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Shared genetic influences between eating disorders and gastrointestinal disease in a large, population-based sample of adult women and men

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Abstract

Background. Some preliminary research suggests higher rates of gastrointestinal disease in individuals with eating disorders (EDs). However, research is limited, and it remains unknown what etiologic factors account for observed associations. This was the first study to examine how EDs and dimensional ED symptoms (e.g. body dissatisfaction, binge eating) are phenotypically and etiologically associated with gastrointestinal disease in a large, population-based twin sample.

Methods. Adult female ($N = 2980$) and male ($N = 2903$) twins from the Michigan State University Twin Registry reported whether they had a lifetime ED (anorexia nervosa, bulimia nervosa, or binge-eating disorder) and completed a measure of dimensional ED symptoms. We coded the presence/absence of lifetime gastrointestinal disease (e.g. inflammatory bowel disease) based on responses to questions regarding chronic illnesses and medications. We first examined whether twins with gastrointestinal disease had higher rates of EDs and ED symptoms, then used correlated factors twin models to investigate genetic and environmental contributions to the overlap between disorders.

Results. Twins with gastrointestinal disease had significantly greater dimensional ED symptoms ($\beta = 0.21$, $p < 0.001$) and odds of a lifetime ED (OR 2.90, $p = 0.001$), regardless of sex. Shared genetic factors fully accounted for the overlap between disorders, with no significant sex differences in etiologic associations.

Conclusions. Comorbidity between EDs and gastrointestinal disease may be explained by overlap in genetic influences, potentially including inflammatory genes implicated in both types of disorders. Screening for gastrointestinal disease in people with EDs, and EDs in those with gastrointestinal disease, is warranted.

Past research has found significant comorbidity between some psychiatric disorders (e.g. anxiety, depression) and gastrointestinal disease, particularly functional gastrointestinal disorders characterized by aberrant gut-brain interactions (e.g. irritable bowel syndrome [IBS], gastroesophageal reflux disease [GERD]) (Rogers et al., 2016; Mohammad et al., 2019; Popa & Dumitrascu, 2015). However, few studies have examined the relationship between eating disorders (EDs) or ED symptoms and gastrointestinal disease despite a strong theoretical basis for an association. Individuals with EDs often report gastrointestinal distress (e.g. bloating, constipation), and ED behaviors such as vomiting, food restriction, binge eating, and laxative abuse can profoundly affect the digestive system (Santonicola et al., 2019). EDs and gastrointestinal diseases also share several putative risk factors, including psychological stress (Caso, Leza, & Menchen, 2008; Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008), changes to the gut microbiome (Seitz, Trinh, & Herpertz-Dahlmann, 2019; Shin, Preidis, Shulman, & Kashyap, 2019), and alterations in genes associated with immune system regulation (Blumberg, 2009; Duncan et al., 2017).

Although few studies exist, initial data suggest a phenotypic association between EDs and both functional and structural (i.e. characterized by physical abnormalities in the gastrointestinal tract) gastrointestinal diseases. In the largest study to date, the odds of having an autoimmune gastrointestinal disease (e.g. celiac disease, Crohn's disease) were twice as high in people receiving ED treatment relative to age- and sex-matched controls (Raevuori et al., 2014). Likewise, elevated ED symptoms (e.g. body dissatisfaction) have been found in individuals receiving treatment for inflammatory bowel disease (IBD; Wabich, Bellaguarda, Joyce, Keefer, and Kinsinger, 2020), and food/eating preoccupations and weight/shape concerns observed in youth with IBD (Nicholas et al., 2007). While there has been a distinct lack of longitudinal research, one study found digestive problems in early childhood predicted elevated

AN symptoms in adolescence (Marchi & Cohen, 1990). These findings suggest gastrointestinal symptoms or diseases may predate EDs rather than solely being a consequence. Nevertheless, as highlighted in a recent review by Staller, Abber, and Murray (2023), there is likely a bi-directional relationship between EDs and gastrointestinal disease. For example, exclusion diets and pain associated with gastrointestinal disease may increase food avoidance, while irregular eating patterns may worsen gastrointestinal dysfunction (Staller et al., 2023). Case reports also suggest some individuals with EDs may exacerbate IBD symptoms to achieve weight loss (e.g. abandoning medications to worsen diarrhea, using stoma for purging) (Ilzarbe et al., 2017).

Despite initial studies suggesting a link between gastrointestinal disease and EDs, several gaps in the literature remain. Studies have largely focused on individuals seeking treatment for an ED (Ilzarbe et al., 2017; Raevuori et al., 2014) or gastrointestinal disease (Ilzarbe et al., 2017; Nicholas et al., 2007; Wabich et al., 2020). However, only 20–30% of people with EDs seek treatment (Hart, Granillo, Jorm, & Paxton, 2011) and treatment-seeking individuals are not representative of all people with EDs (e.g. they may have more severe symptoms; Forrest, Smith, & Swanson, 2017). Research has primarily focused on AN rather than bulimia nervosa (BN), binge-eating disorder (BED), or dimensional symptoms (e.g. binge eating, weight/shape concerns) that are more common than threshold EDs (Goossens, Soenens, & Braet, 2009; Mond et al., 2013) and associated with significant comorbidity and distress (Forney, Haedt-Matt, & Keel, 2014; Mond et al., 2013). Study participants have also been overwhelmingly female (Ilzarbe et al., 2017; Raevuori et al., 2014; Wabich et al., 2020), with little research on males.

It is also not fully clear what factors underlie associations between gastrointestinal diseases and EDs. One possibility is that environmental stressors, such as psychological stress or environmentally-mediated disturbances to the microbiome, may increase risk for both EDs and gastrointestinal disorders (Caso et al., 2008; Lo Sauro et al., 2008; Person & Keefer, 2021). Shared genetic influences may also play a role. Research suggests significant genetic overlap between gastrointestinal diseases and psychiatric phenotypes related to EDs (e.g. post-traumatic stress disorder, major depression; Chen, Zhang, Huang, & Jia, 2023; Zhou et al., 2023). One recent genome-wide association study (GWAS) found a significant genetic correlation between AN and IBS specifically ($r = 0.15$; Gong et al., 2023), though other EDs and dimensional ED symptoms were not examined. Other GWAS studies have identified inflammatory genes that contribute to risk for both AN and autoimmune disorders (Duncan et al., 2017) that could provide a genetic link between EDs and gastrointestinal disease.

A powerful tool for disentangling potential genetic and/or environmental etiology is the classical twin study. Although twin studies are unable to identify the specific genes or environmental factors at play, they can point to the types of mechanisms that might underlie both disorders and their overlap. Etiologic insights from twin research can also inform more targeted studies to identify specific genetic/environmental factors contributing to shared risk.

To date, no twin studies have examined the overlap between EDs and gastrointestinal disease. Consequently, the aims of our study were to examine phenotypic and etiologic associations between gastrointestinal disease broadly defined (e.g. GERD, IBDs, IBS) and EDs in a large, population-based adult twin sample. To address limitations of past research, we examined males and females in all analyses and sex differences in associations. We also examined multiple ED diagnoses (AN, BN, BED) and dimensional ED symptoms to better understand associations with gastrointestinal disease across ED symptom presentations and severity. We expected people with gastrointestinal diseases to have significantly higher rates of ED diagnoses/symptoms. Due to the lack of past research, we did not have hypotheses regarding which types of EDs would be most strongly associated with gastrointestinal disease; however, we expected associations with both threshold EDs and ED symptoms given some prior research suggesting elevated dimensional ED symptoms in people with gastrointestinal disease (Nicholas et al., 2007; Wabich et al., 2020). Finally, we expected some degree of genetic overlap between ED diagnoses/symptoms and gastrointestinal disease based on past GWAS studies, although we did not have specific hypotheses regarding the magnitude of this overlap relative to environmental factors given limited prior research.

Methods

Participants

Analyses included 2980 women (50.7%) and 2903 men (49.4%) aged 18–65 ($M_{age} = 36.57$, S.D. = 8.04) from the Michigan Twins Project (MTP), a population-based twin registry that serves as a recruitment pool for research through the Michigan State University Twin Registry (MSUTR; Burt & Klump, 2013, 2019; Klump & Burt, 2006). Data collection for the current study spanned 2010–2016. MSUTR recruits twins via birth records in collaboration with the Michigan Department of Health and Human Services. Response rates are similar or better than those of other twin registries, and MTP twins are demographically representative of Michigan (Burt & Klump, 2019). See Table 1 for additional demographic and zygosity information.

Measures

Zygosity

Zygosity was determined using a well-validated physical similarity questionnaire completed by each twin (Lykken, Bouchard, McGue, & Tellegen, 1990). This questionnaire is over 95% accurate in determining zygosity based on DNA and serologic testing (Lykken et al., 1990; Peeters, Van Gestel, Vlietinck, Derom, & Derom, 1998).

Dimensional ED symptoms

Dimensional ED symptoms were assessed using a self-report version of the Michigan Twins Project Eating Disorder Survey (MTP-ED), a nine-item questionnaire containing items regarding body dissatisfaction (i.e. distress about body shape), weight preoccupation (i.e. fear of weight gain), and ED behaviors (i.e. dieting, purging, binge eating). Each item is rated from 0 (not true) to 2 (certainly true). MTP-ED scores were prorated if one item was missing and coded as missing if >1 item was missing.

The MTP-ED has been previously validated in men and women. It has strong correlations with other ED measures (e.g. Eating Disorder Examination Questionnaire; Fairburn and Beglin, 1994) and significant associations with anxiety/depressive symptoms (Mikhail et al., 2021, 2023) and (inversely) wellbeing (Mikhail et al., in press). Internal consistency in the current sample is excellent for both women ($\alpha = 0.86$) and men ($\alpha = 0.83$). Both women and men showed good variability in ED symptoms

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Table 1. Descriptive statistics for participant demographics and symptoms ($N = 5883$)

Participant characteristics	Mean (s.d.) or % of sample (N)	Range
Age	36.57 (8.04)	18.08–65.84
Sex		
Female	2980 (50.7%)	–
Male	2903 (49.4%)	–
Zygosity (N listed as number of pairs)		
Complete opposite sex pairs	7 (0.2%)	–
Complete female monozygotic pairs	703 (23.9%)	–
Complete female dizygotic pairs	351 (11.9%)	–
Complete female pairs of unknown zygosity	1 (0.03%)	–
Women without cotwin data (N participants)	863 (14.7%)	–
Complete male monozygotic pairs	549 (18.7%)	–
Complete male dizygotic pairs	257 (8.7%)	–
Complete male pairs of unknown zygosity	1 (0.03%)	–
Men without cotwin data (N participants)	1282 (21.8%)	–
Race and ethnicity		
White (non-Hispanic)	90.6% (5328)	–
Black/African American (non-Hispanic)	5.4% (320)	–
Hispanic/Latinx	1.7% (102)	–
Asian American	0.3% (15)	–
Native American/American Indian	0.2% (14)	–
More than one race	1.1% (66)	–
Other/Unknown	0.7% (38)	–
BMI	27.06 (5.69)	16.46–50.97
Household income	$ 75 021 (57 466)	$0–$ 300 000 +
Education level		
Less than high school	2.9% (170)	–
High school graduate	19.1% (1117)	–
Less than 4 years of college	29.3% (1711)	–
College graduate (4–6 years of college)	35.4% (2071)	–
Post-graduate education	13.3% (779)	–

Symptom measures	Mean (s.d.) or % of sample (N)	Sample range	Possible range	Cronbach's alpha
MTP-ED total score (female)	6.26 (4.22)	0–18	0–18	0.86
MTP-ED total score (male)	3.70 (3.55)	0–16	0–18	0.83
Reported having AN, BN, or BED (female)	5.7% (166)	–	–	–
AN (female)	3.0% (89)	–	–	–
BN (female)	2.6% (76)	–	–	–
BED (female)	2.2% (64)	–	–	–
Reported having AN, BN, or BED (male)	1.2% (34)	–	–	–
AN (male)	0.6% (16)	–	–	–
BN (male)	0.6% (18)	–	–	–
BED (male)	0.7% (20)	–	–	–
Reported having a GI disease (female)	5.3% (158)	–	–	–

(*Continued*)

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Table 1. (*Continued.*)

Symptom measures	Mean (s.d.) or % of sample (*N*)	Sample range	Possible range	Cronbach's alpha
Reported having a GI disease (male)	4.7% (137)	–	–	–
Taking medication for a GI disease (female)	4.3% (127)	–	–	–
Taking medication for a GI disease (male)	4.3% (126)	–	–	–

Note: GI, gastrointestinal; BMI, body mass index; MTP-ED, Michigan Twins Project Eating Disorder Survey self-report; household income, participant and spouse's (if applicable) combined income; AN, anorexia nervosa; BN, bulimia nervosa; BED, binge-eating disorder. The number of complete opposite-sex twin pairs was small because adult opposite-sex twins (i.e. above age 18) were not explicitly recruited by the Michigan Twins Project. We retained these twins and twins without cotwin data in our sample to maximize sample size and include all available participants in phenotypic analyses. N's may not add up to the total N for all variables due to missing values.

(see Table 1), with women having higher mean total scores ($p < 0.001$) that replicate well-documented sex differences in disordered eating.

ED Diagnoses

Participants indicated whether they (1) ever had and (2) had been treated for an ED (AN, BN, or BED) on the MTP checklist of physical and mental health conditions. Because only a minority of people with EDs seek treatment (30.5% in this study, consistent with past estimates; Hart et al., 2011), we included participants who reported having an ED regardless of whether they reported receiving treatment. As expected, lifetime EDs were more common in women (5.7%) than men (1.2%). MTP-ED scores were significantly higher in participants who reported a lifetime ED for both women ($d = 0.82$; $p < 0.001$) and men ($d = 1.26$; $p < 0.001$).

Gastrointestinal disease

While the MTP checklist of physical and mental health conditions did not include items specifically pertaining to gastrointestinal diseases, two items prompted participants to write in whether they had any additional chronic illnesses ('any other chronic illness or disability; if 'Yes', please describe') or were taking any medications ('currently taking any prescription medications; if 'Yes', specify what medications and for what conditions'). These items were used to code the presence of gastrointestinal diseases. A participant was coded as having a gastrointestinal disease if they reported (1) having a disease that primarily affects the gastrointestinal tract, and/or (2) taking a medication predominantly used to treat a gastrointestinal disease, *unless* they specified taking it for a non-gastrointestinal condition. Participants with other health conditions that may involve gastrointestinal symptoms but are not primarily related to gastrointestinal health (e.g. nausea associated with migraines) were classified as *not* having a gastrointestinal disease. The first and second authors (LAP and MEM) developed a coding guide for inclusion/exclusion of gastrointestinal diseases (see online Supplemental Material), then independently coded the presence/absence of gastrointestinal disease for each participant. Interrater reliability was excellent ($\kappa = 0.97$) and all discrepancies were resolved by consensus of the first and second author.

In total, 295 (5.0%) participants reported a gastrointestinal disease, which is consistent with population-level rates (Canavan, West, & Card, 2014; El-Serag, Sweet, Winchester, & Dent, 2014; Xu, Dahlhamer, Zammitti, Wheaton, & Croft, 2018). A few participants provided responses that were difficult to definitively code (e.g. 'chronic pain in my lower right side,' 'autoimmune disorder' without additional specification; $n = 12$, 0.2%) and were excluded from analyses. Participants reported a range of gastrointestinal diseases, including GERD or heartburn ($n = 172$; 58.3% of participants with gastrointestinal diseases), IBS ($n = 23$; 7.8%), Crohn's disease ($n = 18$; 6.1%), ulcerative colitis or colitis ($n = 14$; 4.7%), gastrointestinal ulcers ($n = 8$; 2.7%), diverticulitis ($n = 6$; 2.0%), gastritis ($n = 4$; 1.4%), celiac disease ($n = 3$; 1.0%), gastroparesis ($n = 1$; 0.3%), and colon cancer ($n = 1$; 0.3%) (note that some participants reported >1 gastrointestinal disease). Participants who reported symptoms clearly linked to gastrointestinal health (e.g. 'chronic stomach problems,' 'blood in bowel', 'gastrointestinal disease'; $n = 9$; 3.0%) or reported taking a medication primarily used to treat gastrointestinal disease (e.g. omeprazole, Nexium, Asacol; $n = 46$; 15.6%) but did not name a specific diagnosis were also included in the group with gastrointestinal diseases. The presence of gastrointestinal disease was coded dichotomously (any or no gastrointestinal disease) for primary analyses to maximize power, but phenotypic analyses for subcategories of gastrointestinal diseases are reported in online Supplementary Table S1 and tended to show similar effects across conditions. Unfortunately, *n*s were too small to conduct twin models for each gastrointestinal disease independently. Importantly, phenotypic and twin modeling results were identical if the group with gastrointestinal disease was restricted to individuals currently taking medication for their condition ($n = 253$, 85.8%) (see online Supplementary Tables S2–S4), who would likely have the most severe, active, or formally diagnosed conditions.

Body mass index (BMI)

Individuals with higher BMIs are more likely to experience disordered eating, due in part to weight stigma (Nagata, Garber, Tabler, Murray, & Bibbins-Domingo, 2018; Neumark-Sztainer et al., 2007). Associations between gastrointestinal disease and BMI are nuanced, with elevated rates in people with both high and low BMIs (Mendall, Viran Gunasekera, Joseph John, & Kumar, 2011). We therefore conducted models both with and without BMI calculated from self-reported height and weight to directly assess its impact on results. BMI values above the 99.5th percentile or below the 0.5th percentile in the sample were marked as missing to eliminate extreme values that may reflect errors in self-reported height/weight.

Statistical analyses

Phenotypic analyses

We examined phenotypic associations between gastrointestinal disease and ED symptoms/diagnoses using multilevel models with maximum likelihood estimation and a random intercept at the family level to account for clustering of twins within families. All continuous variables were *z* scored to increase interpretability. We first examined associations between gastrointestinal disease

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and ED symptoms/diagnoses across the full sample. We then added a sex × gastrointestinal disease interaction to examine whether associations significantly differed by sex.

Demographic variables, including household annual income (i.e. sum of the participant's income and their spouse's income, if applicable), age, sex, and race/ethnicity, were included as covariates for analyses of the MTP-ED. Analyses of lifetime ED diagnoses excluded race/ethnicity as a covariate to avoid estimation difficulties resulting from the small number of participants in some racial/ethnic groups (e.g. <20 Asian American and Native American participants); however, results were unchanged if race/ethnicity was instead included as a dichotomized covariate (i.e. White participants compared to participants of color).

Twin analyses

We used correlated factors twin models (Loehlin, 1996) to examine whether observed phenotypic associations were due to overlapping genes and/or environmental factors. We excluded the small number of opposite-sex twin pairs in the sample (7 pairs; 0.2%) from these analyses to prevent biases in parameter estimates that could result from qualitative sex differences in etiologic influences. The full correlated factors twin model with additive genetic influences (A; genetic influences that sum across genes), shared environmental influences (C; environmental influences that increase similarity between cotwins, such as familial food traditions), and nonshared environmental influences (E; environmental influences not shared by cotwins, such as infections that impact the microbiome, and measurement error) is depicted in Fig. 1. The model first estimates the total additive genetic (a_1 in Fig. 1), shared environmental (c_1), and nonshared environmental (e_1) influences on ED symptoms/diagnoses. The model then estimates the total genetic (a_2), shared environmental (c_2), and nonshared environmental (e_2) influences on gastrointestinal disease. Finally, the model estimates correlations between genetic (rA), shared environmental (rC), and nonshared environmental (rE) influences on ED symptoms/diagnoses and gastrointestinal disease. These correlations indicate the extent of overlap between genetic/environmental influences on ED symptoms/diagnoses and gastrointestinal disease.

Analyses were conducted in Mplus version 8.6 (Muthén & Muthén, 1998–2021) using WLSMV estimation (Bandalos, 2014) based on models from Prescott (2004). For analyses of dimensional ED symptoms, age was regressed out of the MTP-ED total score and symptoms were standardized separately in women and men. As with phenotypic analyses, we conducted a second set of models that additionally regressed BMI out of the MTP-ED total score. Following Prescott (2004), analyses of ED diagnoses and gastrointestinal disease used theta parameterization with threshold values estimated in a prior run. Because participants were recruited for the MTP individually rather than by twin pair, only one twin participated in some cases (see Table 1). While this somewhat decreased power for etiologic analyses, inclusion of singleton twins did not influence the pattern of etiologic effects, as findings were unchanged if these twins were excluded (see online Supplementary Table S5).

In addition to the full model, we fit nested submodels to examine whether specific parameters (e.g. correlations between genetic/environmental influences on gastrointestinal disease and EDs) could be constrained to zero without worsening model fit. Twin models with a categorical outcome in Mplus do not provide some of the fit indices traditionally used to compare models, such as AIC/BIC. Consequently, model fit comparisons were made using the Mplus DIFFTEST option, which provides a χ^2 difference test optimized for WLSMV estimation. We also report TLI, RMSEA, and SRMR as indicators of absolute model fit. Model fit is deemed adequate if RMSEA is < 0.80 (Browne & Cudeck, 1993) and TLI ⩾ 0.95 or SRMR ⩽ 0.90 (Hu & Bentler, 1999).

We initially conducted etiologic analyses within a sex constraint framework to examine whether there were any differences in the etiology of the overlap between ED symptoms/diagnoses and gastrointestinal disease in women and men. Etiologic estimates for ED symptoms/diagnoses, gastrointestinal disease, and their overlap could be fully constrained to equality across sex ($ps \geqslant 0.767$ for tests of changes in χ^2 when constraining all

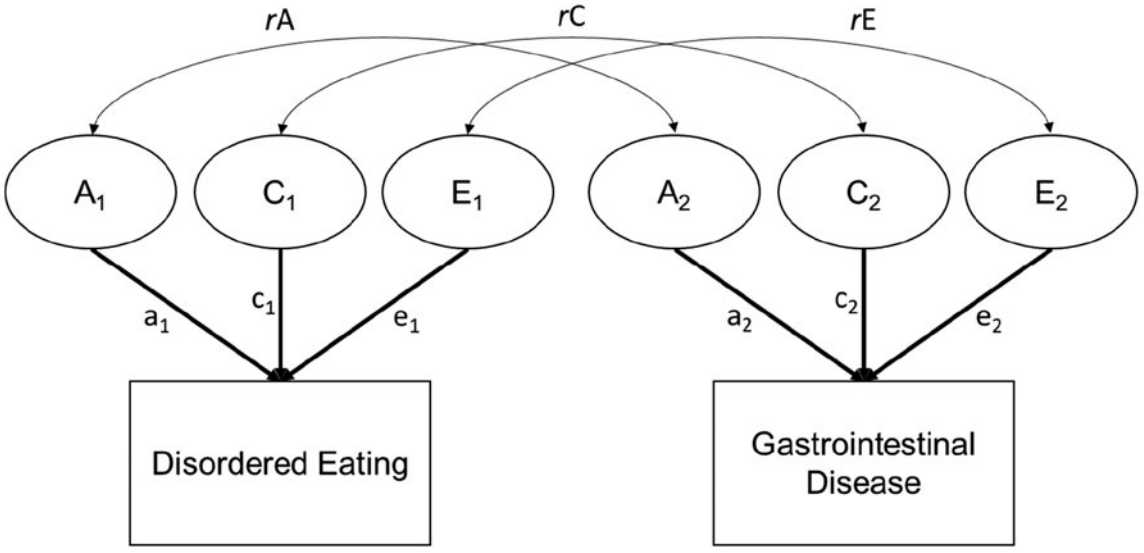

Figure 1. The full correlated factors twin model. Paths from A_1, C_1, and E_1 to disordered eating represent the total additive genetic (a_1), shared environmental (c_1), and nonshared environmental (e_1) influences on disordered eating. Paths from A_2, C_2, and E_2 to gastrointestinal disease represent the total additive genetic (a_2), shared environmental (c_2), and nonshared environmental (e_2) influences on gastrointestinal disease. Curved arrows represent correlations between genetic (rA), shared environmental (rC), and nonshared environmental (rE) influences on disordered eating and gastrointestinal disease.

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parameters to equality), and thus we were able to analyze men and women together in a single model. However, model fitting results for the sex constraint models and estimates in men and women separately are included in online Supplementary Tables S6–S7.

Results

Phenotypic analyses

Participants with gastrointestinal diseases reported significantly greater dimensional ED symptoms after controlling for age, sex, income, and race/ethnicity ($\beta = 0.21$, $p < 0.001$, 95% CI [0.10–0.32]) (see Table 2). Participants with gastrointestinal diseases were also significantly more likely to report having a lifetime ED (OR 2.90, $p = 0.001$, 95% CI [1.54–5.43]). This relationship remained significant in sensitivity analyses excluding one participant who reported receiving lifetime ED treatment and taking a gastrointestinal medication without a specified condition (which may have been prescribed off-label for the ED) (OR 2.68, $p = 0.002$). Among specific ED diagnoses, the association with gastrointestinal disease was only significant for BED (OR 3.98, $p = 0.001$, 95% CI [1.77–8.94]), but odds ratios for AN (OR 1.43, $p = 0.415$) and BN (OR 2.18, $p = 0.058$) were also >1 (see online Supplementary Table S8). Associations between gastrointestinal disease and both dimensional ED symptoms ($\beta = 0.12$, $p = 0.021$, 95% CI [0.02–0.23]) and odds of a lifetime ED (OR 2.45, $p = 0.008$, 95% CI [1.26–4.76]) remained significant after additionally controlling for BMI, albeit slightly attenuated. Associations between gastrointestinal disease and ED symptoms/diagnoses did not significantly differ across sex, but effect sizes tended to be slightly larger for women (see Table 2). Associations also remained significant and were similar or greater in magnitude among participants in young adulthood (ages 18–29), when both EDs and gastrointestinal diseases often onset (see online Supplementary Table S9).

Twin analyses

Model-fitting analyses and parameter estimates for the correlated factors twin models are presented in Tables 3, 4. Consistent with past research in adults (Klump, Culbert, & Sisk, 2017; Trace, Baker, Peñas-Lledó, & Bulik, 2013), we observed significant genetic (total A variance = 48–59%) and nonshared environmental (total E variance = 47–41%) influences on ED symptoms and diagnoses in the full models, with minimal shared environmental influences. Estimates for etiologic influences on gastrointestinal disease were likewise consistent with past research in the full models, with heritability (total A variance = 56–64%) similar to that for IBDs in past twin research (~50–75% for diverticulitis and Crohn's disease; Gordon, Trier Moller, Andersen, & Harbord, 2015; Strate *et al.* 2013). The full model for dimensional ED symptoms also showed significant genetic overlap with gastrointestinal disease (rA = 0.36, 13% of variance shared; see Table 4), but no significant overlap in shared or nonshared environmental influences (i.e. rC and rE were both non-significant). Although non-significant in the full model, the genetic correlation between gastrointestinal disease and ED diagnoses was similar in magnitude (rA = 0.33, 11% of variance shared).

With respect to model fitting, because shared environmental influences on ED symptoms/diagnoses and gastrointestinal disease were minimal in the full models, we first constrained all C variance to zero. This produced non-significant changes in χ^2 (see Table 3). We then compared models that constrained either genetic or nonshared environmental correlations between gastrointestinal disease and ED symptoms/diagnoses to zero. In all cases, the model that constrained the nonshared environmental correlation to zero but retained the genetic correlation was best-fitting, as indicated by non-significant changes in χ^2 and all model fit parameters. These findings indicate all phenotypic overlap between ED symptoms/diagnoses and gastrointestinal disease is due to shared genetic factors. Genetic correlations from the best fitting models were significant between gastrointestinal disease and both ED symptoms ($r = 0.21$, 95% CI [0.10–0.30], 4% of variance shared) and diagnoses ($r = 0.30$, 95% CI [0.09–0.49], 9% of variance shared). These data suggest a moderate degree of overlap in genes that influence ED symptoms/diagnoses and gastrointestinal disease, as well as unique genetic influences on each condition. Genetic correlations between gastrointestinal disease and ED symptoms remained significant after regressing out BMI (see Table 4), indicating the genetic overlap between ED symptoms/diagnoses and gastrointestinal disease is largely independent of genetic influences on body weight.

Discussion

This was the first study to examine associations between gastrointestinal disease and both ED diagnoses and dimensional ED symptoms in a large, population-based sample of men and women, as well as the first to use twin modeling to disentangle genetic and environmental contributions to their comorbidity. We found that people with gastrointestinal diseases exhibited significantly greater dimensional ED symptoms and were significantly more likely to report a lifetime ED. Results were generally consistent across age and sex. Results also remained significant (albeit slightly attenuated) after controlling for BMI, suggesting associations cannot be fully explained by differences in body weight between people with and without gastrointestinal diseases. Associations also remained significant and were similar in magnitude in sensitivity analyses restricting the sample with gastrointestinal diseases to participants currently taking medication for their condition; thus, findings are consistent across different measures and potential severity of gastrointestinal disease. Twin analyses indicated the overlap between gastrointestinal diseases and disordered eating/EDs is due to shared genetic, rather than environmental, factors. Overall, results significantly extend existing research on gastrointestinal disease and EDs by finding a robust association with a likely genetic basis.

The observed phenotypic associations between ED symptoms/diagnoses and gastrointestinal disease are consistent with previous research in smaller, clinical samples that have primarily examined people in active treatment for an ED or gastrointestinal disease (Raevuori et al., 2014; Wabich et al., 2020). Similar findings across settings, differing levels of symptom severity (e.g. dimensional symptoms and threshold diagnoses), and clinical and non-clinical populations suggest a replicable association that is evident across contexts and cannot be attributed to a treatment-seeking bias. Additionally, our findings in males extend previous research; past literature has predominantly focused on females, and similar associations in males suggest shared risk factors across sex. Past literature has also primarily focused on AN, whereas our study examined a range of ED diagnoses and symptoms. Interestingly, we found the strongest association between gastrointestinal disorders and BED (with or without BMI as a covariate), suggesting gastrointestinal disorders are not uniquely related to AN.

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Table 2. Phenotypic associations between gastrointestinal disease and eating disorder (ED) symptoms and diagnoses

Dimensional ED symptoms on the MTP-ED across the full sample				
Predictor	β	S.E.	p	95% Confidence interval
BMI excluded				
Intercept	−0.32	0.02	**<0.001**	[−0.36 to −0.28]
GI disease	0.21	0.06	**<0.001**	[0.10–0.32]
Income	−0.01	0.01	0.494	[−0.04 to 0.02]
Age	0.07	0.02	**<0.001**	[0.04–0.10]
Sex	0.64	0.03	**<0.001**	[0.59–0.70]
Race and ethnicity				
Black/non-Hispanic	−0.11	0.06	0.098	[−0.23 to 0.02]
Hispanic	0.01	0.10	0.928	[−0.19 to 0.21]
Asian American	0.26	0.29	0.371	[−0.31 to 0.82]
Native American	0.23	0.28	0.411	[−0.32 to 0.79]
Multiracial	0.03	0.13	0.809	[−0.22 to 0.28]
Other/Not Specified	0.11	0.17	0.500	[−0.22 to 0.45]
BMI included				
Intercept	−0.35	0.02	**<0.001**	[−0.38 to −0.31]
GI disease	0.12	0.05	**0.021**	[0.02–0.23]
Income	0.03	0.01	**0.015**	[0.01–0.06]
Age	−0.01	0.02	0.647	[−0.04 to 0.02]
Sex	0.70	0.03	**<0.001**	[0.65–0.75]
Race and ethnicity				
Black/non-Hispanic	−0.32	0.06	**<0.001**	[−0.44 to −0.20]
Hispanic	−0.05	0.10	0.638	[−0.24 to 0.15]
Asian American	0.38	0.26	0.138	[−0.12 to 0.89]
Native American	0.18	0.26	0.487	[−0.33 to 0.69]
Multiracial	0.01	0.12	0.904	[−0.23 to 0.26]
Other/Not specified	0.14	0.16	0.386	[−0.18 to 0.46]
BMI	0.38	0.01	**<0.001**	[0.36–0.41]
Dimensional ED symptoms on the MTP-ED with moderation by sex				
Predictor	β	S.E.	p	95% Confidence Interval
BMI excluded				
Intercept	−0.31	0.02	**<0.001**	[−0.35 to −0.27]
GI disease	0.11	0.08	0.175	[−0.05 to 0.27]
Sex	0.63	0.03	**<0.001**	[0.58–0.69]
GI disease × sex	0.19	0.11	0.091	[−0.03 to 0.41]
Income	−0.01	0.01	0.520	[−0.04 to 0.02]
Age	0.07	0.02	**<0.001**	[0.04–0.10]
Race and ethnicity				
Black/non-Hispanic	−0.11	0.06	0.102	[−0.23 to 0.02]
Hispanic	0.01	0.10	0.909	[−0.19 to 0.21]
Asian American	0.26	0.29	0.371	[−0.30 to 0.82]
Native American	0.24	0.28	0.400	[−0.32 to 0.80]

(*Continued*)

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Table 2. (*Continued.*)

Dimensional ED symptoms on the MTP-ED with moderation by sex				
Predictor	*β*	S.E.	*p*	95% Confidence Interval
Multiracial	0.04	0.13	0.780	[−0.21 to 0.29]
Other/Not specified	0.12	0.17	0.495	[−0.22 to 0.45]
BMI included				
Intercept	−0.35	0.02	**<0.001**	[−0.38 to −0.31]
GI disease	0.07	0.08	0.354	[−0.08 to 0.22]
Sex	0.69	0.03	**<0.001**	[0.64–0.75]
GI disease × sex	0.11	0.11	0.315	[−0.10 to 0.32]
Income	0.03	0.01	**0.014**	[0.01–0.06]
Age	−0.01	0.02	0.641	[−0.04 to 0.02]
Race and ethnicity				
Black/non-Hispanic	−0.32	0.06	**<0.001**	[−0.44 to −0.20]
Hispanic	−0.04	0.10	0.647	[−0.24 to 0.15]
Asian American	0.38	0.26	0.138	[−0.12 to 0.89]
Native American	0.18	0.26	0.481	[−0.32 to 0.69]
Multiracial	0.02	0.12	0.881	[−0.22 to 0.26]
Other/Not specified	0.14	0.16	0.384	[−0.18 to 0.46]
BMI	0.38	0.01	**<0.001**	[0.36–0.41]
Lifetime ED diagnoses across the full sample				
Predictor	Odds ratio	S.E.	*p*	95% Confidence interval
BMI excluded				
Intercept	0.003	0.001	**<0.001**	[0.001–0.01]
GI disease	2.90	0.93	**0.001**	[1.54–5.43]
Income	0.85	0.09	0.116	[0.69–1.04]
Age	0.95	0.10	0.592	[0.78–1.16]
Sex	6.88	1.74	**<0.001**	[4.19–11.30]
BMI included				
Intercept	0.004	0.002	**<0.001**	[0.001–0.01]
GI disease	2.45	0.83	**0.008**	[1.26–4.76]
Income	0.86	0.10	0.187	[0.70–1.07]
Age	0.98	0.10	0.874	[0.80–1.21]
Sex	6.52	1.65	**<0.001**	[3.97–10.71]
BMI	0.90	0.08	0.260	[0.75–1.08]
Lifetime ED diagnoses with moderation by sex				
Predictor	Odds ratio	S.E.	*p*	95% Confidence interval
BMI excluded				
Intercept	0.003	0.001	**<0.001**	[0.001–0.01]
GI disease	2.49	1.72	0.189	[0.64–9.68]
Sex	6.76	1.77	**<0.001**	[4.05–11.29]
GI disease × sex	1.21	0.94	0.802	[0.27–5.54]
Income	0.85	0.09	0.118	[0.69–1.04]

(*Continued*)

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Table 2. (*Continued.*)

Lifetime ED diagnoses with moderation by sex				
Predictor	Odds ratio	s.e.	*p*	95% Confidence interval
Age	0.95	0.10	0.590	[0.78–1.16]
BMI included				
Intercept	0.004	0.002	**<0.001**	[0.001–0.01]
GI disease	1.63	1.29	0.540	[0.34–7.70]
Sex	6.26	1.63	**<0.001**	[3.76–10.43]
GI disease × sex	1.68	1.47	0.555	[0.30–9.33]
Income	0.87	0.10	0.191	[0.70–1.07]
Age	0.98	0.10	0.870	[0.80–1.21]
BMI	0.90	0.08	0.257	[0.75–1.08]

Note: BMI, body mass index; MTP-ED, Michigan twins project eating disorder survey total score; GI, gastrointestinal. Reference group for sex is male. For analyses of the MTP-ED, the reference group for race/ethnicity is White/non-Hispanic. Ethnicity was excluded from models of lifetime ED diagnoses to avoid estimation difficulties resulting from the small number of participants in some racial/ethnic groups; however, the overall pattern of results was identical if ethnicity was included as a dichotomous covariate (i.e. comparing White participants to participants of color). Effects significant at $p < 0.05$ are bolded.

Additional research on gastrointestinal disturbances in people with BED and binge eating is needed.

The genetic overlap identified between gastrointestinal disease and ED symptoms/diagnoses also provides novel insight into the potential mechanisms that may drive their co-occurrence. Notably, the magnitude of the genetic correlation between ED diagnoses and gastrointestinal diseases in this sample ($r = 0.30$) was comparable to genetic correlations between AN and psychiatric phenotypes in past GWAS studies ($r = 0.25$ with anxiety disorders, 0.28 with major depressive disorder; Watson et al., 2019), adding to growing evidence that EDs may be best conceptualized as neuro-gastro-metabolic disorders rather than purely psychiatric in nature. Although the current study was unable to examine the specific genes shared between EDs and gastrointestinal diseases, prior research suggests inflammatory genes may play a key role. Inflammation and resulting changes to the gut microbiome can contribute to depression, anxiety, and potentially eating disturbances (Peirce & Alviña, 2019). Individuals with gastrointestinal diseases frequently have elevated inflammatory markers, and those with EDs often have an increased inflammatory response (Bern & O'Brien, 2013; Diaz-Marsa et al., 2021). Molecular genetics studies have also implicated inflammatory genes in risk for

Table 3. Model fit comparisons for correlated factors twin models

Model	$\Delta\chi^2$ (df)	*p*	*TLI*	*RMSEA*	*SRMR*
Disordered eating – BMI not regressed out					
Full model	–	–	0.989	0.014 [0.000–0.028]	0.044
Constrain all C	0.530 (3)	0.912	0.995	0.009 [0.000–0.023]	0.044
Constrain all C, GI and DE E correlation	0.686 (4)	0.953	0.996	0.008 [0.000–0.022]	0.044
Constrain all C, GI and DE A correlation	11.805 (4)	0.019	0.979	0.019 [0.006–0.030]	0.055
Disordered eating – BMI regressed out					
Full model	–	–	0.999	0.005 [0.000–0.022]	0.044
Constrain all C	0.481 (3)	0.923	1.000	0.000 [0.000–0.018]	0.045
Constrain all C, GI and DE E correlation	0.676 (4)	0.954	1.000	0.000 [0.000–0.017]	0.045
Constrain all C, GI and DE A correlation	7.122 (4)	0.130	0.994	0.010 [0.000–0.023]	0.051
Constrain all C, GI and DE E and A correlations	14.855 (5)	0.011	0.982	0.017 [0.000–0.028]	0.057
ED diagnoses					
Full model	–	–	0.998	0.004 [0.000–0.024]	0.067
Constrain all C	0.000 (3)	1.000	1.000	0.000 [0.000–0.018]	0.067
Constrain all C, GI and ED E correlation	0.085 (4)	0.999	1.000	0.000 [0.000–0.016]	0.067
Constrain all C, GI and ED A correlation	5.729 (4)	0.220	0.989	0.008 [0.000–0.024]	0.085
Constrain all C, GI and ED E and A correlations	15.303 (5)	0.009	0.945	0.019 [0.004–0.031]	0.104

Note: DE, disordered eating; ED, eating disorder; GI, gastrointestinal disease; A, additive genetic; C, shared environmental; E, nonshared environmental; BMI, body mass index; $\Delta\chi^2$, change in χ^2; df, degrees of freedom; TLI, Tucker–Lewis index; RMSEA, root mean square error of approximation; SRMR, standardized root mean squared residual. Dashes indicate a parameter is not applicable. 95% confidence interval for RMSEA is presented in brackets. The best-fitting model description is bolded.

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Table 4. Parameter estimates for the full and best-fitting correlated factors twin models

Parameter	Standardized estimates –full model	Standardized estimates –best-fitting model
MTP-ED disordered eating symptoms		
Disordered eating (DE)		
Total A variance	**0.48 [0.28–0.57]**	**0.54 [0.49–0.58]**
Total C variance	0.05 [0.00–0.23]	–
Total E variance	**0.47 [0.42–0.52]**	**0.47 [0.42–0.51]**
GI diseases		
Total A variance	**0.56 [0.17–0.66]**	**0.64 [0.57–0.67]**
Total C variance	0.08 [0.00–0.43]	–
Total E variance	**0.37 [0.33–0.43]**	**0.36 [0.33–0.43]**
Genetic correlation	**0.36 [0.07–1.00]**	**0.21 [0.10–0.30]**
Shared env. correlation	−1.00 [−1.00 to 1.00]	–
Nonshared env. correlation	−0.02 [−0.20 to 0.17]	–
MTP-ED disordered eating symptoms with BMI regressed out		
Disordered eating (DE)		
Total A variance	**0.42 [0.20–0.51]**	**0.48 [0.43–0.53]**
Total C variance	0.05 [0.00–0.25]	–
Total E variance	**0.53 [0.47–0.59]**	**0.52 [0.47–0.57]**
GI diseases		
Total A variance	**0.56 [0.19–0.66]**	**0.64 [0.57–0.67]**
Total C variance	0.08 [0.00–0.43]	–
Total E variance	**0.37 [0.33–0.43]**	**0.36 [0.33–0.43]**
Genetic correlation	**0.35 [0.07–1.00]**	**0.17 [0.07–0.28]**
Shared env. correlation	−1.00 [−1.00 to 1.00]	–
Nonshared env. correlation	−0.04 [−0.22 to 0.14]	–
Eating disorders		
Eating disorders (EDs)		
Total A variance	**0.59 [0.40–0.73]**	**0.59 [0.40–0.73]**
Total C variance	0.00 [0.00–0.00]	–
Total E variance	**0.41 [0.27–0.60]**	**0.41 [0.27–0.60]**
GI diseases		
Total A variance	**0.64 [0.49–0.74]**	**0.64 [0.49–0.74]**
Total C variance	0.00 [0.00–0.00]	–
Total E variance	**0.36 [0.25–0.51]**	**0.36 [0.25–0.51]**
Genetic correlation	0.33 [−0.03 to 0.60]	**0.30 [0.09–0.49]**
Shared env. Correlation	0.77 [−0.98 to 0.99]	–
Nonshared env. Correlation	−0.07 [−0.51 to 0.43]	–

Note: GI, gastrointestinal; env., environmental; A, additive genetic; C, shared environmental; E, nonshared environmental. Dashes represent parameters that were constrained to zero. 95% confidence intervals for path estimates are included in brackets, and significant parameters are bolded.

EDs (Duncan et al., 2017) and gastrointestinal disorders such as Crohn's disease (Franke et al., 2010). The commonality of inflammatory dysregulation across both conditions, along with research suggesting a significant contribution of genetics to chronic inflammation more generally (Ligthart et al., 2018), highlight inflammation as an important possible pathway of shared genetic etiology. Nevertheless, correlations between genetic influences on EDs and gastrointestinal disease were less than unity and most genetic variance was unshared, suggesting unique genetic factors contribute to the development of each condition. These may include genetic influences on temperament (e.g. negative mood states) or body image perception for EDs, and gut function in the case of gastrointestinal disease.

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While this study had many strengths (i.e. large, population-based sample of females and males, examination of a spectrum of ED symptoms and diagnoses), some limitations should be noted. The data did not allow for a way to assess when each condition began. Collecting data on the timeline of disordered eating and gastrointestinal disease onset could help further elucidate their typical developmental trajectory, including potential reciprocal relationships and whether functional and structural gastrointestinal disorders differ in their typical order of onset relative to EDs. It is notable, however, that significant associations between gastrointestinal disease and ED diagnoses/symptoms were already evident in young adulthood (see online Supplementary Table S9) when both conditions often onset.

ED diagnoses and gastrointestinal diseases were self-reported rather than assessed with a clinical interview. Although twin analyses yielded estimates of genetic and environmental influences similar to those for clinician-based diagnoses in prior research (e.g. Ilzarbe *et al.*, 2017; Raevuori *et al.*, 2014), it is important to replicate our findings with clinical diagnoses made via structured interviews. Additionally, some participants with gastrointestinal diseases may not have reported this on the broad items regarding chronic illnesses or medication used to code the presence of gastrointestinal disorders. However, erroneously including participants with gastrointestinal disease in the group with no gastrointestinal disorders would be expected to weaken (rather than amplify) associations with ED symptoms, suggesting effects may be even larger than observed in the current study. Nevertheless, it is important to replicate findings with specific items assessing gastrointestinal disease, or ideally, examination of medical records.

The study was also not able to examine the severity of reported gastrointestinal diseases beyond restricting the sample to those taking medication. It is possible that individuals with more severe gastrointestinal diseases show even greater rates of ED symptoms. We had limited power to examine associations with specific gastrointestinal diseases or draw conclusions about differences in associations across conditions, and larger samples of participants with specific gastrointestinal diseases are needed. We were also unable to examine associations with Avoidant/Restrictive Food Intake Disorder (ARFID) because it was not assessed in the MTP questionnaire. Past work has suggested elevated rates of ARFID in individuals with gastrointestinal disease (e.g. Fink, Simons, Tomasino, Pandit, and Taft, 2022) and research is needed to understand the etiology of this association.

Despite these limitations, our findings have important implications for treatment and research. It is imperative to screen gastrointestinal patients for EDs, as well as to screen ED patients for gastrointestinal diseases. Routine screening for EDs is rare in general (Johnston, Fornai, Cabrini, & Kendrick, 2007), and potentially particularly rare for gastrointestinal patients if symptoms such as restrictive eating are assumed to be a part of the gastrointestinal disease rather than a distinct ED. Gastroenterologists, primary care physicians, and ED specialists should be specifically trained in recognizing when a patient has developed an ED alongside their gastrointestinal disease, and vice versa, as catching either disease before extreme progression occurs could result in a more favorable prognosis. Results also support the critical need for more research on associations between disordered eating and gastrointestinal disease at both phenotypic and etiologic levels.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172300301X

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