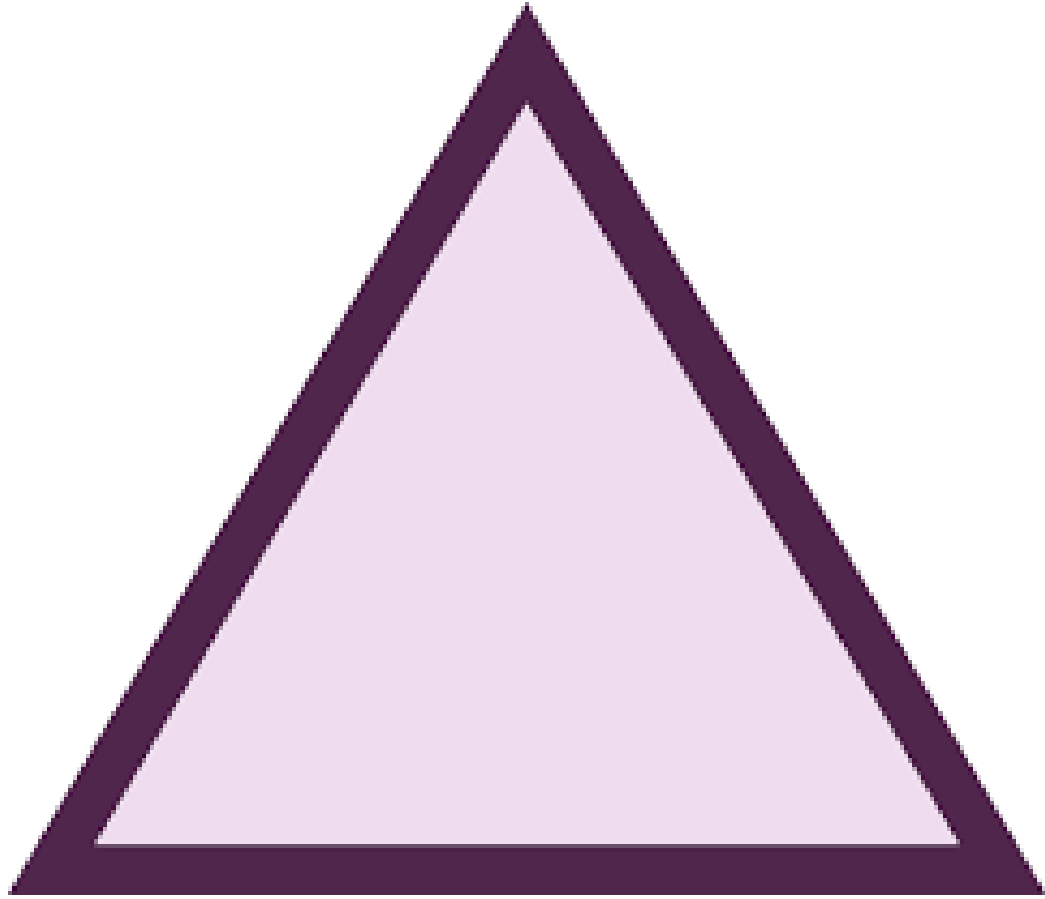




Mendelian randomization

- 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

Imputed data analyses

	N	Variable	OR [95% CI]	P value
Unadjusted	14882	Worry	1.6 [0.93, 2.77]	0.090
	14882	Anxiety disorder	2.85 [1.22, 6.63]	0.016
Adjusted	14882	Worry	1.41 [0.78, 2.56]	0.256
	14882	Anxiety disorder	3.12 [1.14, 8.55]	0.027
Maximally adjusted	14882	Worry	1.34 [0.74, 2.44]	0.332
	14882	Anxiety disorder	2.87 [1.05, 7.82]	0.039

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

Phenotypes & Data Sources

	Study	Resource	Sample size
Worry	Nagel et al., 2018	UK Biobank	348,219
Anxiety Disorder (Case Control)	Otowa et al., 2016	ANGST	5712 cases 11598 controls
Anxiety Disorder (Quantitative)	Otowa et al., 2016	ANGST	18186
Anorexia Nervosa	Duncan et al., 2017	PGC	3495 Cases 10982 Controls

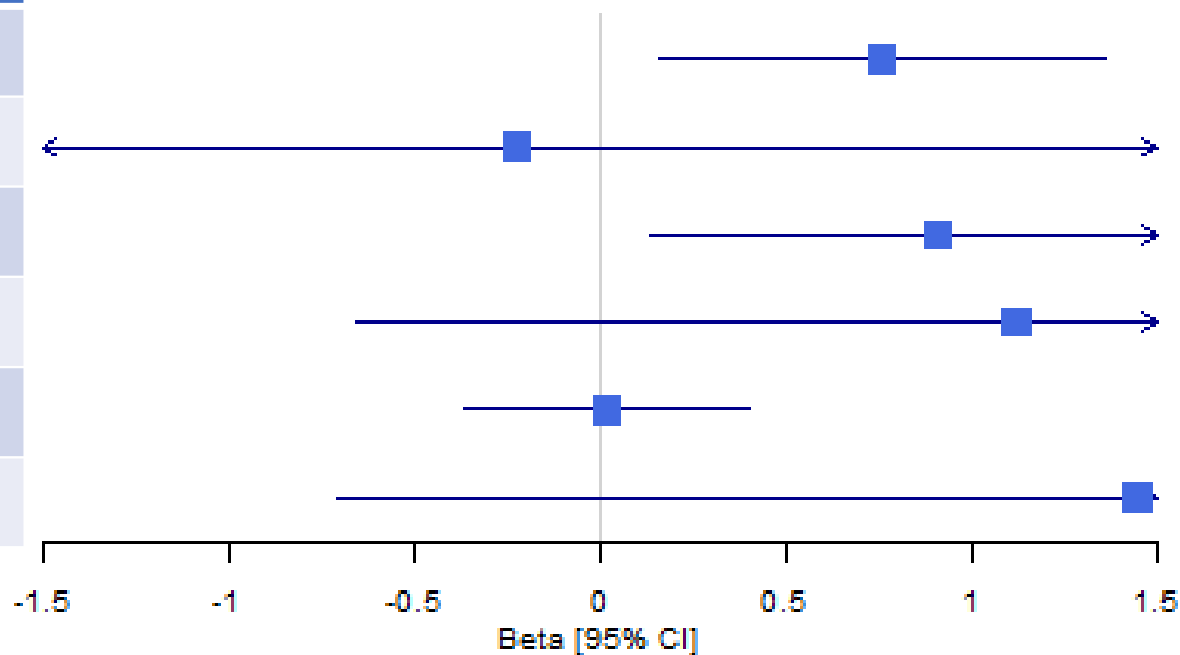
Study 2: Method



- 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

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



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

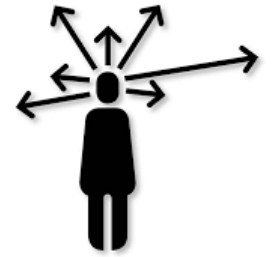


Cross-study summary and implications



- 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





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Questions



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