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A systematic review and secondary data analysis of the interactions between the serotonin transporter 5-HTTLPR polymorphism and environmental and psychological factors in eating disorders

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A systematic review and secondary data analysis of the interactions between the serotonin transporter 5-HTTLPR polymorphism and environmental and psychological factors in eating disorders

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ABSTRACT

Objectives: To summarize and synthesize the growing gene x environment (GxE) research investigating the promoter region of the serotonin transporter gene (5-HTTLPR) in the eating disorders (ED) field, and overcome the common limitation of low sample size, by undertaking a systematic review followed by a secondary data meta-analysis of studies identified by the review. **Method:** A systematic review of articles using PsycINFO, PubMed, and EMBASE was undertaken to identify studies investigating the interaction between 5-HTTLPR and an environmental or psychological factor, with an ED-related outcome variable. Seven studies were identified by the systematic review, with complete data sets of five community ($n=1750$, 64.5% female) and two clinical ($n=426$, 100% female) samples combined to perform four secondary-data analyses: 5-HTTLPR x Traumatic Life Events to predict ED status ($n=909$), 5-HTTLPR x Sexual and Physical Abuse to predict bulimic symptoms ($n=1097$), 5-HTTLPR x Depression to predict bulimic symptoms ($n=1256$), and 5-HTTLPR x Impulsiveness to predict disordered eating

($n=1149$). **Results:** Under a multiplicative model, the low function (s) allele of 5-HTTLPR interacted with traumatic life events and experiencing both sexual and physical abuse (but not only one) to predict increased likelihood of an ED and bulimic symptoms, respectively. However, under an additive model there was also an interaction between sexual and physical abuse considered independently and 5-HTTLPR, and no interaction with traumatic life events. No other GxE interactions were significant.

Conclusion: Early promising results should be followed-up with continued cross-institutional collaboration in order to achieve the large sample sizes necessary for genetic research.

Key words: Eating disorders, gene-environment interaction, 5-HTTLPR, meta-analysis, systematic review, bulimia nervosa.

INTRODUCTION

Over the past decade, etiological models of eating disorders (EDs) have increasingly acknowledged the role of genetics, with twin studies estimating a notable heritable component (approximately 40-60%; Bulik, 2006, 2010; Fairweather-Schmidt & Wade, 2015; Trace et al., 2013). Investigations so far have not consistently identified specific candidate genes associated with increased ED risk, suggesting that hereditary factors in EDs may not operate via simple genetic association (Trace et al., 2013). Hence, studies are now increasingly examining whether environmental factors moderate the influence of candidate genes on risk for pathological eating behaviour. Gene x environment (GxE) interaction research in the ED field is still relatively novel, with early studies identifying potential candidate genes associated with ED risk under specific environmental conditions (e.g., history of abuse; Steiger et al., 2012). In anticipation of the increased popularity of this research focus, it is timely to evaluate the current state of evidence and to highlight existing limitations, in order to guide the direction and methods of future GxE studies in eating pathology.

Previous research examining genetic influences on eating pathology has primarily focused on genes in the serotonin and dopamine systems linked to functions relevant to EDs, including appetite, mood, and reward sensitivity (e.g., *SLC6A4*, *HTR2A*, *DRD2*, *DRD4*, *DAT1*, and *COMT*; see Culbert et al., 2015, and Trace et al., 2013, for a review). Direct genetic association studies have not provided a clear picture of the links between specific genes and EDs or disordered eating symptoms, with many initial significant findings failing to achieve consistent replication (see Calati et al., 2011; Culbert et al., 2015; Lee & Lin, 2010; Scherag et al., 2010; Trace et al., 2013).

One reason for a lack of direct association between allele frequency and ED risk may be that this relationship is moderated by environmental factors. Under the diathesis-stress model of GxE interactions, individuals carrying a 'risk' allele may be more susceptible to EDs when exposed to environmental stressors, but show no differences in outcome in the absence of challenging environmental circumstances, compared to those without the risky genotype (Caspi et al., 2003; Monroe & Simons, 1991). The role of GxE interactions in psychology has gained increasing attention since Caspi and colleagues (2003) found that stressful life events increased susceptibility to depression for those with one or two copies of the short (s) allele of the serotonin transporter gene (5-HTTLPR polymorphism).

Studies have since largely focused on 5-HTTLPR due to its biological relevance to psychiatric disorders (with the s-allele reducing serotonin transporter transcription efficiency; Heils et al., 1996), and early significant findings in the depression literature (Karg et al., 2011). Despite substantial research investigating GxE interactions with 5-HTTLPR and other polymorphisms, many studies are limited by small sample size, and replicability remains a major issue (see Duncan et al., 2014 for a review; Risch et al., 2009). Furthermore, most studies to date failed to control for confounding influences on the GxE interaction by not including all required covariate x gene and covariate x environment contrast terms in

the regression model (Keller, 2014). Studies examining case-control samples have also tended to evaluate the GxE effect using logistic regression and have thus tested departures from a multiplicative model of interaction, which is believed to be less biologically plausible than an additive model (Rothman, 1976; Rothman & Greenland, 1998).

GxE studies of candidate genes in eating pathology have been scarce. A recent review by Culbert et al. (2015) highlighted the heterogeneity of candidate GxE research in eating pathology. Their investigation identified five studies examining candidate GxE interactions with eating pathology outcome variables. Two studies reported a significant GxE interaction for 5-HTTLPR (Karwautz et al., 2011, parenting styles; Akkermann et al., 2012, traumatic life events), while one study investigating a psychological factor did not (Racine et al., 2009, impulsivity). The two remaining studies examined other genes (*NR3C1* x childhood abuse, Steiger et al., 2011; *BDNF* x restricted food intake; Akkermann et al., 2011), finding significant interactions to predict bulimia nervosa (BN) spectrum pathology. This paper presents a good start in summarising candidate GxE literature in eating disorders (although it was not a systematic review and thus omitted several studies, e.g., Stoltenberg et al., 2012; van Strien et al., 2010), and reflects the growing focus on gene x environment interactions in the eating disorders field.

While candidate GxE research in eating pathology is still in its infancy, it is not premature to consider how to best utilise academic resources to avoid the pitfalls GxE research has faced in other fields, such as lack of consistent replication and small sample sizes (Dick et al., 2015). This will aid greater accuracy in GxE findings, which is a vital step in increasing understanding of how individual differences at the genetic level can influence susceptibility to eating pathology. In the depression field, a protocol for a collaborative meta-analysis to achieve these aims has been published ($N = 33,761$), with authors aiming to re-analyse their data using a standardised analysis script to increase consistency of analytic methods and phenotypic definitions (Culverhouse et al., 2013). Future collaborations could

integrate complete datasets for combined re-analysis rather than relying on summary statistics. No such study has been undertaken in the ED field so far.

Thus, the present study aims to provide a systematic, detailed overview and re-analysis of current GxE studies investigating 5-HTTLPR in eating pathology, to clarify the current state of knowledge and to encourage future research to build upon this via continued focus on replication of published findings and multi-institute collaborations to achieve larger sample sizes. Specifically, it will examine, via a systematic review, existing studies that have analysed how the interaction between 5-HTTLPR and an environmental or psychological factor influences ED status or sub-threshold ED symptomatology. Secondary data meta-analyses to re-analyse GxE interactions using larger sample sizes with appropriate control of confounding variables as per Keller (2014) will then be performed by aggregating the results of three or more existing studies in a series of smaller analyses. Each analysis will be tested according to the multiplicative model of interaction, for consistency with prior research, and also according to the additive model of interaction, because of the possibility that this better represents and may be more sensitive to identifying gene x environment interactions. This study will be reported according to PRISMA guidelines where applicable (Moher et al., 2010).

Systematic review

Inclusion criteria and search strategy

The databases PsycINFO, PubMed, and EMBASE were searched through to January 2016 by two authors (V.R. and D.O) using the search terms ("eating disorder*" or "disordered eating" or "anorexi*" or "bulimi*" or "binge eating" or "emotional eating" or "dietary restraint") + ("gene environment interaction" or "gene" or "allele"), limited to "human only" and English language. Inclusion criteria included testing an interaction between 5-HTTLPR and an environmental or psychological factor, with eating pathology as the outcome variable. Eating pathology included a clinical-level diagnosis or a

measure of disordered eating (e.g., dieting, body dissatisfaction). Studies examining body mass index (BMI) or weight gain as the outcome variable, or examining twin samples rather than candidate genes, were excluded to maintain a focussed investigation of 5-HTTLPR. While not technically an ‘environmental’ factor, psychological factors were included in the search as in many cases such variables are implicated in the aetiology of EDs and may influence how a genetic variant modifies risk for EDs (e.g., impulsivity in BN, Steiger et al., 2005). Indeed, many studies have investigated psychological factors within a GxE framework both in the ED literature (Akkermann et al., 2011; Racine et al., 2009; Mata & Gotlib, 2011; van Strien et al., 2010) and in other psychopathologies (Lu et al., 2011; Mandelli et al., 2009; Wang et al., 2013). Results were limited to published studies. A total of 1353 papers were initially identified (701 duplicates), with 35 selected for closer reading. Of these, 7 papers met criteria for the systematic review, with a summary provided in Figure 1.

--- Insert Figure 1 about here ----

Quality appraisal

Quality of each study in the systematic review was evaluated using Downs and Black’s (1998) framework. As this tool was created to assess clinical trials, criteria were adapted to evaluate GxE research in eating disorders, with 14 non-applicable criteria excluded. A brief description of the items is presented, with notes in parentheses detailing changes in their current application:

- 1) Clear description of the hypothesis/aim/objectives; 2) Clear description of main outcomes in introduction/method; 3) Participant characteristics clearly described (as appropriate for GxE and ED research); 4) Clear description of main findings; 5) Characteristics of participants lost to follow-up described; 6) Exact probability values reported (or confidence intervals included); 7) Participants representative of population (including clinical, but not convenience samples); 8) Any “data-dredging” explicitly noted; 9) Appropriate statistical tests used; 10) Main outcome measures valid and reliable; 11)

Participants in different groups (if case-control study) recruited contemporaneously; 12) Adequate adjustment for (potential) confounding variables (e.g., BMI; according to Keller (2014), this requires inclusion of all covariate x gene and covariate x environment interaction terms in the model); and 13) Sufficient power (to detect a GxE interaction, as guided by Duncan & Keller, 2011).

Studies were evaluated independently by two coders, V.R. and D.O., and cross-checked for consistency. Discrepancies were discussed amongst the raters with a third author (I.K.) consulted where necessary. Another author with particular expertise in statistical methods in psychology (M.F.T.) additionally evaluated criterion 9. To avoid biases or conflicts of interest, no other co-authors provided input to the evaluation.

Table 1 presents results of the quality evaluation. Discrepancy between coders was lower than 5%. The evaluation found that studies largely adopted valid and reliable methods with good reporting of results. The main issues pertained to insufficient power to detect the small-to-medium effect sizes likely involved in GxE interactions (Duncan & Keller, 2011), and that no study properly controlled for potential confounds on the interaction effect by including covariate x gene and covariate x environment interaction terms (Keller, 2014). Some studies tested three-category polymorphic groupings using cross-product terms in regression models, which was recently suggested to be statistically flawed due to the possibility of both false positive and negative results (Aliev et al., 2014). Nonetheless, the studies present promising initial findings and constitute good building blocks for continued GxE analyses in the field.

--- Insert Table 1 about here ---

Summary of findings

The systematic review identified 7 studies (see Table 2). Samples were from North American or European countries and n varied from 50 to 584. Participants were mainly adolescents and young adults, with mean age spanning from 13.4 years to 25.6 years. Five studies investigated community samples (total $N = 2017$, 78.0% female), with two of these studies investigating mixed gender samples. Two studies examined clinical ED patients ($N = 348$, 100% female), with one of these a discordant sister-pair sample ($N = 128$ controls, 100% female).

Three studies found a significant 5-HTTLPR x Traumatic Life Events interaction, although each predicted a different ED pathology; two disordered eating (Akkermann et al., 2012 – EDI-2 Bulimia subscale only; Stoltenberg et al., 2012 – EAT-26 total score) and one Anorexia Nervosa (AN) diagnosis (Karwautz et al., 2011). Notably, unlike in Akkermann et al. (2012) and Stoltenberg et al. (2012), Karwautz et al. (2011) found an interaction only when analysing risky parenting styles and not for broader traumatic life events. One study found a significant sexual abuse x 5-HTTLPR interaction (Akkermann et al., 2012, predicting EDI-2 Bulimia and Drive for Thinness scales), while the other did not (Steiger et al., 2007, predicting BN-spectrum clinical diagnosis). Neither study reported a significant physical abuse x 5-HTTLPR interaction. Mata and Gotlib (2011) and van Strien et al. (2010) both reported a significant depression x 5-HTTLPR interaction in predicting overeating and emotional eating, respectively, although this effect was only for the *s/s* genotype in the former study. Racine et al. (2009) found no interaction between 5-HTTLPR or *HTR2A* (T102C polymorphism) and impulsivity or dietary restraint in predicting binge eating or emotional eating symptoms.

-- Insert Table 2 about here ---

Secondary Data Meta-Analyses

Method

Inclusion criteria

From the final 7 studies identified through systematic review, those that tested equivalent environmental or psychological variables were considered for a secondary data meta-analysis. Six suitable studies were identified (see Figure 1). Data from one additional study (Richardson et al., 2008) were included in the secondary data analysis but not the systematic review, as it contained relevant variables (drawing from the same larger sample as Steiger et al., 2007), but did not explicitly analyse the GxE interaction with an ED-specific outcome in their publication. Authors were contacted with a request to provide data for re-analysis and an invitation to join the present study. All authors contributed their data via email attachment as an SPSS or Microsoft Excel file. Variables sought included participant ID, age, gender, BMI (if assessed), 5-HTTLPR genotype, and item-level data for the environmental and ED variables.

Design

Data from six studies (Akkermann et al., 2012; Karwautz et al., 2011; Racine et al., 2009; Richardson et al., 2008; Stoltenberg et al., 2012; Steiger et al., 2007; and van Strien et al., 2010) were combined to test four separate secondary data analyses: 5-HTTLPR x Traumatic Life Events to predict ED diagnosis or equivalent, 5-HTTLPR x Sexual and/or Physical Abuse to predict a BN-spectrum ED or equivalent, 5-HTTLPR x Depression to predict BN-spectrum ED or equivalent, and 5-HTTLPR x Impulsiveness to predict ED diagnosis or equivalent.

Data synthesis

Full data sets from each study were provided. Overlapping participant data in Steiger et al. (2007) and Richardson et al. (2008) were removed by contributing authors prior to sending their data. Karwautz et al. (2011) was part of a European multi-centre collaboration (*The European Project*) and data for the present study were drawn from the larger unpublished sample, including additional data from clinical BN patients. Data from The European Project were only included if they contained item-level responses to the Oxford Risk Factor Inventory (ORFI; Fairburn et al., 1998) to ensure consistent measurement of the environmental factor 'traumatic life events' across studies. Item-level data were unavailable from some participating research centres and therefore the present sample size does not match Karwautz et al.'s (2011) publication, but includes additional participants with a BN diagnosis.

Prior to combining datasets according to the below-mentioned procedures, missing data were imputed at the item-level where necessary using the median value (Tabachnick & Fidell, 2013), with missingness lower than 5%. Participants with missing genetic data or summary scales (where item-level data were unavailable), were excluded from the analyses.

Measures of environmental and psychological factors used across studies were heterogeneous to varying extents. Most studies utilised different scales to assess ED status or examined different elements of disordered eating. Therefore, a complex process was necessary to integrate the variables to achieve compatibility for combined analysis, which is summarised below. Participant 5-HTTLPR genotypes across each study were coded as s-allele present (s/s and s/l genotypes) or s-allele absent (l/l genotype), as the s-allele is argued to function in a genetically dominant manner (Lesch et al., 1996).

Analysis 1 - Traumatic life events: Traumatic life events were determined according to 17 events (e.g., traumas/accidents, abuse, major health problems) that overlapped between scales used in Akkermann et al. (2012; self-devised scale), and Stoltenberg et al. (2012; Traumatic Antecedent

Questionnaire, Herman & van der Kolk, 1987). Fourteen of these events overlapped with The European Project (ORFI; Fairburn et al., 1998) data, which was scaled to match the 18-item (0-17 events) solution.

ED status or equivalent was determined by a total score above 5 and 3 on the Drive For Thinness and Bulimia Scales of the Eating Disorder Inventory-2 (EDI-2; Garner, 1991a), respectively, which are the recommended scale-level cut-offs for clinical-level disordered eating (Nevonen & Broberg, 2001; Norring & Sohlberg, 1988). In Stoltenberg et al. (2012), ED status or equivalent was determined by a total score of 20 or greater on the Eating Attitudes Test-26 (EAT-26; Garner et al., 1982), the established cut-off for likely clinical-level eating pathology. A semi-structured clinical interview, the EATATE (Anderluh et al., 2009), was used to identify ED diagnosis based on DSM-IV criteria (American Psychiatric Association [APA], 2000) in the European Project.

Analysis 2 - Sexual and physical abuse: Sexual abuse and physical abuse were coded dichotomously in the European Project and Akkermann et al. (2012), and re-coded into yes/no format in Richardson et al. (2008) and Steiger et al. (2007) if participants endorsed anything above 'low' sexual or physical abuse, and in Stoltenberg et al. (2012) if abuse was 'occasional' or greater. BN status or equivalent was established based on whether participant responses to items on the EDI-2 (Garner, 1991a) in Akkermann et al. (2012) and on the EAT-26 (Garner et al., 1982) in Stoltenberg et al. (2012) endorsed DSM-IV (APA, 2000) BN-criteria, namely, engaging in regular binge eating, with loss of control, and engagement in compensatory behaviour. In addition, participants whose scores on the EDI-2 Bulimia scale and EAT-26 Bulimia and Food Preoccupation scale were substantially elevated, suggesting likely clinical-range BN, were classified in the BN group. BN was determined according to the EATATE (Anderluh et al., 2009) and DSM-IV criteria (APA, 2000) in the European Project, and by the Eating Disorders Examination (EDE; Fairburn & Cooper, 1993) in Steiger et al. (2007) and Richardson et al. (2008).

Analysis 3 - Depression: Depression was coded dichotomously in the European Project using the ORFI (Fairburn et al., 1998) and in Richardson et al. (2008) as determined by the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I, First et al., 1996). Dimensional measurements were obtained in Akkermann et al. (2012) via the self-report version of the Montgomery-Åsberg Depression Rating Scale (MADRS-S; Montgomery & Åsberg, 1979), and van Strien et al. (2010) via the Depressive Mood List (Kandel & Davies, 1982). For compatibility with the European Project and Richardson et al. (2008), these were dichotomised. A cut-off score of 15 was selected for the MADRS-S according to research examining criterion validity (Svanborg & Åsberg, 2001; Svanborg & Ekselius, 2003). No cut-off score has been established for the Depressive Mood List. However, as there was complete overlap between these measures, participant scores on the Depressive Mood List were scaled to match MADRS-S responses and the same cut-off value was applied. BN status or equivalent was determined as in Analysis 2 for the European Project, Richardson et al. (2008), and Akkermann et al. (2012). BN status was based on participant responses to categorical questions investigating binge frequency, loss of control, and engagement in compensatory behaviours in van Strien et al. (2010).

Analysis 4 - Impulsiveness: All studies assessed impulsiveness using the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). ED status or equivalent was determined as in Analysis 1 for Akkermann et al. (2012) and Stoltenberg et al. (2012), while for Racine et al. (2009) this was determined by a mean score of 2.3 or greater on a self-report version of the EDE (EDE-Q; adopted from Fairburn & Cooper, 1993), as suggested by Mond and colleagues (2004).

Statistical analyses

Analyses were conducted using binary logistic regression to test main and interaction effects of 5-HTTLPR and the environmental or psychological factor in predicting ED/BN status. 5-HTTLPR was coded according to presence or absence of the low-function s-allele. In light of past findings suggesting

the s-allele operates in a genetically dominant manner (e.g., Lesch et al., 1996), and in order to avoid issues relating to multiple testing, genotype grouping (s/s, s/l, l/l) was not investigated. All analyses controlled for age by including the age, age x environment, and age x 5-HTTLPR terms to the overall model. BMI was also controlled for where data were available. These interaction terms are necessary to adequately control for potential confounders, although have been omitted from most GxE investigations in psychiatry to date (Keller, 2014). It was not possible to control for sex due to frequency distribution issues in the logistic regression. When examining sex differences by comparing a female only sub-sample to the overall sample in each analysis (a male-only sub-sample was not possible to due to frequency distribution), results were similar across all analyses, therefore only results for the larger, complete sample are displayed.

Finally, whereas the interaction term between gene and environmental or psychological factor is sufficient for testing a GxE interaction in logistic regression under a multiplicative model (as per past studies; e.g., Caspi et al., 2003, Karwautz et al., 2012, Steiger et al., 2012, also see Munafò et al., 2009), three additional statistics were computed to quantify the interaction from an additive perspective: the relative excess risk due to interaction (RERI), the attributable portion due to the interaction (AP), and the synergy index (S). When an interaction is present in the data, RERI and AP will be greater than 0, whereas S will be greater than 1. These additive models were conducted using Stata version 13. Estimates of these interaction effects were derived from relative risk ratios rather than odds ratios, as: (1) the formulae for RERI, AP, and S were designed to use with RR values, and (2) substituting OR values for RR values in these formula will over-estimate the interaction effects in cases where the baseline prevalence is not rare (e.g., greater than 10% prevalence; VanderWeele & Knol, 2014). To facilitate calculation of RR values, the two continuous predictors – traumatic experiences and impulsivity – were converted into categorical forms. Trauma history was split into no instances reported versus 1+ instances reported. As the appropriate cut-point for the impulsivity measure is unclear, several

percentiles were trialled (5th, 10th, 15th, 20th, and 25th). Substantive conclusions did not change depending on the cut-off applied, and as such, results are reported for the lowest cut-off (5th percentile) to conceptually reflect those with lowest reported levels of impulsivity.

Results

Analysis 1: Traumatic Life Events

The sample comprised 909 individuals (65.7% female), from the following studies: two community samples, Stoltenberg et al. (2012; $N = 436$, 65.1% female), Akkermann et al. (2012; $N = 369$, 56.6% female), and a discordant sister-pair sample, the European Project ($N = 104$, 100% female).

Overall, 169 (18.6%) participants met criteria for an ED or equivalent. 5-HTTLPR frequencies (l/l = 333, l/s = 415, s/s = 161) met the Hardy-Weinberg equilibrium, $\chi^2 = 2.55$, $df = 1$, $p > .05$. Traumatic Life Events were scored 0 to 17, ($M = 2.38$ events, $SD = 2.54$), and were positively skewed. Results of the logistic regression are displayed in Table 3.

As evident in Table 3, while there was no effect of traumatic events or genotype alone, presence of the s-allele was related to significantly greater likelihood of an ED for those who had experienced more traumatic life events compared to those with the l/l genotype ($OR = 1.23$, see Figure 2). A small but significant main effect of age was also noted. From an additive perspective however, none of the interaction indices reported significant findings to support an interaction effect: RERI = $-.90$ (95% CIs: $-4.17, 2.36$), $p = .587$; AP = $-.53$ (95% CIs: $-2.85, 1.79$), $p = .654$; and S = 0.44 (95% CIs: $.01, 16.53$), $p = .657$.

--- Insert Table 3 about here ---

Analysis 2: Sexual and/or Physical Abuse

The sample comprised 1097 individuals (71.8% female), from the following studies: two community samples, Stoltenberg et al. (2012; $N = 436$, 65.1% female), Akkermann et al. (2012; $N = 369$,

56.6% female), one clinical sample from Steiger et al. (2007) and Richardson et al. (2008), ($N = 127$, 100% female) and a discordant sister-pair sample, the European Project ($N = 168$, 63% controls, 100% female).

Overall, 221 (20.1%) participants met criteria for BN or equivalent. Three-hundred and fourteen (28.5%) participants reported experiencing physical abuse, 165 (15%) reported sexual abuse, and 85 (7.7%) reported both physical and sexual abuse. 5-HTTLPR frequencies (l/l = 407, l/s = 492, s/s = 201) deviated from the Hardy-Weinberg equilibrium, $\chi^2 = 5.85$, $df = 1$, $p = .02$.

Results outlined in Table 3 show significant main effects for sexual abuse ($OR = 8.56$), physical abuse ($OR = 4.79$), and both sexual and physical abuse combined ($OR = 11.53$). There was a significant GxE interaction ($OR = 3.15$), whereby participants with the s-allele who experienced both sexual and physical abuse were more likely to endorse BN status compared to those with the l/l genotype (Figure 2). There was a main effect of age, and increased likelihood of BN was also significantly predicted by an interaction between (younger) age and each of the abuse variables.

From an additive perspective, a number of the interaction indices displayed significant findings to also support an interaction effect for physical abuse: RERI = 1.32 (95% CIs: .06, 2.58), $p = .040$; AP = .40 (95% CIs: .09, .72), $p = .012$; but not S = 2.40 (95% CIs: .81, 7.13), $p = .116$, and to support an interaction for sexual abuse RERI = 2.26 (95% CIs: .05, 4.47), $p = .045$; AP = .49 (95% CIs: .13, .85), $p = .007$; but not S = 2.70 (95% CIs: .82, 8.90), $p = .102$. All indices supported an interaction on additive scale for both sexual and physical abuse x 5-HTTLPR, RERI = 5.16 (95% CIs: .73, 9.60), $p = .022$; AP = .70 (95% CIs: .43, .98), $p < .001$; S = 5.41 (95% CIs: 1.10, 26.71), $p = .038$.

--- Insert Figure 2 about here ---

Analysis 3: Depression

The sample comprised 1254 individuals (62.5% female), from the following studies: two community samples, Akkermann et al. (2012; $N = 369$, 56.6% female), and van Strien et al. (2010; $N = 623$, 51.2% female), one clinical sample, Richardson et al. (2008; $N = 89$, 100% female) and a discordant sister-pair sample, the European Project ($N = 168$, 63% controls, 100% female).

Overall, 172 (13.7%) participants met criteria for BN or equivalent, while 184 (14.7%) participants met criteria for depressed mood. 5-HTTLPR frequencies (l/l = 438, l/s = 612, s/s = 205) met the Hardy-Weinberg equilibrium, $\chi^2 = .14$, $df = 1$, $p > .05$. Results of the logistic regression revealed no main or interaction effects of depression and 5-HTTLPR in predicting BN status (Table 3). Similar to the pattern observed in Analysis 2, younger age interacted with depressive status to predict greater likelihood of BN. There was also no support for an interaction effect under an additive model, RERI = .15 (95% CIs: -.95, 1.26), $p = .785$ and AP = .13 (95% CIs: -.77, 1.03), $p = .778$. S could not be reliably computed for this interaction.

Analysis 4: Impulsiveness

The sample comprised 1122 individuals (72.2% female) from three community samples, Stoltenberg et al. (2012; $N = 436$, 65.1% female), Akkermann et al. (2012; $N = 369$, 56.6% female), and Racine et al. (2009; $N = 317$, 100% female).

Overall, 224 (20.0%) participants met ED criteria or equivalent. 5-HTTLPR frequencies (l/l = 384, l/s = 545, s/s = 193) met the Hardy-Weinberg equilibrium, $\chi^2 < .01$, $df = 1$, $p > .05$. Impulsivity was measured using the Barratt Impulsiveness Scale Version 11 (BIS-11; Patton, et al., 1995), and was normally distributed. Data did not meet the assumption of linearity between continuous independent variables and the logit ($p = .003$), suggesting that results may present an underestimation of the

relationship (Hosmer & Lemeshow, 1989). Results of the logistic regression revealed no main or interaction effects of impulsiveness and 5-HTTLPR in predicting ED status (Table 3), which was supported by the indices measuring additive interaction, RERI = -1.18 (95% CIs: -4.22, 1.86), $p = .448$; AP = -.85 (95% CIs: -2.49, .78), $p = .307$; and S = .24 (95% CIs: .03, 1.83), $p = .170$.

Discussion

To our knowledge, this is the first systematic review and secondary data meta-analysis investigating the role of 5-HTTLPR x environment and psychological factor interactions in risk for eating pathology. The aim was to summarise and re-analyse existing GxE research on eating disorder-related outcomes investigating the 5-HTTLPR polymorphism, in the largest sample tested to date, in order to elucidate the current state of knowledge and provide guidance for future GxE studies in the field. Results of the secondary data meta-analysis revealed that when testing deviations from an additive model of interaction, the experience of sexual abuse, physical abuse, and both sexual and physical abuse each interacted with the s-allele of 5-HTTLPR to predict increased risk of bulimia-spectrum eating pathology. The significant interaction between 5-HTTLPR and both sexual and physical abuse (but not only one) was also supported from a multiplicative perspective, although there was no support for sexual abuse or physical abuse considered alone. In addition, there was a significant interaction between traumatic life events and 5-HTTLPR to predict an increased risk of eating pathology under the multiplicative model only. No effects were noted for the potential risk factors of depression and impulsiveness under either model.

Other noteworthy results include the large direct effects of sexual abuse and physical abuse on BN-spectrum disorders, an association demonstrated in previous meta-analyses (Chen et al., 2010; Norman et al., 2012; Smolak & Murnen, 2002). Conversely, there were no main effects of 5-HTTLPR

genotype in any analyses, contrary to some past findings (Calati et al., 2011; Lee & Lin, 2010), although aligned with others (Castellini et al., 2012; Solmi et al., 2016).

The current GxE findings suggest that individuals with the 'risky' genotype may be relatively resilient to low levels of environmental risk, but disproportionately affected by greater environmental adversity (e.g., experiencing numerous types of abuse). From a biological perspective, it is plausible that this may function via the lowered serotonin transcription associated with the s-allele of 5-HTTLPR, leading to reduced availability of a key neurotransmitter in the stress response system (van Eekelen et al., 2012).

The present results demonstrate some links to findings in the depression field, where greater traumatic life events, including childhood abuse, have been found to interact with 5-HTTLPR to predict depression (Karg et al., 2011; Nugent et al., 2011), although the interaction between life events and 5-HTTLPR is not undisputed (Munafò et al., 2009; Risch et al., 2009). One caveat is that 'traumatic life events' is a heterogenous concept. The types of events measured, scaling process, timing of events, age of participants, etc., may vary greatly, perhaps accounting for some inconsistency in GxE findings in the depression field (Uher & McGuffin, 2008). Careful consideration of these factors is encouraged for future analyses.

Aside from consistent measurement of environmental variables, another key issue affecting GxE research is low statistical power. Use of small sample sizes with insufficient power to detect GxE interactions has been a major point of criticism in GxE research for increasing risk of both false negative and false positive findings (Button et al., 2013). Sample sizes necessary to detect GxE effects are far bigger than typically involved in psychology (Luan et al., 2001), with one calculation of minimum sample size necessary to detect a large GxE interaction effect at 80% power, assuming no measurement error, $N = 600$ (Duncan & Keller, 2011). This increases substantially if only moderate effect sizes are involved. The

median sample size of studies identified by the systematic review was 288, which is considered substantial in the ED field but lacking for genetic analyses. This is a particularly challenging limitation in light of the difficulty of obtaining genetic samples and highlights the immense value of the present collaboration, which has allowed us to utilise existing resources to maximize sample size and further knowledge regarding GxE effects in eating pathology.

One factor that may yet affect accuracy of the present findings is the possibility of publication bias amongst the studies identified by the systematic review. This has been noted in past GxE research, with one review reporting that significant findings were observed in 96% of initial GxE investigations but in only 27% of subsequent replication attempts (Duncan & Keller, 2011; Duncan et al., 2014). However, others argue that many instances of non-replication are related to methodological issues, including inadequate measurement of traumatic life events (Caspi et al., 2010; Monroe & Reid, 2008). In any case, the tendency for positive findings to be more readily published, and null findings perhaps less likely to be initially submitted, can have a large effect on the accuracy of published studies by inflating false positive results (Dick et al., 2015; Ioannidis et al., 2014). It is therefore vital, for the success of future collaborative meta-analyses, for researchers to publish both significant and non-significant findings and for journals to support this initiative, while emphasising the use of reliable environmental measures.

Aside from the benefits of large sample sizes and resource efficiency in the present investigation, it further improved upon existing GxE research in eating pathology by correctly controlling for the potential effect of confounding variables (Keller, 2014). The inclusion of all necessary interaction terms was also facilitated by the large sample sizes investigated, and should be aimed for in future studies. Another strength of the present study was that it examined GxE interactions under both additive and multiplicative models of interaction. Most previous studies using a logistic regression model to assess their data have tested deviations from a multiplicative model. Conversely, studies of

community samples with continuous outcome variables typically use linear regression models, which test deviations from an additive model. As the two methods produce somewhat different results, with the latter generally more conservative, caution should be taken in comparing the results of these models, and indeed, this may account for some of the discrepant findings in GxE research.

The present secondary data meta-analysis is not without limitations, primarily due to the need to harmonise heterogeneous datasets, which tested both community and clinical samples and contained varied measures of environmental and psychological factors and eating symptoms. The investigation of the 5-HTTLPR x depression interaction was in particular hindered by variability in the measurement of depression between studies. These methodological issues may explain why this interaction was not found to be significant in the present analysis, contrary to findings in two of the initial studies (Mata & Gotlib, 2011; van Strien et al., 2010).

Nonetheless, the present study provides a detailed overview of current GxE findings involving 5-HTTLPR in the ED field, including studies assessing psychological variables. Subsequent research should focus on continued replication with large sample sizes, possibly best achieved through ongoing collaboration between researchers, given the resource-intensive nature of genetic research and scarcity of clinical ED samples. Such investigations would be best facilitated by researchers adopting standardised, or easily comparable, measures of environmental and psychological factors and eating symptoms that have excellent psychometric properties. Selection of measures should be carefully deliberated, both to maximise construct validity and to reduce measurement error, which can substantially increase statistical power (Bakermans-Kranenburg & van IJzendoorn, 2014). Polymorphisms and environmental or psychological factors selected should also be carefully justified, particularly in light of sample size restrictions (Dick et al., 2015).

Future studies may also benefit from adopting a differential susceptibility approach to GxE investigations. This hypothesis posits that certain alleles may be better conceptualised as conferring 'plasticity' in response to environmental stimuli, with alleles linked to poorer outcomes under negative environments conversely linked to better outcomes in positive environments (Belsky & Pluess, 2009). Such an analysis was not possible in the current paper due to lack of data assessing positive environments, however this pattern has been demonstrated for various polymorphisms, including 5-HTTLPR, in non-ED literature (see Bakermans-Kranenburg & van IJzendoorn, 2011, for a meta-analysis; Hankin et al., 2011). Accordingly, studies should include environmental measures that range from positive to negative in nature, such as parenting, peer relationships, or positive life events.

In sum, the present collaboration constitutes a large step forward in increasing knowledge of how genetics may moderate the manner in which environmental and psychological influences affect the likelihood of ED development. Given the ongoing uncertainty regarding why thus far identified risk factors appear to contribute towards ED development for some individuals but not others, genetics may be an important missing puzzle piece in identifying the source of individual variation in susceptibility to eating pathology.

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Table 1

Downs and Black (1998) Checklist for Methodological Quality, adapted to evaluate studies identified in a systematic review of the role of 5-HTTLPR x environment interactions in risk for eating pathology

Study	1	2	3	4	5	6	7	8	9	10	11	12	13
Steiger et al.	1	1	1	1	N/A	1	1	1	1	1	N/A	0	0
Racine et al.	1	1	1	1	X	1	0	1	1	1	N/A	0	0
Mata & Gotlib	1	1	1	1	0	1	0	1	1	1	N/A	0	0
van Strien et al.	1	1	1	1	1	0	1	1	1	1	N/A	0	0
Karwautz et al.	1	1	1	1	N/A	1	1	1	1	1	1	0	0
Akkermann et al.	1	1	1	1	0	1	1	1	1	1	N/A	0	0
Stoltenberg et al.	1	1	1	1	N/A	1	0	1	1	1	N/A	0	0

1 = Criteria met 0 = Criteria not met X = Unable to determine N/A = Criteria not applicable. A description of each item is provided under the heading *Quality Appraisal* in the Method section.

Table 2
 Studies Examining 5-HTTLPR x Environment Interactions in Eating Pathology

Author (year)	Total No. of Participants (No. Women)	Mean age, yrs (SD)	Clinical sample	5-HTTLPR Genotype %	Outcome (measures)	Environmental factor	Results
Steiger et al., (2007)	92 (92)	25.4(6.4)	BN	<i>LL LS SS</i> 34 47 20	BN (EDE, EAT-26, DSM-IV diagnosis)	Childhood sexual/physical abuse, (CTI)	No significant interactions
Racine et al., (2009)	344 (344)	19 (1.4)	No	27 56 17	Binge eating (MEBS), Emotional eating (DEBQ)	Impulsivity (Barratt Impulsiveness Scale) Dietary restraint (EDE-Q/DEBQ composite)	No significant interactions
Mata & Gotlib (2011)	50(50)	13.9(1.9)	No	28 44 28	Overeating (EDI-C)	Depression (CDI)	Interaction between s/s (but not s/l) genotype and depression
van Strien et al., (2010)	584 (295)	13.4 (0.6) 15.2 (0.5)	No	32 50 18	Emotional, eating (DEBQ)	Depression (Depressive Mood List)	Interaction b/w s-allele and depression on DEBQ scores
Karwautz et al., (2011)	256 (128 discordant sister-pairs)	25.6 (8.4)	Half AN	38 43 18	AN (EATATE-I interview, DSM-IV diagnosis)	Life events (Oxford Risk Factor Inventory)	Interaction between s-allele and life events, specifically problematic parenting styles
Akkermann et al., (2012)	252(252)	17.8(0.5)	No	103 (l/l) 136 (s/-)	Drive for thinness, Bulimia (EDI-2)	Life events (self-devised scale), including sexual, physical, and emotional abuse	Interaction between s-allele and life events on bulimia only (interaction with sexual abuse for both outcomes, none for physical abuse)
Stoltenberg et al., (2012)	439 (284)	22.5 (6.2)	No	33 46 21	Disordered eating (EAT-26)	Life events (Traumatic Antecedent Questionnaire)	Interaction between s-allele and traumatic events for females only

Notes. GxE = gene x environment interaction; AN = anorexia nervosa; BN = bulimia nervosa; CDI = Children's Depression Inventory (Kovacs, 1985), CTI = Childhood Trauma Interview (Fink et al., 1995); DEBQ = Dutch Eating Behavior Questionnaire (van Strien, 2002); EAT-26 = Eating Attitudes Test (Garner et al., 1982); EATATE-I = EATATE Lifetime Diagnostic Interview (Anderluh et al., 2009); EDE = Eating Disorders Examination (Fairburn & Cooper,

1993); EDI-2 = Eating Disorders Inventory-2 (Garner, 1991a); EDI-C = Eating Disorders Inventory for Children and Adolescents (Garner, 1991b); MEBS = Minnesota Eating Behavior Survey (von Ranson et al., 2005). Results are significant at $p < .05$ unless otherwise specified.

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Table 3

Main and Interaction Effects of 5-HTTLPR s-allele and each environmental factor, controlling for age (and BMI where possible) by including all covariate x gene and covariate x environment interaction terms, in predicting ED Status (Analyses 1 and 4) and BN status (Analyses 2 and 3).

	B	Odds Ratio	95% CI for Odds Ratio		Sig.
			Lower	Upper	
<u>Analysis 1: Traumatic life events (N= 909)</u>					
Constant	-4.02				
5-HTTLPR	1.01	2.75	.78	9.70	.115
Traumatic Events	.01	.91	.82	1.25	.906
5-HTTLPR x Traumatic Events	.21	1.23	1.06	1.44	.006
Age	.12	1.12	1.07	1.18	< .001
Age x 5-HTTLPR	-.06	.94	.89	.99	.029
Age x Traumatic Events	-.002	1.00	.99	1.00	.432
<u>Analysis 2: Sexual/Physical abuse (N= 1097)</u>					
<i>Sexual abuse</i>					
Constant	-4.77				
5-HTTLPR	.49	1.64	.50	5.32	.413
Sexual Abuse	2.15	8.56	2.16	33.92	.002
5-HTTLPR x Sexual Abuse	.53	1.69	.74	3.89	.214
Age	.14	1.15	1.10	1.19	< .001
Age x 5-HTTLPR	-.02	.98	.94	1.03	.516
Age x Sexual Abuse	-.06	.94	.90	.99	.013
<i>Physical abuse</i>					
Constant	-4.98				
5-HTTLPR	.45	1.57	.47	5.22	.461
Physical Abuse	1.57	4.79	1.37	16.70	.014
5-HTTLPR x Physical Abuse	.53	1.70	.85	3.41	.135
Age	.14	1.15	1.10	1.21	< .001
Age x 5-HTTLPR	-.02	.99	.94	1.03	.536
Age x Physical Abuse	-.05	.95	.91	.99	.045
<i>Sexual and Physical abuse</i>					
Constant	-4.77				
5-HTTLPR	.63	1.88	.59	6.04	.288
Sexual and Physical Abuse	2.45	11.53	2.26	58.68	.003
5-HTTLPR x Sexual and Physical Abuse	1.15	3.15	1.09	9.09	.034
Age	.14	1.15	1.10	1.19	< .001
Age x 5-HTTLPR	-.02	.98	.93	1.03	.381
Age x Sexual and Physical Abuse	-.08	.92	.87	.97	.003
<u>Analysis 3: Depression (N=</u>					

1254)

Constant	-7.39				
5-HTTLPR	-.25	.78	.07	8.52	.780
Depression	.13	1.14	.05	24.77	.934
5-HTTLPR x Depression	.88	2.41	.74	7.88	.146
Age	.26	1.30	1.10	1.54	.003
BMI	.03	1.03	.85	1.24	.770
Age x BMI	-.001	1.00	.99	1.01	.821
Age x 5-HTTLPR	.04	1.04	.96	1.11	.338
Age x Depression	-.10	.91	.84	.98	.011
BMI x 5-HTTLPR	-.02	.98	.90	1.08	.724
BMI x Depression	.07	1.08	.96	1.21	.205

Analysis 4: Impulsivity (N=1114)

Constant	-2.59				
5-HTTLPR	.46	1.59	.14	18.06	.710
Impulsiveness	.001	1.00	.95	1.06	.971
5-HTTLPR x Impulsiveness	.01	1.01	.98	1.05	.500
Age	.03	1.03	.88	1.19	.733
Age x 5-HTTLPR	-.04	.96	.90	1.03	.245
Age x Impulsiveness	<.01	1.00	1.00	1.00	.816

Odds ratio = Exp(B).

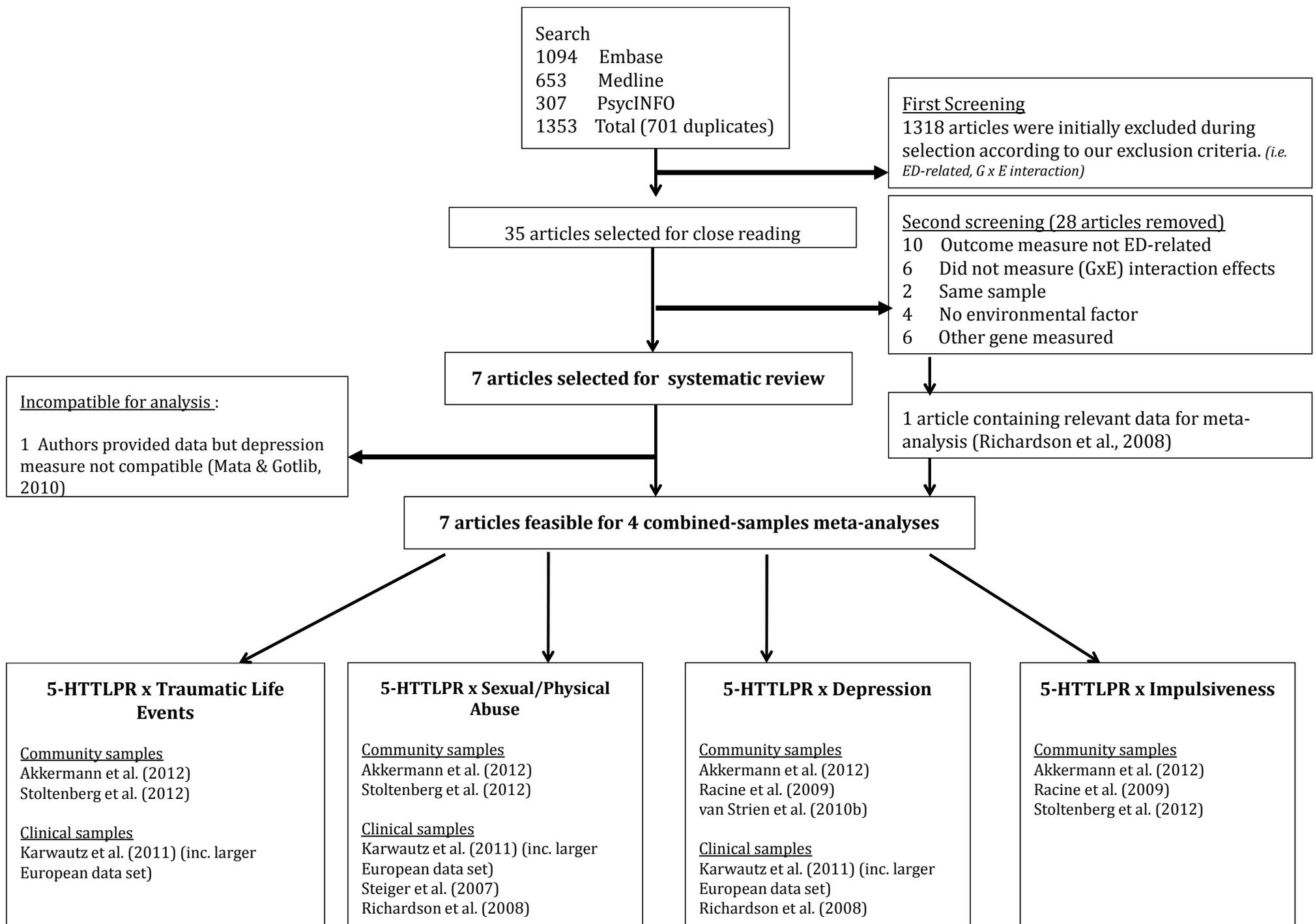


Figure 1. Flow chart depicting selection of papers for systematic review and secondary data meta-analyses based on analysis of 5-HTTLPR x environment interaction with an ED-related outcome variable.

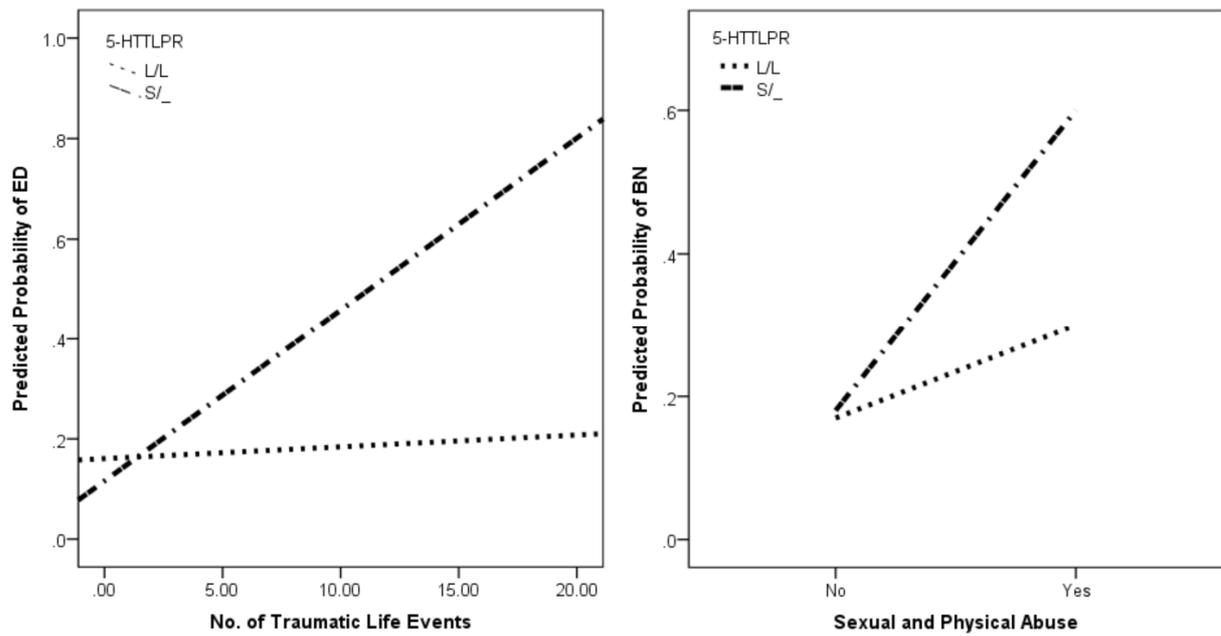


Figure 2. Significant GxE interactions between 5-HTTLPR and environmental factors 1) Traumatic life events, and 2) Sexual and physical abuse.

Contributors

Ms. Rozenblat was responsible for conducting all analyses and preparing all sections of the manuscript. Ms. Ong contributed to the systematic review section, including searching, recording results, evaluating the studies, and contributing to that section of the manuscript. Drs. Krug and Fuller- Tyszkiewicz contributed to study design and editing drafts of the manuscript, and Dr. Fuller- Tyszkiewicz also contributed to the analyses section. Remaining authors were involved in the collection of data. All authors contributed to and approved the final manuscript.

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