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Distal-to-proximal etiologically relevant variables associated with the general (*p*) and specific factors of psychopathology

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Background: The general factor of psychopathology, often denoted as *p*, captures the common variance among a broad range of psychiatric symptoms. Specific factors are co-modeled based on subsets of closely related symptoms. This paper investigated the extent to which wide-ranging genetic, personal, and environmental etiologically relevant variables are associated with *p* and specific psychopathology factors. **Methods:** Using data from four waves (ages 11–19) of TRAILS, we modeled a bifactor model of *p* and four specific factors [internalizing, externalizing, ADHD, Autism Spectrum Disorder (ASD)]. Next, we examined the associations of 19 etiologically relevant variables with these psychology factors using path models that organized the variables according to the distal-to-proximal risk principle. **Results:** Collectively, the etiologically relevant factors, including temperament traits, accounted for 55% of *p*'s variance, 46% in ADHD, 35% in externalizing, 19% in internalizing, and 7% in ASD. The low 7% is due to insufficient unique variance in ASD indicators that load more strongly on *p*. Excluding temperament, variables accounted for 29% variance in *p*, 9% ADHD, 14% EXT, 7% INT, and 4% ASD. Most etiologically relevant factors were generic, predicting *p*. In addition, we identified effects on specific factors in addition to effects on *p* (e.g., parental SES, executive functioning); only effects on specific factors (e.g., parental rejection); opposite effects on different factors [e.g., diurnal cortisol (high INT but low EXT, *p*); developmental delay (high ASD and *p* but low EXT)]. Frustration, family functioning, parental psychopathology, executive functioning, and fearfulness had strong effects on *p*. **Conclusions:** (1) Strong generic effects on *p* suggest that etiologically relevant factors and psychopathology tend to cluster in persons. (2) While many factors predict *p*, additional as well as opposite effects on specific factors indicate the relevance of specific psychopathology factors in understanding mental disorder. (3) High frustration, neurodevelopmental problems, and a disadvantaged family environment primarily characterize *p*. **Keywords:** Psychopathology.

Background

Recent years have seen an increased interest in the general factor of psychopathology (often denoted as '*p*'), which captures the variance common to a broad range of psychiatric symptoms into a single index. The *p* factor parallels the *g* factor in research on cognitive abilities and has its roots in the observation that symptoms from different syndrome classes of psychopathology often correlate positively. Next to *p*'s common variance, specific factors are modeled that capture variance common to smaller subsets of closely related symptoms, typically internalizing (INT) and externalizing (EXT) problems, in addition to thought problems, attention problems, and/or autism spectrum problems (Bloemen et al., 2018; Caspi & Moffitt, 2018; Holzinger & Swineford, 1937; Laceulle, Vollebergh, & Ormel, 2015; Michelini et al., 2019). In combination with these specific factors, *p* provides a useful representation of the structure of psychopathology (Caspi et al., 2014; Caspi & Moffitt, 2018; Laceulle et al., 2015; Lahey et al., 2012; Lahey, Moore, Kaczkurkin, & Zald, 2021).

Recently, a stream of research has emerged that attempted to establish what *p* represents. Multiple interpretations have been proposed, ranging from substantive transdiagnostic mechanisms (e.g., insufficient executive control to down-regulate negative emotions) to common transdiagnostic features of psychopathology (disability, distress) (Caspi & Moffitt, 2018; Ip et al., 2021; Kotov et al., 2021; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; Levin-Aspenson, Watson, Clark, & Zimmerman, 2021; Phillips et al., 2022; Smith, Atkinson, Davis, Riley, & Oltmanns, 2020; Sprooten, Franke, & Greven, 2022). Although an agreed-upon interpretation of *p* is lacking, *p* in the literal sense represents a statistical abstraction, a summary measure derived from the covariance among different types of symptoms as measured during a particular period (Caspi & Moffitt, 2018; Levin-Aspenson et al., 2021).

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As such, *p* appears to be a useful summary index of an individual's liability to a broad range of psychopathology during this period.

Examining etiologically relevant (i.e., risk and protective) factors that account for individual differences in *p* may not only advance insight into the meaning of *p* but may also inform on *generic influences* (i.e., factors that influence the risk of multiple disorders). Likewise, identification of etiologically relevant factors that influence one or more specific psychopathology factors (dimensions) is important as well: stripped from their shared variance, some factors may have additional effects on one or more specific psychopathology factors on top of their effect on *p*, thereby increasing their generic nature. From the extent to which additional effects of etiologically relevant factors on specific psychopathology dimensions are present, insight is gained into whether *p* is central, or less central, for our understanding of psychopathology, which is an important issue. Finally, some etiologically relevant factors may be unrelated to *p* but related to one or more specific psychopathology factors. Given that *p* captures the shared symptom variance, opposite effects of etiologically relevant variables on specific psychopathology factors may emerge, for instance between the internalizing and externalizing dimensions. These are the issues addressed in the current study.

While we model a hierarchy of assumed relationships that link unidirectional associations from a variety of putative risk and protective factors to *p* and specific psychopathology dimensions in a path model (Figure 1), it is important to emphasize from the start that our observational study design does not allow the establishment of causal links. Therefore, we avoid terms such as determinant, causal, and influence and use 'etiologically relevant factor' instead. We do use terms as etiology and risk or protective factor but only in general and not in relation to the TRAILS variables and analysis. Likewise, the terms predictor and effect do not have causal significance but simply refer to the regression effects of these factors in our path model.

Selection of etiologically relevant factors

Recent reviews have identified etiologically relevant factors that predict comorbidity and general psychopathology (Lahey et al., 2017; Lynch, Sunderland, Newton, & Chapman, 2021; Uher & Zwicker, 2017). Lynch and colleagues' systematic review is especially relevant for the current study as they identified 'transdiagnostic risk and protective factors' that have been replicated in at least two independent samples of youth (10–24 years). Their list included polygenic risk scores for ADHD and schizophrenia, gender, reduced gray matter volume, executive functioning deficits, early pubertal timing/onset of menarche, maternal depression, stressful life events, and a variety of temperament and personality traits (negative affectivity, low extroversion, low effortful control, high neuroticism, high rumination, and openness). Figure 1 shows the etiologically relevant factors that the TRacking Adolescents' Individual Lives Survey (TRAILS) has assessed, including many of the factors listed by Lynch plus some additional factors.

Three structural equation models of distal-to-proximal risk and protective factors

To model the unidirectional relationships between the etiologically relevant factors themselves and with *p* and specific psychopathology dimensions, we used the *distal-to-proximal principle* in the hypothesized causal chain. This principle is consistent with the influential bioecological systems model (Bronfenbrenner & Ceci, 1994) and has been applied implicitly by Kendler in his integrative etiologic structural equation model (SEM) of depression (Kendler, Gardner, & Prescott, 2002). For instance, the relation with *p* is rather distal for genetic risk as indexed by polygenic risk scores (PRS), less distal for perinatal problem as well as IQ and executive functioning but more proximal for family functioning and child temperament.

We developed three models according to the presence or absence of temperament. The etiologic status of temperament is controversial due to the relatively close conceptual and operational relationship between temperament traits and psychopathology. Opinions about the etiologic value of temperament-psychopathology associations vary from informative to tautological (Hyatt et al., 2019; Kotov, Gamez, Schmidt, & Watson, 2010; Nigg, 2006; Ormel, Riese, & Rosmalen, 2012; Rosenström et al., 2019). Model 1 linked the temperamental traits to *p* and the four specific psychopathology factors. Model 2 linked all non-temperamental variables to *p* and the specific factors. Model 3 combined the two models (Figure 1). It is important to emphasize that the models, especially their unidirectional nature, represent strong simplifications of the real world. For example, while parental rearing co-shapes child temperament, child temperament in turn influences parenting behaviors (Kochanska & Kim, 2020; Scarr & Mccartney, 1983).

We positioned variables with more or less similar distance to psychopathology at the same level in the distal-to-proximal hierarchy (Figure 1), admitting some arbitrariness (especially regarding the intermediate levels) to keep the model manageable. The top level consists of the exogenous polygenic risk scores that may have effects on all lower levels. The next two rather heterogeneous levels consist of lifetime parental psychopathology, parental SES, perinatal problems, and developmental delay on level 2, and IQ, executive functioning, emotion recognition, and diurnal cortisol on level 3. The idea here is that the latter four are probably somewhat

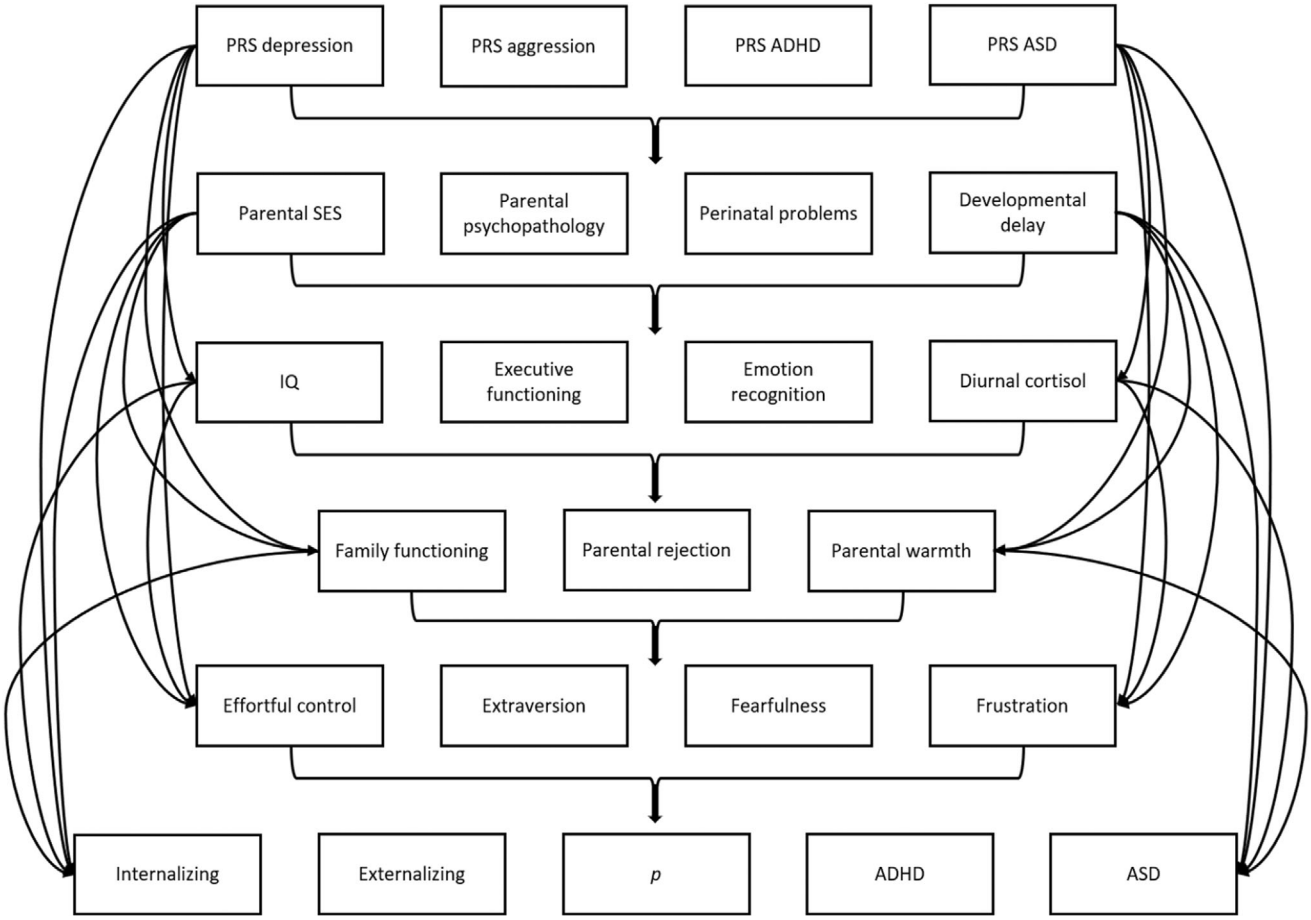

Figure 1 Distal-to-proximal etiologically relevant factors of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology. ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; IQ, intelligence quotient; *p*, general factor of psychopathology; PRS, polygenic risk score; SES, socio-economic status. The arrows depict direct (only to the level directly below; bold arrow) and indirect (to each lower level; thin arrows) paths from etiologically relevant factors to psychopathology

more dependent on the first four than the other way around. This relative difference in dependency also applies to level 4 (family functioning, parental rejection, and warmth) and the upstream level 3. Although strong evidence for this ordering is not available, the mean correlation between the variables at these levels is small (.05 between levels 3 and 4 and .09 between levels 2 en 3) suggesting that it is highly unlikely that strong bidirectional effects between these levels exist.

This does not hold for the two most proximal levels: 4 (family functioning, parental rejection, and warmth) and 5 (the four child temperament traits) given the evidence of rather strong bidirectional influences between child temperament and parenting behavior and family functioning. The average correlation between levels 4 and 5 (.20) is substantially stronger than those between the levels 2, 3, and 4. Therefore, we developed three models according to the presence or absence of child temperament in the model.

Aims and research questions

The main aim of this study is to examine to what extent we can account for individual differences in *p* using a broad range of etiologically relevant factors that have been assessed in TRAILS. Likewise, we will address how well the same etiologically relevant factors account for individual differences in four specific psychopathology factors from which the shared variance (captured in *p*) has been removed. By comparing how etiologically relevant factors explain *p* relative to how they explain the specific factors, we hope to advance insight into the meaning and relevance of *p*, as well as the relevance of specific psychopathology factors for understanding mental disorder. Another related aim is to examine to what extent etiologically relevant factors have generic or specific associations with psychopathology.

Methods

Sample

Participants came from both the population-based cohort and the enriched high-risk cohort of the TRacking Adolescents' Individual Lives Survey (TRAILS) (de Winter et al., 2005; Oldehinkel et al., 2015; Ormel et al., 2012). The population cohort follows 2,230 adolescents [baseline response rate 76.0%, mean age at T1 = 11.1 (*SD* = 0.6 years)] from urban and rural areas in the Northern Netherlands every 2–3 years.

The high-risk cohort follows 543 adolescents [baseline response rate 43.0%, mean age at T1 = 10.9 (*SD* = 0.5 years)] that had been referred to one of two child psychiatric outpatient clinics in the Northern Netherlands, at any point in life before enrolment in the study. Data were collected every 2–3 years. Each assessment wave was approved by the national ethical committee (CCMO, www.ccmo.nl) and written informed consent was obtained from both the parents and adolescents. Detailed descriptions of the study are given elsewhere (de Winter et al., 2005; Nederhof et al., 2012; Oldehinkel et al., 2015).

The current study uses data from waves 1–4. Follow-up response rates were 96% [M age = 13.6 (*SD* = 0.5)] at T2, 81% [16.3 (0.7)] at T3, and 84.3% at T4 [19.1 (0.60)]. Participants were slightly more likely to drop out at any of the follow-up measurements if they had low socioeconomic status, were male, had a non-western ethnicity, divorced parents, low IQ and academic achievement, poor physical health, or behavior and substance use problems (Ormel et al., 2012). Non-response showed little to no association with recent self-reports of anxiety and mood problems, urbanization, parental religiousness, or being an only child (Oldehinkel et al., 2015). The dataset analyzed in this study is subject to the European Union's General Data Protection Regulation and can be requested by means of a publication plan. More information can be found at the study website: https://www.trails.nl/en/hoofdmenu/data/data-use. All codebooks are available from: https://easy.dans.knaw.nl/ui/home.

Measures

The questionnaires and tasks have shown good psychometric properties (Achenbach, Ivanova, & Rescorla, 2017; Brunnekreef, 2007; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000; Epstein, Baldwin, & Bishop, 1983; Hartman, Luteijn, Serra, & Minderaa, 2006; Markus, 2003; Silverstein, 1972). Appendices S1–S6 present detailed information on questionnaires and variables.

Psychopathology symptoms. *Parent-reported symptoms* were assessed at waves 1–4 with the Child Behavior Checklist (CBCL) and Child Social Behavior Questionnaire (CSBQ) (Achenbach et al., 2017; Achenbach & Rescorla, 2001; Hartman et al., 2006). The current study used the symptom domains anxious-depressed, somatic complaints, aggressive behavior, delinquent behavior, and attention problems of the CBCL. The CSBQ assessed reduced contact and social interests, difficulties in understanding social information, stereotyped behavior, fear of and resistance to change, behavior/emotions not optimally tuned to the situation, and orientation problems in time, place, or activity.

Self-reported symptoms were assessed at waves 1–4 with the Youth Self-Report (YSR) and Revised Child Anxiety and Depression Scale (RCADS) (Achenbach et al., 2017; Chorpita et al., 2000). The current study used the symptom domains anxious-depressed, somatic complaints, aggressive behavior, delinquent behavior, and attention problems of the YSR. The RCADS was used to assess Panic Disorder.

Teacher-reported symptoms were assessed at waves 1–3 with the Teacher's Checklist of Psychopathology (TCP) (Achenbach et al., 2017). Item scores were adapted to be consistent with the coding of the CBCL and YSR. The current study used the symptom domains anxious-depressed, somatic complaints, aggressive behavior, delinquent behavior, and attention problems.

Polygenic risk scores: Subsamples of both cohorts [i.e., population cohort 1,539 of 2,230 (at wave 3) and high-risk cohort 424 of 543 (at wave 2)] were genotyped. DNA was extracted from blood samples or, in a small proportion of participants, buccal swabs (Cytobrush; $n = 360$) using a manual salting out procedure as described by Miller, Dykes, and Polesky (1988). Genotyping was performed on the Golden Gate Illumina BeadStation 500 and the Infinium™ HumanCytoSNP-12 v2.1 BeadChip platforms (Illumina Inc., San Diego, CA, USA), according to the manufacturers' protocols. These datasets were merged and checked for genotype concordance. Four PRSs were generated: depression, aggression, ADHD, and ASD. For each PRS, we derived estimates at 16 different significance thresholds. The estimates at these thresholds were combined using principal component analysis in R (Table S1).

Parental socio-economic status: The participants' SES was constructed at waves 1 and 4. Parental SES was computed by averaging the educational level of the father and the mother, the occupational level of the father and mother, and the household income level using the International Standard Classification for Occupations (Ganzeboom & Treiman, 1996). Missing values (e.g., when the information was only available for one parent) did not affect the association of SES with other variables. In SPSS, variables were averaged across waves to create a final, stable, SES ($r = .845$).

Perinatal problems: The perinatal problems index was computed by summing the scores for pregnancy and delivery problems (i.e., each rated on a four-point scale ranging from 0 'not at all' to 3 'very difficult'). One additional point was added for each of the following possibilities: incubation following birth, oxygen administration after birth, jaundice, blood transfusion after birth, maternal physical problems, maternal social problems, or maternal psychological problems in the first month after birth. All variables were parent-rated and assessed at wave 1 (Marsman, Rosmalen, Oldehinkel, Ormel, & Buitelaar, 2009).

Developmental delay: The participants' developmental delay was constructed by combining the age of first steps, age of first words, and motor development using confirmatory factor analysis in Mplus (Table S4). All variables were parent-rated and assessed at wave 1 (Emond, Ormel, Veenstra, & Oldehinkel, 2007).

Lifetime parental psychopathology: Mental health problems (i.e., antisocial behavior, addiction, ADHD, ASD, depression, anxiety) of the father and/or mother were assessed at waves 1 and 3. If the parent only indicated having symptoms, we scored a one, and if they additionally indicated impairment and/or treatment, we scored a two. Information on the validity of the wave-specific indices is detailed elsewhere (Ormel et al., 2005). For instance, the lifetime prevalence rates of the TRAILS biological parents are by and large comparable to the CIDI-DSM-IV lifetime rates obtained by direct interviewing in the large population-based NEMESIS study; the exception being fathers' rates for anxiety disorder and substance dependence that were substantially too low. The overall index was computed by averaging the sum indices of the measure that was administered twice 9–10 years apart ($r = .542$).

Intelligence quotient: The participants' intelligence quotient (IQ) was assessed at wave 1. The vocabulary and block design subtests from the Wechsler Intelligence Scale for Children Revised (WISC-R) were used to construct an IQ score that ranged from 45 to 149 (Silverstein, 1972).

Executive functioning: Executive functioning was assessed at wave 1 using computerized tasks from the Amsterdam Neuropsychological Tasks program (ANT) (De

Sonneville, 1999). Psychomotor speed, pattern search, working memory, cognitive flexibility, response inhibition, sustained attention, and feedback responsiveness were merged into one executive functioning variable using confirmatory factor analysis in Mplus (Table S2).

Emotion recognition: Emotion recognition was assessed at wave 1 using computerized tasks from the Amsterdam Neuropsychological Tasks program (ANT) (De Sonneville, 1999). Four of the six emotions (sadness, anger, fear, and disgust) were merged into one emotion recognition variable using confirmatory factor analysis in Mplus (Table S3).

Diurnal cortisol: At wave 1, participants collected three samples of saliva (i.e., directly after waking up, half an hour later, and at 20:00 hr), using the Salivette sampling device. Collection of salivary cortisol is a relatively stress-free approach that avoids confounding by stress responses (Schmidt, 1997). Moreover, associations between saliva cortisol levels and serum cortisol concentrations are high (Kirschbaum & Hellhammer, 1989). To construct a measure of participants' diurnal cortisol, the area under the curve with respect to the ground (AUCg) was calculated using the trapezoid method (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Child temperament: Temperament was assessed with the parent version of the Early Adolescent Temperament Questionnaire Revised (EATQ-R) at waves 1, 3, and 4 (Capaldi & Rothbart, 1992; Oldehinkel, Hartman, de Winter, Veenstra, & Ormel, 2004). We used effortful control, extraversion, fearfulness, and frustration. The scores were averaged across waves (averaged correlations among the three waves were: r_{EFC} = .566; $r_{Extraversion}$ = .556; r_{Fear} = .399; $r_{Frustration}$ = .485).

Family functioning: Parent-reported family functioning was assessed with the family assessment device (FAD) at waves 1–4 (Epstein et al., 1983). The score was averaged across waves 1–4 in SPSS (r = .502).

Parental rearing: Parental warmth and parental rejection were assessed by the child with the Egna Minnen Betraffande Uppfostran Child (EMBU-C) at waves 1 and 4 (Markus, 2003). Parental warmth was computed by averaging the wave 1 and wave 4 scores of the EMBU-C warmth scale (r = .282). Parental rejection was constructed by combining the score on the rejection scale of the EMBU-C (i.e., average of waves 1 and 4 [r = .240]) with the wave 4 total parental aggression toward child trauma score using confirmatory factor analysis in Mplus (Table S5).

Analysis

First, we estimated the bifactor model based on 12 symptom factors (Figure 2; Appendix S7). Each symptom factor was represented by the corresponding subdomain of all informants (if assessed by multiple informants) across all waves. In addition, informant (same informant across waves) and wave factors (different measures of psychopathology per wave) were included to partial out the variance that could be attributed to this specific informant or wave, respectively. The symptom factors were then used to estimate the general factor and four specific factors: internalizing, externalizing, ADHD, and ASD. This distinction among four specific factors was based on extensive empirical research in a previous study by Noordhof, Krueger, Ormel, Oldehinkel, and Hartman (2015) on the TRAILS data. This paper showed the need to model not only ASD but also ADHD as two separate neurodevelopmental problem domains, in turn, separate from INT and EXT. Each dimension was represented by at least three symptom factors (Figure 2). The general factor was represented by all 12 symptom factors. Factor scores of the *p*, INT, EXT, ADHD, and ASD factors were saved for the subsequent modeling step. We used the regression method to estimate factor scores and the H-, ω- and Factor Score Determinacy (FSD) coefficients to evaluate the reliability of all factors.

Next, we integrated the factor scores of the general and specific factors and the etiologically relevant variables in our structural equation model (Figure 1). The full path model distinguishes five different levels, the etiologically relevant variables at each level were linked to the etiologically relevant variables at all lower levels, and to the general and specific factors. Associations between variables at the same level were modeled as correlations. We fitted three path models: Model 1 used only the temperament traits, model 2 used all variables except for the temperament traits, and model 3 used the full path model with all variables represented in Figure 1. When excluding the PRSs (missingness = 38.9%) and diurnal cortisol (missingness = 27.2%), the maximum proportion of missing data varied from 0% for perinatal problems to 2.7% for a family environment, with an average missingness of 0.8%. While we are aware that the missing at random principle was not upheld, the relatively low missingness of most variables as well as the low correlations of the PRSs and diurnal cortisol that have high missingness with the variables potentially explaining this missingness in our data (e.g., SES, IQ), indicate that this violation is unlikely to strongly impact our results. That is, it has been shown that if the missingness of a variable is lower than 25% or the correlation between the variable with over 25% missingness and the variable potentially explaining this missingness is below 0.4, the effect of including correlates of missingness as auxiliary covariates in the analysis is negligible (Graham, 2003; Newsom, 2023). Since at least one of these criteria holds for all etiologically relevant factors in our model we think that the use of auxiliary variables as covariates in the model would not have changed the estimates. By extension this indicates that the violation of the missing at random principle does in this case not impact the results.

Both the bifactor and the path models were estimated within a structural equation modeling framework in Mplus 8 (Muthén & Muthén, 2017). Specifically, we used Confirmatory Factor Analysis and Path Analysis with full maximum likelihood estimation and robust standard errors (MLR). Continuous variables were standardized for all analyses. The path model yields estimates of direct effects, referring to the direct regression effect of Y on X, indirect effects (the sum of the indirect regression effects of Y on X via other variables in the model), and total effects (sum of direct and indirect effects). Mplus code and model estimates of the bifactor and path models are provided in Appendices S13–S20.

Evaluation of effect sizes in the path models

For three reasons we do not follow Cohen's (2013) criteria for the interpretation of effect sizes. First, the traditional Cohen guidelines are much too stringent because they do not acknowledge that seemingly small effects can matter in the long run, albeit not very consequentially in a single episode (Abelson, 1985; Funder & Ozer, 2019). Second, in our complex, multifactorial, model we expect to find associations that we regard as meaningful, but which are all small or negligible according to Cohen's criteria. Compare our work, for example, with genetics: individual SNP effects are tiny yet are valid and replicable and we would never consider labeling these according to Cohen's rules because we know that only tiny SNP effects are to be expected. Third, from a practical point of view, we had to order the numerous estimated associations in terms of their strength to help the reader making sense of the findings. Therefore, we describe path effects in the range ($.05 \leq \beta \leq .10$) as weak, ($.11 \leq \beta \leq .20$ as moderate, and ($\beta > .20$) as strong. In

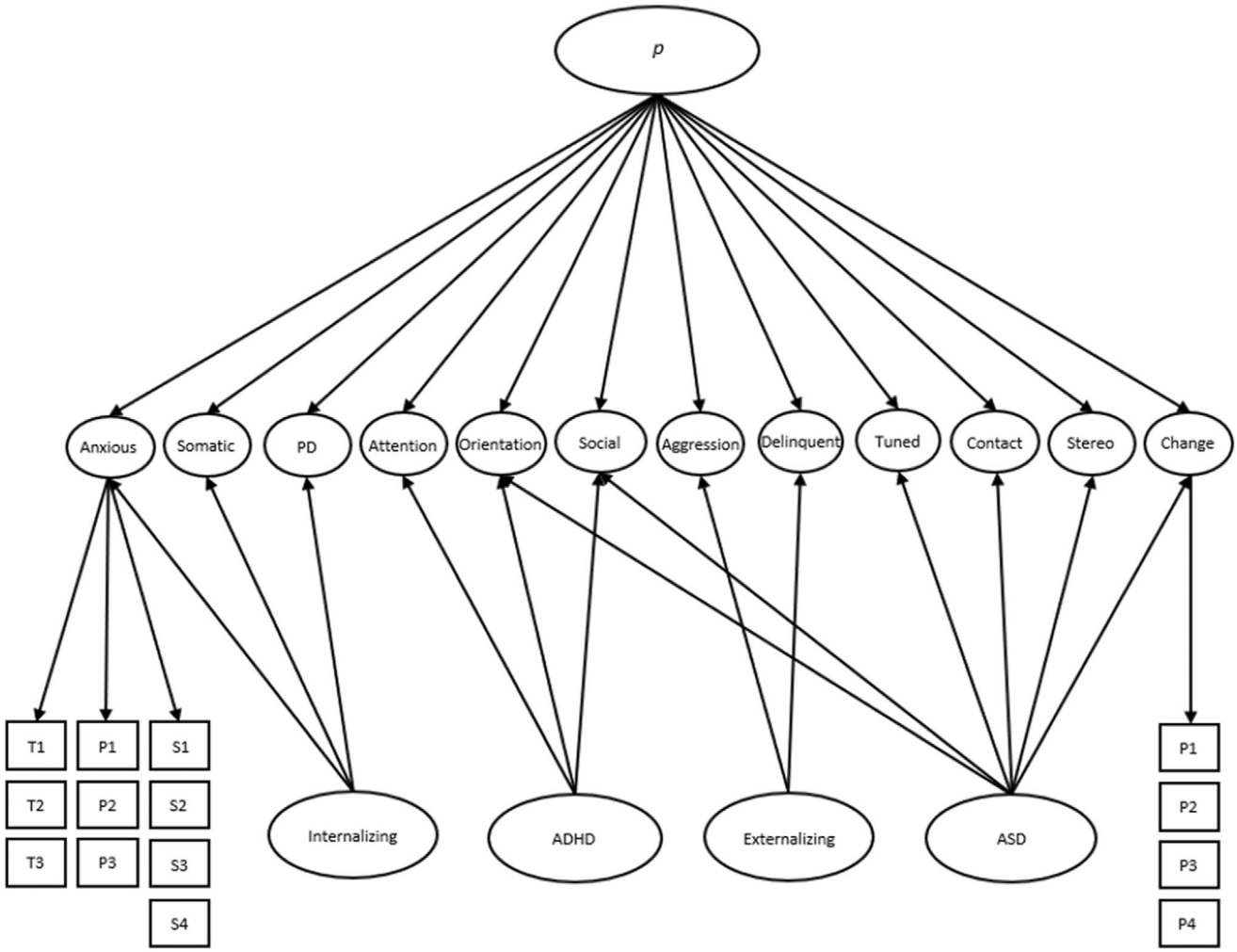

Figure 2 Bifactor model of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology. ADHD, Attention-Deficit/Hyperactivity Disorder; aggression, aggressive behavior; Anxious, anxious-depressed; ASD, Autism Spectrum Disorder; Attention, attention problems; change, fear and resistance to change; contact, reduced contact; delinquent, delinquent behavior; orientation, orientation problems; *p*, general factor of psychopathology; P, parent-report; PD, Panic Disorder; S, self-report; 1 refers to wave 1; 2 refers to wave 2; 3 refers to wave 3; 4 refers to wave 4; social, difficulties in understanding social information; Somatic, Somatic complaints; stereo, stereotyped behavior; T, teacher-report; tuned, behavior/emotions not optimally tuned to situation. Anxious and Change serve as convenient examples to display that every symptom factor is represented by the corresponding subdomains of all informants (if assessed by multiple informants) across all waves

addition, to be able to compare path effects across psychopathology factors, we used, admittedly somewhat arbitrary, a beta difference of $\beta \geq .05$ if this corresponded with a *z*-score difference of $Z > 1.96$ (which indicates a statistically significant two-sided *t*-test at the level of .05) to highlight one effect as larger than any other. Although an effect size of 0.05 is rather small for the explanation of single events, it is potentially consequential in the not very long run as eloquently demonstrated by Abelson (1985).

Results

Model fit of the bifactor model and H-, ω- and FSD coefficients of its factors

The bifactor model estimated *p* and four higher order factors based on 12 symptom factors. Given its complexity, model fit was adequate: RMSEA = 0.03, CFI = 0.91, and SRMR = 0.07. Standardized factor loadings of the 12 symptom factors on *p* range from 0.54 (panic) to 0.84 (fear of and resistance to change) and are substantial for the specific INT, EXT, and ADHD factors as well ($\beta > .6$ with two exceptions), but lower for ASD ($\beta \sim .3$) (Appendix S7). These loading patterns are mostly in line with the H-, ω- and FSD coefficients, indicating that the reliability is excellent for the *p* (H = 0.93; ω = 0.97; FSD = 0.92), moderate for the EXT (H = 0.69; ω = 0.96; FSD = 0.88) and ADHD (H = 0.60; ω = 0.96; FSD = 0.88), and low for the INT (H = 0.56; ω = 0.87; FSD = 0.70) and ASD (H = 0.43; ω = 0.95; FSD = 0.75) factors (Appendix S22).

We want to further point out that even though we included the higher order specific ASD factor in our subsequent analyses, we are aware that there is limited unique variance in the ASD items left after the variance attributed to the general factor is partitioned. Even so, we think that this neither decreased the validity of the ASD factor nor resulted

in any major bias although it undoubtedly strongly reduced the statistical power to identify statistically significant associations between the etiologically relevant predictors and the specific ASD factor. This viewpoint is supported by our finding that while only a few distal-to-proximal etiologically relevant variables for the specific ASD factor were found, they were fully in line with what would be expected (developmental delay, extraversion, frustration, parental SES).

Efforts to increase the variance of the ASD factor are described in Appendix S21. Although we succeeded herein by fixing the residual variance of multiple indicators to zero (AnxDep, Aggression, Attention, Tuned, Orientation and Contact), we had no clear rationale for these changes in the model (why these residuals and not others) and accordingly considered this a suboptimal model. Alternative results of our subsequent analyses when using this revised model are provided in Tables S13 and S14.

Model fit of the path models

Tables 1 and 2 present the fit, variance explained, and the total effects of the etiologically relevant factors of path models 1 and 2 in which we integrated the psychopathology and etiologically relevant factors. Appendix S8 presents the total effects of path model 3 and Appendix S9 the correlations between the etiologically relevant and psychopathology factors. Model fit was acceptable although the RMSEA values are below the standard threshold: RMSEA = 0.12, CFI = 0.91, and SRMR = 0.04 for model 1 (only temperament traits); RMSEA = 0.14, CFI = 0.92, and SRMR = 0.03 for model 2 (non-temperament variables); and RMSEA = 0.11, CFI = 0.94, and SRMR = 0.03 for model 3 (all variables). The PCLOSE values of all three models are significant (0.00) meaning that the probability that the RMSEA values are smaller than 0.05 is very low. However, of the three model fit indices presented, the RMSEA is the one that is most sensitive to the degrees of freedom. As a consequence of the large number of parameters estimated in our analyses the degrees of freedom of our models are quite low. This might explain why the other indices are acceptable while the RMSEA and PCLOSE are not.

Model 1 (only temperament) accounted for 49% of the variance in *p*, 43% in ADHD, 29% in EXT, 15% in INT, and 3% in ASD. In model 2 (non-temperament variables) these percentages dropped to 29% for *p*, to 9% for ADHD, 14% in EXT, 7% in INT, and 4% in ASD. Finally, model 3 (all variables) accounted for 55% in *p*, 46% in ADHD, 35% in EXT, 19% in INT, and only 7% in ASD.

We describe path effects in the range ($.05 \leq \beta \leq .10$) as weak, ($.11 \leq \beta \leq .20$ as moderate, and ($\beta > .20$) as strong.

Effects of temperament traits on psychopathology – model 1

As the most proximal etiologic factor, child temperament effects were extensive and highly generic (Table 1). *p* was strongly associated with frustration and to a lesser extent fearfulness. INT was strongly associated with fearfulness and EXT with frustration. ADHD was strongly associated with low effortful control and to a lesser extent with extraversion. Associations with ASD were weaker, with only a moderate association with low extraversion. This pattern of results indicates that apart from generic effects on *p*, temperament traits are linked to different types of psychopathology.

Some traits had opposite effects: Extraversion is associated with higher EXT and ADHD ($\beta \sim .24$) but less ASD and *p* ($\beta \sim -.15$). Fearfulness is associated with higher INT ($\beta = .41$) and *p* ($\beta = .26$) but less EXT ($\beta = -.24$) and ADHD ($\beta = -.09$).

Effects of non-temperament variables on psychopathology—model 2

Effects on p. All non-temperament variables except emotion recognition and parental warmth had an effect on *p* (Table 2). Among these, strong effects of family functioning ($\beta = -.27$) and parental psychopathology ($\beta = .25$) stand out. Perinatal problems, parental psychopathology, developmental delay, executive functioning, family functioning, and parental rejection had moderate effects on *p*. Generic effects were thus widespread: 13 of the 15 non-temperament variables had an effect on *p* and 11 on at least two specific factors. Only emotion recognition did not have a generic effect (as it predicted only EXT). Three variables had stronger effects on *p* than on any specific psychopathology factor (i.e., difference in $\beta \geq .05$ and $Z > 1.96$): perinatal problems, parental psychopathology, and family functioning. Except for parental SES, all variables had similar or larger direct than indirect effects on *p* (Appendix S10 and Tables S6 and S7).

Effects on specific psychopathology factors. Most effects of the non-temperament variables on specific psychopathology factors are weak or moderate. Regarding INT, PRS depression, parental psychopathology, and parental warmth had moderate effects. Regarding EXT, parental rejection has a strong effect, and parental SES, developmental delay, and family functioning moderate effects. Regarding ADHD, parental psychopathology and executive functioning have moderate effects, and regarding ASD, developmental delay and parental SES. Parental rejection ($\beta = .21$) has a stronger effect on EXT than on any other specific factor. Most variables had similar or larger direct than indirect effects on specific psychopathology factors (≥0.05) (Appendix S10 and Tables S6 and S7).

Table 1 Total effects of distal-to-proximal etiologically relevant variables of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology if only the temperament traits are included in the model (model 1)

	Internalizing	Externalizing	ADHD	ASD	General factor
Effortful control	0.14 (0.1 to 0.19)*	−0.22 (−0.26 to −0.18)*	−0.7 (−0.73 to −0.66)*	0.01 (−0.04 to 0.06)	−0.16 (−0.2 to −0.12)*
Extraversion	0.08 (0.04 to 0.13)*	0.23 (0.19 to 0.27)*	0.24 (0.2 to 0.27)*	−0.15 (−0.19 to −0.1)*	−0.14 (−0.17 to −0.1)*
Fearfulness	0.41 (0.37 to 0.46)*	−0.24 (−0.29 to −0.19)*	−0.09 (−0.13 to −0.05)*	−0.07 (−0.14 to 0)	0.26 (0.21 to 0.31)*
Frustration	−0.04 (−0.1 to 0.01)	0.49 (0.44 to 0.54)*	−0.03 (−0.08 to 0.02)	0.1 (0.02 to 0.18)*	0.4 (0.34 to 0.45)*
Explained variance	0.15	0.29	0.43	0.03	0.49

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder;
*Significant at .05 level. (Residual) covariance among all variables at the same level and between externalizing and ADHD freed. *Model fit*: RMSEA = 0.12, CFI = 0.91, and SRMR = 0.04.

While most variables have similar effects on *p* and one or more specific factors, some have opposite effects. Developmental delay is associated with higher ASD and *p* (β ~ .13) but with lower EXT (β = −.12); diurnal cortisol with lower EXT, ADHD, ASD, and *p* (β ~ −.08) but higher INT (β = .08); and parental warmth is unrelated to *p* but associated with higher INT (β = .11) and lower ASD (β = −.07).

Full model: All variables included—model 3

Adding the temperament traits to model 2 provides information about the indirect effects of non-temperament variables on *p* that 'run' via temperament traits. At least half of the total effect of PRS depression, parental psychopathology, and executive functioning 'ran' via temperament. As expected, the effects of temperament variables in the full model were slightly smaller than in model 1 while the total effects of the non-temperament variables were very similar to those in model 2 (Appendices S8 and S10, and Tables S8 and S9).

Sensitivity analysis

The sensitivity analysis indicated that afore described findings with regard to the effects of the etiologically relevant variables on *p* and the specific INT, EXT, ADHD, and ASD factors remain largely unaltered when participants who were not genotyped were removed (Appendix S11 and Tables S10 and S12).

Discussion

In this study, we used a bifactor model to estimate the general and four specific factors of psychopathology: *p*, INT, EXT, ADHD, and ASD. The decision to distinguish these four specific factors was based on extensive empirical research in a previous study by Noordhof, Krueger, Ormel, Oldehinkel, and Hartman (2015) on the TRAILS data. These general and specific psychopathology factors were, in turn, predicted by distal-to-proximal etiologically relevant factors in a path model. Our study showed that collectively a broad range of etiologically relevant variables have a stronger association with *p* than with any of the specific psychopathology factors. In addition to predicting *p*, almost all etiologically relevant factors predicted specific psychopathology factor(s). There were some relative differences in strength such that perinatal problems, parental psychopathology, and poor family functioning were more strongly associated with *p* than with any specific psychopathology factor. Conversely, parental rejection was more strongly associated with EXT than with any other psychopathology factor. These findings underline the relevance of the bifactor psychopathology model and the selected etiologically relevant factors. Given the controversial status of

Table 2 Total effects of distal-to-proximal etiologically relevant variables of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology if only non-temperament variables are included in the model (model 2)

	Internalizing	Externalizing	ADHD	ASD	General factor
PRS depression	0.12 (0.06 to 0.17)*	0.02 (−0.03 to 0.07)	0 (−0.05 to 0.05)	−0.05 (−0.1 to 0)	0.07 (0.02 to 0.12)*
PRS aggression	0.01 (−0.04 to 0.06)	0.09 (0.04 to 0.14)*	0.04 (−0.01 to 0.09)	−0.01 (−0.06 to 0.04)	0.05 (0 to 0.1)*
PRS ADHD	0.03 (−0.03 to 0.08)	0.1 (0.04 to 0.15)*	0.09 (0.04 to 0.14)*	0.04 (−0.02 to 0.09)	0.09 (0.03 to 0.14)*
PRS ASD	−0.01 (−0.06 to 0.04)	−0.02 (−0.07 to 0.03)	0.03 (−0.02 to 0.08)	0.01 (−0.04 to 0.06)	0.07 (0.02 to 0.12)*
Parental SES	−0.09 (−0.12 to −0.05)*	−0.13 (−0.17 to −0.09)*	-0.09 (−0.13 to −0.05)*	−0.1 (−0.14 to −0.06)*	−0.1 (−0.13 to −0.06)*
Perinatal problems	0.04 (0 to 0.08)	0 (−0.04 to 0.04)	0.06 (0.01 to 0.1)*	0.07 (0.03 to 0.12)*	0.15 (0.11 to 0.19)*
Parental psychopathology	0.11 (0.07 to 0.15)*	0.09 (0.05 to 0.14)*	0.11 (0.07 to 0.16)*	0.02 (−0.02 to 0.07)	0.25 (0.21 to 0.29)*
Developmental delay	−0.03 (−0.07 to 0.01)	−0.12 (−0.16 to −0.08)*	0.03 (−0.01 to 0.07)	0.11 (0.07 to 0.15)*	0.14 (0.1 to 0.18)*
IQ	−0.07 (−0.12 to −0.03)*	−0.05 (−0.09 to −0.01)*	−0.07 (−0.12 to −0.03)*	−0.01 (−0.05 to 0.03)	−0.06 (−0.1 to −0.02)*
Executive functioning	0.02 (−0.03 to 0.07)	−0.05 (−0.1 to 0)*	−0.15 (−0.2 to −0.1)*	−0.03 (−0.09 to 0.03)	−0.18 (−0.23 to −0.13)*
Emotion recognition	0.01 (−0.03 to 0.06)	0.07 (0.02 to 0.12)*	0 (−0.05 to 0.05)	0 (−0.05 to 0.05)	0.05 (0 to 0.1)
Diurnal cortisol (AUCg)	0.09 (0.04 to 0.14)*	−0.07 (−0.11 to −0.03)*	−0.09 (−0.14 to −0.05)*	−0.06 (−0.1 to −0.01)*	−0.1 (−0.14 to −0.06)*
Family functioning	−0.05 (−0.09 to −0.01)*	−0.15 (−0.19 to −0.11)*	−0.06 (−0.1 to −0.02)*	−0.06 (−0.1 to −0.02)*	−0.27 (−0.31 to −0.23)*
Parental warmth	0.11 (0.07 to 0.15)*	−0.01 (−0.05 to 0.03)	−0.03 (−0.07 to 0.02)	−0.07 (−0.11 to −0.03)*	0 (−0.04 to 0.03)
Parental rejection	0.08 (0.04 to 0.13)*	0.21 (0.16 to 0.25)*	0.09 (0.05 to 0.13)*	0 (−0.05 to 0.05)	0.15 (0.11 to 0.19)*
Explained variance	0.07	0.15	0.10	0.05	0.31

ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; AUCg, area under the curve with respect to the ground; IQ, Intelligence quotient; PRS, Polygenic risk score; SES, Socio-economic status.

*Significant at .05 level. (Residual) covariance among all variables at the same level and between externalizing and ADHD freed. *Model fit*: RMSEA = 0.14, CFI = 0.92, and SRMR = 0.03.

temperament as a predictor of psychopathology (Hyatt et al., 2019; Kotov, Gamez, Schmidt, & Watson, 2010; Nigg, 2006; Ormel et al., 2012; Rosenström et al., 2019), we fitted path models with and without temperament traits. Total explained variance in psychopathology dropped substantially when we excluded the temperament predictors, for example, from 55% to 29% for *p*. The drop indicates the strength of the temperament-psychopathology relationship and validates our choice to fit these different models. Although temperament traits had strong links with psychopathology, the relevance of non-temperament etiologically relevant variables should not be underestimated. Most of the latter were associated not only with *p* but with specific factors as well, with three strongly and nine moderately with either *p* or specific factors. Only PRS ASD did not predict any specific psychopathology factor, and only two did not predict *p*. These findings corroborate the generic nature of the non-temperament etiologically relevant factors as well as the relevance of the specific psychopathology factors for understanding psychiatric disorders.

The findings are consistent with an extensive literature showing that most personal and environmental risk and protective factors have transdiagnostic (i.e. generic) significance (Cerdá, Sagdeo, Johnson, & Galea, 2010; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Lee, Yen-Chen, & Jordan, 2021; Lu et al., 2021; Lynch et al., 2021; Uher & Zwicker, 2017). Regarding *environmental* factors, we showed, for example, that low SES, poor family functioning, and parental rejection were strongly associated with both *p* and specific factors and therefore highly generic. These associations illustrate the broad significance of psychopathology in children's most important environment, the family (Conway, Raposa, Hammen, & Brennan, 2018). Regarding *personal* factors (e.g., PRS, developmental delay, executive functioning, diurnal cortisol), our findings fit well with recent findings from genome-wide association studies (GWAS). The GWASs have documented a large degree of genetic overlap among psychiatric disorders and the involvement of neurodevelopmental processes in the development of psychopathology (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Grotzinger et al., 2019; Smoller et al., 2019; Sullivan & Geschwind, 2019; Waldman, Poore, Luningham, & Yang, 2020). The Cross-Disorder Group of the Psychiatric Genomics Consortium's meta-analysis across eight psychiatric disorders showed that >75% genome-wide significant single nucleotide polymorphisms (SNPs) had generic effects on at least two psychiatric disorders. It was additionally shown that the generic loci are located within genes that show heightened expression in the brain throughout the lifespan, beginning prenatally and playing prominent roles in neurodevelopmental processes (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019, p. 1469). Consistent with this finding, we showed generic effects of the four PRS variables, as well as strong associations of developmental delay, perinatal problems, and poor executive functioning with *p*.

Temperament associations with psychopathology factors were extensive and, like family influences and neurodevelopmental factors, highly generic. *P* was most strongly associated with frustration and to a lesser extent with low extraversion and fearfulness. Apart from these generic effects, temperamental strengths and vulnerabilities were linked to specific psychopathology factors as well. This is in line with previous literature (Chetcuti et al., 2021; Hyatt et al., 2019; Nigg, 2006, 2022; Rosenström et al., 2019). Here we extend these previous findings by showing that even though temperament traits converge in *p*, the associations with specific factors remain. The etiological meaning of these temperament findings remains unclear and is likely partly tautological. This may apply in particular to effortful control given both substantial content overlap and the strong association with ADHD. However, it is unlikely that the associations between temperament traits and psychopathology factors are *only* due to content overlap as they are part of a broader literature indicating that the extremes of normally distributed temperament traits blend into (dimensional but skewed) psychopathology. Recently, Hyatt and colleagues provided strong support for this dimensional model of personality and psychopathology by showing that similar neuroanatomical correlates underlie specific personality traits and symptoms of psychopathology (Hyatt et al., 2019).

Modeling psychopathology as a bifactor model and splitting the variance in a general factor uncorrelated with specific psychopathology factors facilitated the detection of opposite effects as it allows studying psychopathology 'without comorbidity' (Aristodemou & Fried, 2020; Caspi & Moffitt, 2018; Langan, Stewart, & Smith, 2013; Lynch et al., 2021). Illustrating this, developmental delay predicts higher ASD and *p* but lower EXT; diurnal cortisol predicts lower EXT, ADHD, ASD, and *p* but higher INT; parental warmth is unrelated to *p* but associated with higher INT ($\beta = .11$) and lower ASD ($\beta = -.07$); and extraversion predicts higher EXT and ADHD but lower ASD and *p*. Detecting opposite effects is especially relevant in relation to risk and protective factors that have subtle effects that are more difficult to detect, and which often yield conflicting findings in the literature (e.g., diurnal cortisol) (Dietrich et al., 2013).

Our findings are almost entirely in line with Lynch and colleagues' review on the link between 'transdiagnostic risk and protective factors' and 'general psychopathology', in as far as similar factors were included. Although Lynch et al. did not include parental SES, developmental delay, IQ, diurnal cortisol, family functioning, and parental rearing;

they found evidence from two or more independent samples for a role of genetic risk, maternal depression, negative affectivity, being male, executive functioning deficits, low extraversion, low effortful control, and neuroticism. The similarities in findings further strengthen the growing body of support for transdiagnostic approaches to future research as well as treatment and prevention.

An unexpected finding is the lack of association between both IQ and EF and ASD scores. This may seem surprising given what is known about these cognitive skills in research on ASD. We think that the lack of association has two causes. First, most variance of the ASD items goes to the general factor [which is associated with lower IQ and lower EF, respectively −0.06 (−0.1 to −0.02)* and −0.18 (−0.23 to −0.13)*]. This is also the main cause of the limited unique variance of the ASD factor. Second, and importantly, in TRAILS, few individuals with ASD have mild or more severe intellectual impairment. Thus, youth with high ASD symptoms can still be high functioning, with average or high IQ and executive functioning scores.

Overall, the findings underline the relevance of the bifactor model and the selected etiologically relevant factors. However, the significance of the ASD factor as an independent specific psychopathology factor is not clear given its low reliable variance due to relatively low loadings of its symptom indicators as compared to their strong loadings on *p* (Hancock & Mueller, 2001; Hoffmann et al., 2022). It is possible that the complexity of the data we used to fit the bifactor model (4-wave multi-informant data) is favoring the general factor at the expense of specific factors. Anyway, we do not think that the modest-to-poor reliability has biased the discrimination of the etiologically relevant factors for the different specific psychopathology factors but the strength of the associations may have been underestimated. In general, the effects of the non-temperament etiologically relevant variables on psychopathology factors are small. However, small effect sizes are small for the explanation of single events but potentially consequential in the not very long run as eloquently demonstrated by Abelson (1985).

Our findings on *p* advance insight into the meaning of *p* in childhood and adolescence. In line with recent work our results suggest that *p* reflects dysregulation (Deutz et al., 2020; Phillips et al., 2022; Selzam, Coleman, Caspi, Moffitt, & Plomin, 2018; Tackett et al., 2013). The findings point to the interplay of neurodevelopmental problems and temperamental traits on the one hand, and the environmental, especially family-related risks on the other hand (Conway et al., 2018; Lynch et al., 2021; Sprooten et al., 2022; Uher & Zwicker, 2017).

Limitations of our study need consideration. First, as already emphasized in the introduction, the causal status of the etiologically relevant factors is unknown. In line with this, the interpretation of the relationships between PRSs, environmental risks, and psychopathology is probably more complex than our model suggests (Pingault et al., 2022). Second, our approach to create latent constructs based on multiple informants and averaging data collected at multiple ages enabled us to model stable individual differences based on what the reports from multiple informants have in common. Although this approach is most relevant for our aim of unraveling etiologically relevant factors, it precluded us from exploring possible informant-specific or age-specific effects. Third, our sample has selective dropout. Although attrition was limited to 17% across four waves, more disadvantaged participants, notably low SES, are somewhat underrepresented (de Winter et al., 2005; Nederhof et al., 2012).

To conclude, transdiagnostic research aimed at the detection of risk and protective factors in which psychiatric problems are both lumped and split is still rare (Hartman, 2021). This study used a bifactor model to capture the shared variance between different types of psychopathology as distinct from their specific variance. The estimated *p* factor is indicative of strong comorbidity indicating that different types of psychopathology rarely occur in isolation but rather cluster within persons. In addition, we know from the literature that risk factors are correlated (Cummings, Caporino, & Kendall, 2014; Lai, Lombardo, & Baron-Cohen, 2014; Lynch et al., 2021; Thapar & Cooper, 2016) and in our study we likewise found substantial correlations between etiologically relevant factors (see Appendix S12, Figures S1–S3). Thus, risk factors also tend to cluster within persons. The first important finding of this study is that clustering of risk factors and comorbidity are linked: both personal and environmental risk factors are largely generic, predicting *p* and often additional specific factors of psychopathology; we were able to show this in an elegant model using the principle of distal-proximal. Assuming at least partly causal links, these predominantly generic associations imply that a large gain in mental health could be achieved by preventive action on generic risk factors. A second important finding is that while, on the contrary, many etiologically relevant factors converge in *p*, we also identified factors with (a) effects on specific factors in addition to effects on *p*, and (b) opposite effects. These two types of effects indicate that both *p* and specific psychopathology factors are needed to understand psychiatric disorders. Finally, the findings suggest that *p* can be characterized by high frustration, neurodevelopmental problems, and a disadvantaged family environment.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Additional information symptoms and etiologically-relevant variables.
Appendix S2. Additional information on polygenic risk scores.
Appendix S3. Additional information on Amsterdam Neuropsychological Tasks.
Appendix S4. Additional information on cortisol.
Appendix S5. Additional references.
Appendix S6. Fit statistics of the latent variables.
Appendix S7. Model fit and standardized factor loadings of the bifactor model.
Appendix S8. Total effects of distal-to-proximal etiologically-relevant variables of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology of the full model (model 3).
Appendix S9. Pearson correlations between etiologically-relevant variables and the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology.
Appendix S10. Direct and indirect effects of distal-to-proximal etiologically-relevant variables on general and specific internalizing, externalizing, ADHD, and ASD psychopathology factors.
Appendix S11. Total, direct, and indirect effects of distal-to-proximal etiologically-relevant variables on the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology, when the participants that have not been genotyped were removed.
Appendix S12. Structural equation models.
Appendix S13. Mplus code bifactor model.
Appendix S14. Mplus code if only the temperament traits are included in the model (model 1).
Appendix S15. Mplus code if only non-temperament variables are included in the model (model 2).
Appendix S16. Mplus code of the full model (model 3).
Appendix S17. Standardized factor loadings and estimated (residual) covariances of the bifactor model.
Appendix S18. Standardized factor loadings and estimated (residual) covariances if only the temperament traits are included in the model (model 1).
Appendix S19. Standardized factor loadings and estimated (residual) covariances if only non-temperament variables are included in the model (model 2).
Appendix S20. Standardized factor loadings and estimated (residual) covariances of the full model (model 3).
Appendix S21. Efforts to increase the variance in the specific ASD factor.
Appendix S22. Additional fit statistics of the bifactor model.
Table S1. Principal component loadings of polygenic risk scores.
Table S2. Model fit and standardized factor loadings of executive functioning.
Table S3. Model fit and standardized factor loadings of emotion recognition.
Table S4. Model fit and standardized factor loadings of developmental delay.
Table S5. Model fit and standardized factor loadings of parental rejection.
Table S6. Direct effects of distal-to-proximal etiologically-relevant variables of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology if only non-temperament variables are included in the model (model 2).
Table S7. Indirect effects of distal-to-proximal etiologically-relevant variables of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology if only non-temperament variables are included in the model (model 2).
Table S8. Direct effects of distal-to-proximal etiologically-relevant variables of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology in the full model (model 3).
Table S9. Indirect effects of distal-to-proximal etiologically-relevant variables of the general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology in the full model (model 3).
Table S10. Total effects of the etiologically-relevant variables of the psychopathology factors.
Table S11. Direct effects of the etiologically-relevant variables of the psychopathology factors.
Table S12. Indirect effects of the etiologically-relevant variables of the psychopathology factors.
Table S13. Total effects of distal-to-proximal etiologically-relevant variables of the *revised* general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology if only the temperament traits are included in the model (model 1).
Table S14. Total effects of distal-to-proximal etiologically-relevant variables of the *revised* general and specific internalizing, externalizing, ADHD, and ASD factors of psychopathology if only non-temperament variables are included in the model (model 2).
Figure S1. Significant ($p < .05$) paths if only the temperament traits are included in the model (model 1).
Figure S2. Significant ($p < .05$) paths if only non-temperament variables are included in the model (model 2).
Figure S3. Significant ($p < .05$) paths of the full model (model 3).

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Data availability statement

The dataset analysed in this study is subject to the European Union's General Data Protection Regulation and can be requested by means of a publication plan. More information can be found at the study website: https://www.trails.nl/en/hoofdmenu/data/data-use. All codebooks are available from: https://easy.dans.knaw.nl/ui/home.

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Key points

- Transdiagnostic research aimed at understanding the etiology of psychopathology is still rare. The bifactor model permits to split the covariance among psychiatric symptoms into a general (*p*) and specific factors, allowing their separate study.
- Major personal and environmental etiologically relevant factors have largely generic effects (i.e., predict *p*).
- Many etiologically relevant factors predict one or more specific psychopathology factors in addition to *p* and some have opposite effects, indicating that specific psychopathology factors (INT, EXT, ADHD, ASD) remain relevant for understanding psychiatric disorders.
- High frustration, neurodevelopmental delay, and a disadvantaged family environment primarily characterize *p*.
- Treatment, prevention, and research may advance by focusing on *p*, and its risk and protective factors.

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