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（生後 18 か月時の気質プロファイルによる
8-9 歳時の ASD 特性・ADHD 特性の高さおよび併存の予測：HBC Study）

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Temperament Profiles at Age 18 Months as Distinctive Predictors of Elevated ASD- and ADHD-Trait Scores and Their Co-Occurrence at Age 8–9: HBC Study

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Abstract
Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) can be traced back to specific early childhood temperament patterns. However, no unique pattern has been identified for their co-occurrence. Given that children with both traits often require more clinical attention, this study aimed to discover such patterns by examining three temperament domains measured during early childhood—Surgency/Extraversion (SE), Negative Affectivity (NA), and Effortful Control (EC)—and their association with group membership defined as being above the cut-off points for either ASD- or ADHD-trait scores or their co-occurrence at school age. We enrolled 814 children from a birth cohort, assessing temperament at 18 months using the Early Childhood Behavior Questionnaire, and ASD- and ADHD-trait scores at ages 8–9 using the Social Responsiveness Scale-2 and ADHD-Rating Scale. Group membership was determined by clinically significant symptoms, defined as +1 SD after standardizing scores by age and sex. Multinomial regression analyses examined associations between temperament domain scores and group membership (ASD-dominant, ADHD-dominant, co-occurring, neither-ASD-nor-ADHD). The co-occurring group showed a unique temperament profile, with higher scores in both NA and EC (OR in NA = 1.48, 95% confidence interval (CI): 1.11 to 1.96 and OR in EC = 1.61, 95% CI: 1.18 to 2.20), distinct from the patterns shown by the ASD-dominant and ADHD-dominant groups. The combination of high NA and EC scores uniquely characterizes the co-occurring group, highlighting the need for early temperament assessments to identify children potentially requiring clinical attention for both ASD and ADHD traits.

Keywords ASD · ADHD · Temperament · Childhood · Japan

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Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are highly co-occurring neurodevelopmental conditions that share clinical features, including onset during childhood and variable trajectories throughout the lifespan (Lord et al., 2020; Posner et al., 2020). Children with co-occurring conditions often have greater challenges in cognitive functioning, psychopathology, and daily life (Yerys et al., 2009, 2019; Bedford et al., 2019; Chandler et al., 2022). An attempt to uncover unique early temperament patterns in children who would develop co-occurring condition later in childhood will enable more targeted clinical and psychosocial interventions not only for the children but also relief for families compared to single-conditioned populations (Gargaro et al., 2011; Mansour et al., 2021; Hours et al., 2022).

The early behavioral phenotypes of ASD and ADHD are already present, with both physiological and behavioral manifestations, well before any formal diagnosis. It is important to use early behavioral phenotypes, both to ensure valid diagnostic outcomes and to evaluate how these phenotypes emerge and how the phenotypic overlap develops, to effectively deliver appropriate preventative and therapeutic interventions in the early stage of life in those children (Sonuga-Barke & Halperin, 2010; Klin et al., 2020; Posner et al., 2020).

Prior studies have sought to understand the relevance of child temperament as an early behavioral phenotype related to psychopathology, stating that it captures “the responsiveness and regulation of biological emotions, movements, and attention” (Rothbart & Derryberry, 2002). The hypothesis is that aberrant patterns of early temperament lead to psychopathology; temperament and psychopathology share etiological underpinnings and represent opposite ends of the same underlying continuum (Visser et al., 2016; Chetcuti et al., 2021). Following this, understanding early temperament profiles can lead to the prediction of specific psychopathologies, such as the co-occurrence of ASD and ADHD.

Extant literature has identified three temperament domains in children at ages 1.5 to 3, and a link has been suggested to the brain (Posner & Rothbart, 2018). The three domains are Surgency/Extraversion (SE), Negative Affectivity (NA), and Effortful Control (EC) (Rothbart, 1981; Rothbart & Bates, 2006). SE refers to an individual’s tendency to be active and sociable, showing strong reactions to stimuli and new situations, and frequently expressing positive emotions. NA indicates a predisposition to experience unpleasant emotions, such as anger, anxiety and sadness more intensely and frequently. EC describes the ability to regulate one’s behaviors and emotions, focusing attention on achieving goals, and controlling impulses (Rothbart & Bates, 2006; Rothbart, 2007). According to recent review papers (Visser et al., 2016; Chetcuti et al., 2021), relatively well-replicated findings show that a low level of SE is associated with ASD and a high level of SE is associated with ADHD, while a high level of NA is associated with both. However, findings regarding the relevance of EC are mixed. EC is a domain of self-regulation, involving attentional control and emotional regulation connected to the formulation of higher-order domains, including executive attention, which helps resolve conflict (Posner & Rothbart, 2018), and executive function, a family of mental processes when paying attention (Diamond, 2013). EC is also considered under the rubric of temperament, but this regulatory element emerges later in development than reactive traits, and continues developing throughout childhood and into adolescence (Rothbart et al., 2003). Since impairment of these higher-order functions is associated with clinical difficulties, such as difficulties in problem solving and in judgment, early temperament is likely to represent predictive markers of atypical development and difficulty in daily life more effectively than clinical phenotypes emerging later (Visser et al., 2016). Thus, specific temperament patterns including difficulties in EC are likely to point to clinical concerns and to point to the need for early intervention before formal diagnoses are established. The major aim of this study is to evaluate whether patterns of temperament in early childhood, particularly abnormalities in EC, could help identify children who have clinical challenges, particularly the co-occurrence of the elevated ASD- and ADHD-trait scores, as well as looking for differences in temperament profiles of those with the co-occurrence from those with elevated ASD- but not ADHD-trait scores, and those with elevated ADHD- but not ASD-trait scores.

Importantly, the present study sought to overcome some of the methodological constraints found in prior studies. First, we adopted a longitudinal design with a long follow-up. Most of the early findings relied largely on cross-sectional associations at one time-point; some were based on a longitudinal design but with a short follow-up time. Since the average age at diagnosis of ADHD is during school years (e.g. Knott et al., 2024), the follow-up period should be extended to at least elementary school age. Second, we did not enroll clinical or high-risk populations but adopted a population-based sample, capturing traits using standardized measures instead of clinical diagnoses. This attempt reflects an idea that originated from the Research Domain Criteria (RDoC) framework (National Institute of Mental Health, 2011) and is critical to understand the etiology and associated early phenotypes related to ASD and ADHD. It is of great importance in understanding the etiology and associated early phenotypes associated with ASD and ADHD.

Enrollment based on clinical diagnoses of ASD or ADHD required that the individuals have symptoms of some functional impairment (American Psychiatric Association, 2022). This procedure compromises phenotypical continuity of ASD and of ADHD and even misses information of those who have sub-threshold syndromes. Furthermore, it is critical to note that the current diagnostic systems have been made based on predominantly male clinical populations, with ASD and ADHD in girls frequently overlooked because of sex- and gender-related contextual factors, including camouflaging more likely to be employed by girls (Lai et al., 2022). To minimize these concerns, we defined those with clinically significant traits of ASD, ADHD and of both, instead of using diagnostic outcomes, by using cutoffs for established trait scores standardized by age and sex.

The present study examined associations between three temperament domains measured at age 18 months (SE, NA, and EC) and four groups of children defined by a combination of being above or below the cut-off points (≥1SD) for ASD- and ADHD-trait scores measured at age 8–9, consisting of ASD-dominant, ADHD-dominant, co-occurring, and neither-ASD-nor-ADHD groups. We hypothesized that EC is specifically associated with the co-occurring group, different from other groups.

Method

Participants

This study was conducted as part of the Hamamatsu Birth Cohort for Mothers and Children (HBC Study; Tsuchiya et al., 2010; Takagai et al., 2016), an ongoing prospective study that began in 2007. The HBC Study included all pregnant women (n = 1,138) and their children (n = 1,258) who gave birth at Hamamatsu University Hospital or Kato Maternity Clinic, Hamamatsu city, between November 2007 and March 2011. The participating children were representative of Japanese children regarding their demographic characteristics and standardized test scores (Nishimura et al., 2022).

Figure 1 shows that the study excluded 442 children who missed either the 18-month or the age 8–9 follow-up and two children diagnosed with Down syndrome, leaving 814 of the original 1,258 children (64.7%).

All the procedures used in this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. They were all approved by the Life Sciences and Medical Research Ethics Committee of Hamamatsu University School of Medicine (24–67, 24–237, 25–143, 25–283, E14-062, E14-062-1, E14-062-3, 17–037, 17-037-3, 19–145, 20–233). Written informed consent to participate in the study was

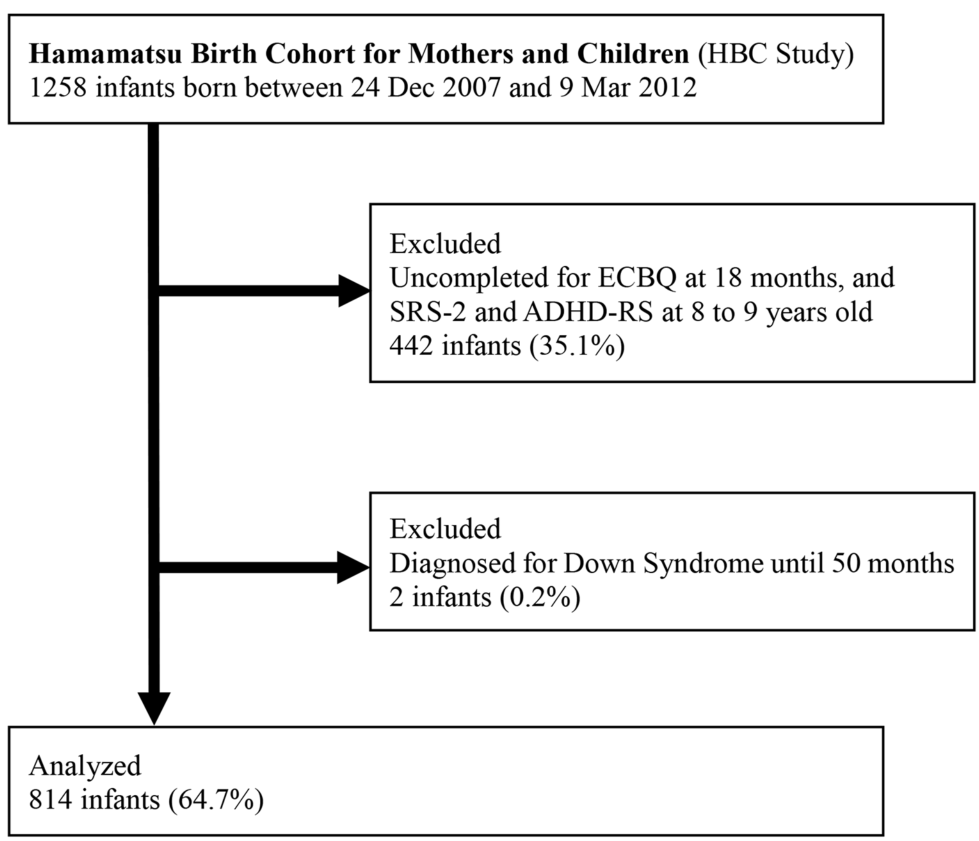

Fig. 1 Flow-chart of study participants

obtained from all parents and, when possible, oral consent was obtained from their children. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Measures

Child Temperament at Age 18 Months

To measure children's temperament, the Japanese version (Sukigara et al., 2015), of the Early Childhood Behavior Questionnaire (ECBQ: Putnam et al., 2006) was used based on reports of the children at age 18 months by their parents or caretakers. The Japanese version of the ECBQ consists of three domains (SE, NA, EC). Domain SE consists of 5 subdomains: "Impulsivity" (10 items), "Activity Level" (12 items), "High-Intensity Pleasure" (12 items), "Sociability" (8 items) and "Positive Anticipation" (11 items). Domain NA consists of 8 subdomains: "Discomfort" (10 items), "Fear" (10 items), "Motor Activation" (11 items), "Sadness" (8 items), "Perceptual Sensitivity" (12 items), "Shyness" (12 items), "Soothability" (9 items) and "Frustration" (12 items). Domain EC consists of 5 subdomains: "Inhibitory Control" (12 items), "Attention Shifting" (12 items), "Low-Intensity Pleasure" (11 items), "Cuddliness" (12 items) and "Attention Focusing" (12 items). According to the developers of the ECBQ, Impulsivity, one of the subdomain of SE, is defined as 'the speed of response initiation', and Inhibitory Control, one of the subdomain of EC, is defined as 'the capacity to stop, moderate, or refrain from a behavior under instruction' (Putnam et al., 2006). Each of the 201 items ranges from 1 to 7, and the mean score for each domain was used in the analyses. The score for EC was reversed to align the direction of the characteristics of the other two domain scores, with the higher score indicating more likely to have problems and/or difficulties associated with each domain. All temperament scores were standardized.

ASD Trait at Age 8–9

The Japanese version of the Social Responsiveness Scale Second Edition (SRS-2, Kamio et al., 2013), self-administered by a parent, was used to measure ASD-trait score. A total of 65 items, each ranging between 0 and 3, were converted into T-scores (mean 50, standard deviation 10). Additionally, the reported cutoff values (60 points, +1SD) denote "ASD positive" and complies with clinical significance for screening in Japanese representative samples of females and males (Kamio et al., 2013).

ADHD Trait at Age 8–9

ADHD-trait score was assessed in the parent report using the Japanese version of the ADHD-Rating Scale (ADHD-RS, DuPaul et al., 2016). A total of 18 items, with each ranging between 0 and 3 were converted to percentile ranks based on Japanese representative female and male samples (Tanaka et al., 2016). Additionally, the reported cutoff values (85th percentile) that comply with clinical significance for screening in Japan (Tanaka et al., 2016) were applied to denote "ADHD positive". Statistically, the 85th percentile also corresponds with a T-score of 60 (expected percentile is approximately the 84th percentile) for the definition of ASD positive.

Covariates

The actual age in months at the time of measurement at age 8–9, sex, birth weight, birth order, age of mothers and fathers at the child's birth, years of education of mothers and fathers, and annual household income at the child's birth were selected as covariates, being associated either with child temperament, or with ASD or ADHD traits. Information on parents' demographic and socioeconomic characteristics was collected from mothers through face-to-face interviews during their second trimester. Information on infant sex, birth weight, and date of birth was collected directly from medical records.

Statistical Analysis

First, scores from the clinical rating scales (ASD and ADHD) were standardized based on age and sex. The scores were dichotomized using + 1SD cut-off points to form ASD positive/negative and ADHD positive/negative. Following this, all participating children were grouped into four as follows: ASD-dominant group (ASD positive/ADHD negative), ADHD-dominant group (ASD negative/ADHD positive), co-occurring group (ASD positive/ADHD positive) and neither-ASD-nor-ADHD group (ASD negative/ADHD negative). We then conducted multinomial logistic regression analyses to examine the association between each temperament domain score and a multinomial categorical variable representing the four groups. First, a univariate multinomial regression analysis was used to test the association between each the temperament score and the variable representing the four groups (Model 1). This was followed by a multivariable, multinomial regression analysis with the three temperament domains together without covariates (Model 2). Finally, the same multivariable analysis was conducted with covariates (Model 3).

Stata version 17.0 was used for all the analyses. As an adjustment for multiple comparisons by two outcomes (i.e., ASD and ADHD traits), a p-value < 0.025 (= 0.05/2) was chosen as a margin of statistical significance.

Results

Participant Characteristics

Table 1 shows the demographic characteristics of the study participants. 814 participants aged 8–9 (51.2% boys) were included in the study. Excluded participants had lower age of both parents at child's birth, mother's education, and annual household income than those included in this study.

Table 2 showed a group comparison of the temperament domain scores, the ASD- and ADHD-trait scores of the study participants. Overall, the NA and EC domain scores were the lowest in the neither-ASD-nor-ADHD group, while the SE domain score was the lowest in the ASD-dominant group. These patterns were not consistent for both sexes.

Table 1 Demographic characteristics of participating children and parents (*N* = 814)

	N (%) or Mean (SD)	Data Range
Child Characteristics		
Child sex (Boys)	417 (51.2%)	
Birth Order		
First	407 (50.0%)	
Second	300 (36.9%)	
Third or later	107 (13.1%)	
Multiple Birth	28 (3.4%)	
Birthweight (grams)	2927 (446)	1064–4286
Gestational age at birth (weeks)	38.9 (1.60)	29.6–42.1
Age at the measurement (months)		
Measurement of temperament	18.61 (0.69)	16.6–23.1
Measurement of outcomes	107.47 (2.15)	101.4–118.5
Temperament domain scores of ECBQ		
Surgency/Extraversion	4.38 (0.78)	2.19–6.58
Negative Affectivity	2.73 (0.53)	1.44–4.49
Effortful Control (reversed)	3.97 (0.53)	2.50–5.47
ASD symptom scores of SRS-2*	50.92 (9.83)	33–101
ADHD symptom scores of ADHD-RS**	51.52 (29.16)	10–98
Parental Characteristics		
Annual Household Income (million JPY)	6.18(2.85)	1.00–27.00
Age of mother at child's birth (years)	32.0(5.0)	17.7–44.9
Age of father at child's birth (years)	33.7(5.8)	19.6–53.4
Mother's education (years)	14.0(1.9)	9–22
Father's education (years)	14.2(2.7)	9–26

* T-score (Population mean and SD: 50 and 10, respectively)

** percentile rank

As expected, the ASD-trait score was the lowest in the neither-ASD-nor-ADHD group second to the ADHD-dominant group, whereas the ADHD-trait score was the lowest in the neither-ASD-nor-ADHD group second to the ASD-dominant group. These patterns were consistent for both sexes.

Associations of Temperament at Age 18 Months With ASD-Dominant, ADHD-Dominant, and the Co-Occurring Groups at Age 8–9

In the multinomial regression analysis (Table 3, Model 3), the SE domain score was inversely (odds ratio (OR) = 0.70, 95%CI: 0.54 to 0.91) and the NA domain score positively (OR = 1.51, 95%CI: 1.17 to 1.94) associated with the ASD-dominant group after adjustment for covariates. The SE domain scores were positively associated with the ADHD-dominant group (OR = 1.56, 95%CI: 1.15 to 2.12). The NA domain scores (OR = 1.48, 95%CI: 1.11 to 1.96) and the EC domain scores were positively associated with the co-occurring group (OR = 1.61, 95%CI: 1.18 to 2.20). Other associations did not reach statistical significance. In this analysis, covariates showed significant associations with the group membership (Table 3, Model 3). Years of father's education was inversely associated with the ASD-dominant group (OR = 0.60, 95%CI: 0.42 to 0.84) and with the co-occurring group (OR = 0.55, 95%CI: 0.39 to 0.79) but not with other groups, whereas years of mother's education was positively associated only with the ASD-dominant group (OR = 1.61, 95%CI: 1.14 to 2.27) but not with other groups. Being male or first-born was not associated with any of the groups.

All the participating children were divided into four groups, according to the combination of ASD "positive" vs. "negative" and ADHD "positive" vs. "negative," as follows: ASD-dominant group (ASD "positive" and ADHD "negative"), ADHD-dominant group (ASD "negative" and ADHD "positive"), co-occurring group (ASD "positive" and ADHD "positive") and neither-ASD-nor-ADHD group (ASD negative and ADHD negative). The reported cutoff value (T-score 60 for Social Responsiveness Scale– 2, Japanese version) that complies with clinical significance for screening of ASD in Japan (Kamio et al., 2013) was applied to define ASD "positive" (≥ 60) and "negative" (< 60), and the reported cutoff value (the 85th percentile for ADHD-Rating Scale, Japanese version) that complies with clinical significance for screening of ADHD in Japan (Tanaka et al., 2016) was applied to define ADHD "positive" (≥ 85) and "negative" (< 85)

We also conducted additional analyses stratified by sex (Table 4). Some notable differences between sexes in the associations of our interest were found. First, the SE domain score was inversely and significantly associated with the ASD-dominant group in boys (OR = 0.63,

Table 2 Demographic characteristics of the participating children divided into the four groups

	neither-ASD-nor-ADHD [1]	ASD-dominant [2]	ADHD-dominant [3]	Co-occurring [4]	Comparison
N (Total)	628	73	56	57	
N (Girls)	314	31	26	26	
N (Boys)	314	42	30	31	
Temperament domain scores of ECBQ					
Surgency/Extraversion					
Total	4.36 (0.78)	4.16 (0.82)	4.67 (0.73)	4.56 (0.65)	1, 3, 4 > 2
Girls	4.31 (0.82)	4.28 (0.81)	4.75 (0.64)	4.46 (0.70)	n.s.
Boys	4.40(0.73)	4.08 (0.82)	4.60 (0.79)	4.64 (0.61)	1, 3, 4 > 2
Negative Affectivity					
Total	2.70 (0.53)	2.89 (0.47)	2.66 (0.53)	2.92 (0.56)	2, 4 > 1, 3
Girls	2.73 (0.54)	2.97 (0.49)	2.68 (0.48)	3.07 (0.55)	2, 4 > 1 4 > 3
Boys	2.68 (0.53)	2.83 (0.45)	2.65 (0.57)	2.79 (0.54)	n.s.
Effortful Control (reversed)					
Total	3.93 (0.52)	4.01 (0.51)	4.11 (0.55)	4.21 (0.52)	3, 4 > 1
Girls	3.88 (0.50)	4.08 (0.42)	4.05 (0.51)	4.13 (0.52)	4 > 1
Boys	3.99 (0.54)	3.96 (0.57)	4.17 (0.58)	4.28 (0.52)	4 > 1, 2
ASD symptom scores of SRS-2 (T-score)					
Total	48.52 (4.50)	62.05 (4.55)	52.18 (3.15)	66.14 (6.30)	2, 4 > 3 > 1
Girls	48.37 (4.40)	62.00 (4.05)	51.81 (3.30)	67.23 (6.21)	2, 4 > 3 > 1
Boys	48.67 (4.61)	62.10 (4.93)	52.50 (3.03)	65.19 (6.32)	2, 4 > 3 > 1
ADHD symptom scores of ADHD-RS (percentile rank)					
Total	43.30 (26.27)	62.29 (22.68)	89.02 (3.11)	91.39 (3.76)	3, 4 > 2 > 1
Girls	43.79 (27.46)	67.42 (18.16)	89.08 (2.19)	90.81 (3.49)	3, 4 > 2 > 1
Boys	42.82 (25.07)	58.50 (25.04)	88.97 (3.76)	91.87 (3.97)	3, 4 > 2 > 1

Mean and standard deviation

The Kruskal–Wallis equality-of-populations rank test was performed, followed by Dunn's test (Dinno, 2015)

95%CI: 0.44 to 0.89, p=.009), but not significantly in girls (OR = 0.81, 95%CI: 0.53 to 1.23). Second, the SE domain score was positively and significantly associated with the ADHD-dominant group in girls (OR = 1.78, 95%CI: 1.11 to 2.86, p=.017) but not significantly in boys (OR = 1.46, 95%CI: 0.97 to 2.22, p=.07). Third, the NA domain score was positively and significantly associated with the co-occurring group in girls (OR = 1.89, 95%CI: 1.25 to 2.87, p=.003) but not in boys (OR = 1.21, 95%CI: 0.81 to 1.80, p=.36). Fourth, the EC domain score was positively and significantly associated with the co-occurring group in boys (OR = 1.66, 95%CI: 1.10 to 2.50, p=.016) but not in girls (OR = 1.64, 95%CI: 1.00 to 2.70, p=.052). Also, the patterns of the associations and no associations found in Table 3 were invariably observed in both sexes, including the positive association of the SE domain score and no association of the EC domain score with the ASD-dominant group, no association of the NA and EC domain scores with the ADHD-dominant group, and no association of the SE domain score with the co-occurring group.

Furthermore, we conducted a sensitivity analysis where cutoff scores of 65 of the SRS-2 T-score, instead of 60 in the original analysis, and of the 93rd percentile of the ADHD-RS, instead of the 85th percentile in the original analysis, were set. As a result (Supplementary Table 1), the overall patterns of associations and no associations with the group membership remained unchanged. Notable differences from the original analysis include no significant association of the SE domain score with the ASD-dominant group (n = 54; OR = 0.72, 95%CI: 0.53 to 0.98, p=.034), no significant association of the SE domain score with the ADHD-dominant group (n = 15; OR = 1.50, 95%CI: 0.85 to 2.63, p=.16), and no significant association of the NA domain score with the co-occurring group (n = 19; OR = 1.33, 95%CI: 0.83 to 2.13), whereas a significant association of the NA domain score with the ASD-dominant group (OR = 1.72, 95%CI: 1.29 to 2.29, p < .001) and a significant association of the EC domain score with the co-occurring group (OR = 2.05, 95%CI: 1.22 to 3.43, p=.006) remained unchanged. The magnitude of these association was rather increased in the sensitivity analysis.

Table 3 Associations between temperament profiles at age 18 months and the ASD-dominant group, the ADHD-dominant group, and the co-occurring group in comparison with neither-ASD-non-ADHD group at age 8–9. Multinomial regression analyses with odds ratios, 95% confidence intervals, and the p-values

	Model 1	Model 2	Model 3
neither-ASD-nor-ADHD group (*n*=628)	1 (reference)	1 (reference)	1 (reference)
ASD-dominant group (*n*=73)			
Surgency/Extraversion*	0.77 (0.60, 0.98) 0.032	**0.69** (0.54, 0.90) 0.005	**0.70** (0.54, 0.91) 0.008
Negative Affectivity*	**1.45** (1.13, 1.84) 0.003	**1.48** (0.14, 3.24) 0.002	**1.51** (1.17, 1.94) 0.001
Effortful Control*	1.16 (0.91, 1.49) 0.227	1.22 (0.94, 1.59) 0.140	1.21 (0.92, 1.58) 0.175
Child Sex (boys)**			1.10 (0.83, 1.46) 0.500
Father's Education (Year)**			**0.60** (0.42, 0.84) 0.003
Mother's Education (Year)**			**1.61** (1.14, 2.27) 0.006
Birth Order (First-born)**			0.93 (0.68, 1.27) 0.634
ADHD-dominant group (*n*=56)			
Surgency/Extraversion*	**1.52** (1.14, 2.03) 0.004	**1.45** (1.08, 1.95) 0.014	**1.56** (1.15, 2.12) 0.005
Negative Affectivity*	0.94 (0.71, 1.25) 0.681	0.88 (0.66, 1.17) 0.380	0.88 (0.65, 1.18) 0.398
Effortful Control*	**1.43** (1.08, 1.90) 0.013	1.32 (0.99, 1.76) 0.056	1.32 (0.98, 1.78) 0.071
Child Sex (boys)**			1.16 (0.90, 1.50) 0.255
Father's Education (Year)**			1.04 (0.78, 1.39) 0.785
Mother's Education (Year)**			0.92 (0.69, 1.23) 0.574
Birth Order (First-born)**			**0.63** (047, 0.85) 0.003
Co-occurring group (*n*=57)			
Surgency/Extraversion*	1.29 (0.98, 1.71) 0.073	1.11 (0.83, 1.48) 0.493	1.08 (0.80, 1.46) 0.602
Negative Affectivity*	**1.50**(1.14, 1.96) 0.004	**1.42** (1.08, 1.87) 0.013	**1.48** (1.11, 1.96) 0.007
Effortful Control*	**1.72** (1.29, 2.29) <0.001	**1.64** (1.21, 2.22) 0.001	**1.61** (1.18, 2.20) 0.003
Child Sex (boys)**			1.13 (0.85, 1.51) 0.400

Table 3 (continued)

	Model 1	Model 2	Model 3
Father's Education (Year)**			**0.55** (0.39, 0.79) 0.001
Mother's Education (Year)**			0.91 (0.64, 1.28) 0.587
Birth Order (First-born)**			0.85 (0.63, 1.13) 0.260

Top row: ORs (odds ratios) per one unit change in temperament domain scores, middle row: 95% confidential intervals (in brackets), bottom row: p-values

* A higher score indicates a higher level of difficulties

** Covariates that showed significant associations with any one of the groups in Model 3

Discussion

The present study examined associations between three temperament domains measured at age 18 months (SE, NA, and EC) among four groups of children: ASD-dominant, ADHD-dominant, co-occurring, and neither-ASD-nor-ADHD groups at age 8–9. This is the first study to elucidate an early temperament profile of children who later show traits of both ASD and ADHD in a longitudinal study. There were two major findings. First, ASD-dominant, ADHD-dominant, and the co-occurring groups showed different patterns of early temperament profiles: the lower SE and higher NA scores associated with the ASD-dominant group; the higher SE score associated with the ADHD-dominant group; and the higher NA and EC scores associated with the co-occurring group. When this multinomial regression analysis was conducted separately on both sexes, some associations were no longer statistically significant due to the reduced sample size; however, the pattern of the higher EC score associated with the co-occurring group remained consistent. Second, the early temperament profile of the co-occurring group was not merely a superimposition of the profiles of the ASD-dominant and the ADHD-dominant groups. Instead, the high score of the EC domain was specifically associated only with the co-occurring group; this association remained significant in a sensitivity analysis where the cut-off scores of ASD and ADHD traits were set differently. Children with elevated scores of both ASD and ADHD traits are likely to experience greater difficulties (both in frequencies and magnitude) in various aspects of daily life resulting from cognitive challenges (Yerys et al., 2009, 2019; Bedford et al., 2019; Chandler et al., 2022). The current study can help identifying such children and support them more effectively, thereby achieving better neurodevelopmental skills (e.g. Ishikawa-Omori et al., 2022; Nakagawa et al., 2024) and increasing mental health (e.g. Hoffman et al., 2019; Morales et al., 2022) of the children.

Temperament Profile at Age 18 Months and ASD-Dominant, and ADHD-Dominant, and the Co-Occurring Groups at Age 8–9

As expected, two temperament domains (i.e., SE and NA) were associated with the ASD-dominant group, consistent with the early studies, indicating that broadly atypical patterns of early temperament predict the emergence of ASD trait in high-risk preschoolers (Clifford et al., 2013; Garon et al., 2016; Chetcuti et al., 2021; Konke et al., 2022). However, contrary to a prior study examining children diagnosed with ASD (Samyn et al., 2011), we were unable to find an association between the EC domain and ASD. The difference between the previous study and ours is that we separated children showing ASD trait but not showing ADHD trait from those showing both types of trait; early studies are not likely to have considered both ASD and ADHD status simultaneously.

The direction of the association between the SE domain and the ASD-dominant group was inverse, whereas it was opposite for the ADHD-dominant group, consistent with early studies (Johnson et al., 2015; Visser et al., 2016; Kostyrka-Allchorne et al., 2020). Further, an association of a higher SE score with the ADHD-dominant group was also consistent with a study of a high-risk population (Konke et al., 2022). However, the association between the NA domain and ADHD found in prior studies (Barkley, 2014; Willoughby et al., 2017; Tobarra-Sanchez et al., 2022; Joseph et al., 2023) was not replicated in our study. The lack of an association between the NA domain and the ADHD-dominant group in the current study is likely because the previous studies did not separate children showing ADHD but without ASD traits.

In the present study, patterns of distinctive temperament profiles specifically related to the ASD-dominant group, the ADHD-dominant group, and the co-occurring group were found (Table 2). What is new in this study is that the combination of high NA and high EC scores shows as a

Table 4 Associations between temperament profiles at age 18 months and the ASD-dominant group, the ADHD- dominant group, and the co-occurring group in comparison with non-ASD-non-ADHD group at age 8–9, stratified by sex. Multinomial regression analyses with odds ratios, 95% confidence intervals, and the p-values

	Analysis for girls (n=397)			Analysis for boys (n=417)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	neither-ASD-nor-ADHD group (n=314)			neither-ASD-nor-ADHD group (n=314)		
	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	ASD-dominant group (n=31)			**ASD-dominant group** (n=42)		
Surgency/Extraversion*	0.95 (0.66, 1.38) 0.804	0.77 (0.51, 1.15) 0.205	0.81 (0.53, 1.23) 0.318	**0.64** (0.46, 0.89) 0.008	**0.62** (0.44, 0.87) 0.005	**0.63** (0.44, 0.89) 0.009
Negative Affectivity*	**1.55** (1.08, 2.24) 0.018	**1.57** (1.08, 2.27) 0.018	**1.54** (1.06, 2.24) 0.023	1.37 (0.99, 1.90) 0.061	**1.44** (1.03, 2.01) 0.031	**1.49** (1.05, 2.10) 0.024
Effortful Control*	1.56 (1.05, 2.31) 0.026	**1.66** (1.08, 2.56) 0.020	1.59 (1.02, 2.49) 0.040	0.94 (0.68, 1.30) 0.711	0.96 (0.68, 1.35) 0.800	1.16 (0.85, 1.58) 0.350
	ADHD-dominant group (n=26)			**ADHD-dominant group** (n=30)		
Surgency/Extraversion*	**1.85** (1.19, 2.89) 0.006	**1.78** (1.12, 2.83) 0.015	**1.78** (1.11, 2.86) 0.017	1.31 (0.89, 1.93) 0.174	1.26 (0.85, 1.87) 0.253	1.46 (0.97, 2.22) 0.073
Negative Affectivity*	0.92 (0.60, 1.39) 0.682	0.84 (0.55, 1.30) 0.439	0.85 (0.54, 1.33) 0.476	0.96 (0.66, 1.41) 0.847	0.90 (0.61, 1.33) 0.499	0.91 (0.60, 1.38) 0.665
Effortful Control*	1.45 (0.96, 2.21) 0.081	1.23 (0.81, 1.78) 0.333	1.22 (0.79, 1.75) 0.372	1.41 (0.96, 2.08) 0.079	1.38 (0.93, 2.03) 0.107	1.38 (0.91, 2.09) 0.126
	Co-occurring group (n=26)			**Co-occurring group** (n=31)		
Surgency/Extraversion*	1.17 (0.78, 1.77) 0.444	0.92 (0.59, 1.44) 0.719	0.90 (0.57, 1.42) 0.660	1.39 (0.94, 2.04) 0.095	1.26 (0.85, 1.86) 0.248	1.20 (0.80, 1.80) 0.384
Negative Affectivity*	**1.84** (1.24, 2.73) 0.003	**1.80** (1.20, 2.69) 0.004	**1.89** (1.25, 2.87) 0.003	1.25 (0.86, 1.81) 0.245	1.15 (0.78, 1.69) 0.475	1.21 (0.81, 1.80) 0.355
Effortful Control*	**1.71** (1.11, 2.63) 0.015	**1.72** (1.07, 2.78) 0.025	1.64 (1.00, 2.70) 0.052	**1.72** (1.17, 2.54) 0.006	**1.63** (1.09, 2.43) 0.016	**1.66** (1.10, 2.50) 0.016

Top row: ORs (odds ratios) per one unit change in temperament domain scores, middle row: 95% confidential intervals (in brackets), bottom row: p-values

All the participating children were divided into four groups, according to the combination of ASD "positive" vs. "negative" and ADHD "positive" vs. "negative," as follows: ASD-dominant group (ASD "positive" and ADHD "negative"), ADHD-dominant group (ASD "negative" and ADHD "positive"), co-occurring group (ASD "positive" and ADHD "positive") and neither-ASD-nor-ADHD group (ASD negative and ADHD negative). The reported cutoff value (T-score 60 for Social Responsiveness Scale– 2, Japanese version) that complies with clinical significance for screening of ASD in Japan (Kamio et al., 2013) was applied to define ASD "positive" (≥ 60) and "negative" (<60), and the reported cutoff value (the 85th percentile for ADHD-Rating Scale, Japanese version) that complies with clinical significance for screening of ADHD in Japan (Tanaka et al., 2016) was applied to define ADHD "positive" (≥ 85) and "negative" (<85)

Model 1: Univariate multinomial regression analyses were used to test the association between each temperament domain z-scores and the variable representing the four groups, respectively

Model 2: A multivariable, multinomial regression analysis with the three temperament domains was conducted with no covariates entered

Model 3: The multivariable analysis denoted as Model 2 adjusted by available covariates (sex, birth weight, birth order, age of mothers and fathers at the child's birth, years of education of mothers and fathers, and annual household income at the child's birth)

* A higher score indicates a higher level of difficulties

specifically predictive indicator for the co-occurring group. A classical hypothetical view involving ASD and ADHD co-occurrence reviewed by Johnson et al. (2015) show that the temperament profiles of the co-occurring group should have been a superimposition of temperament profiles of the two groups (i.e., the ASD-dominant and the ADHD-dominant). However, our study shows that the co-morbid group may be different from the single-morbid groups in the EC domain. Of note, EC, a latent factor representing self-regulation (Posner & Rothbart, 2018), is predictive of executive functioning, and is associated with general psychopathology, particularly externalizing problems (Lynch et al., 2021). Furthermore, poor EC has also been shown to be associated with developmental coordination disorder (DCD) (Nakagawa et al., 2016; Sofologi et al., 2021), possibly through a link between motor and executive functions (Fogel et al., 2023). Since difficulties in executive functions are likely to lead to difficulties in daily life, a high EC score (low effortful control) is anticipated to predict daily difficulties, but also to predict a co-occurring condition of elevated ASD- and ADHD- trait scores. In other words, the co-occurrence of the two traits is likely to result in daily life difficulties more often than in ASD-dominant and ADHD-dominant populations, possibly after substantial involvement of prefrontal cortex in the development of executive function around age 4 years (Posner et al., 2016; Fiske & Holmboe, 2019). Care should be taken when reading the findings in Table 2, however, as the OR for EC domain in association with the ADHD-dominant group was not statistically significant although it departed substantially from the odds of 1 (OR = 1.32, 95%CI: 0.98 to 1.78, p = .07). A range of severity of executive dysfunction is generally seen in both ASD and ADHD, although relevant domains of such dysfunction differ between ASD and ADHD (Lawson et al., 2015). Since evidence is accumulating that executive function is not only a cognitive component but also is an indicator predicting clinical diagnoses of ASD and ADHD (Harkness et al., 2024), the EC domain score at an early age is an important predictor of co-occurrence of ASD and ADHD traits in children from the general population. Our findings warrant further research for a temperament measure in early childhood to seek for emerging psychopathology and to provide clues for identifying high-risk children by virtue of developing co-occurring ASD and ADHD.

A novel approach in this study was that we defined "positive" in either ASD or ADHD using age- and sex-standardized phenotypical scales. This approach helped us to see the relevance of examining early temperament for subsequent risks of developmental psychopathology (Chetcuti et al., 2021) in both sexes, especially because ASD and ADHD phenotypes are frequently overlooked in girls. For example, girls are better able to mobilize various compensation strategies and to show more subtle hyperactivity compared to boys leading to misdiagnosis (Lai et al., 2022). Hence, identifying the high-risk group by virtue of co-occurring conditions using age- and sex-adjusted parent report phenotypical scales is a valid approach. However, we should be reminded that the underlying mechanisms linking early temperament and later phenotypes may differ in girls and boys, possibly an interplay with genetic loading anticipated (St. John et al., 2023).

Limitations and Strengths

This study has a few limitations. First, approximately 35% of initial participants to our cohort study were excluded from the analysis. A comparison of the analyzed and excluded participants showed small but significant differences in household income at birth, age of parents at birth, and maternal education. We checked for any substantial difference in the effect estimates between the models with these variables included and excluded but none were found. Second, the ECBQ, SRS-2, and ADHD-RS are all parent-reported questionnaires, which may have led to information bias. Although these are standard procedures, we conducted interviews with the parents to confirm their input and minimize information bias. Third, we had to use parent-reported rating scales for clinically relevant categories about ASD and ADHD as no actual diagnostic information was available. We have a scale-derived categorical cutoff that may not fully approximate the diagnoses in question. Fourth, temperament measures in the ECBQ were assessed only at one time point during the second year of life. SE and NA develop during the first year of life, while EC develops more during the second year of life, when the child becomes more consciously aware of the outer world (Gartstein et al., 2013). In addition to this, we did not consider potentially relevant developmental levels, including cognitive ability, and adaptive functioning skills, which might have interacted with the associations we found.

Balancing the limitations, our study design has many advantages, considering the representativeness of the general population, large sample size, and longitudinal follow-up by age 8–9 with minimal dropouts. The data are expected to reflect developmental psychopathology in general, not just snapshots of clinical population.

Conclusion

Distinctive temperament profiles at age 18 months were associated with the ASD-dominant, ADHD-dominant, and the co-occurring groups at age 8–9. A pattern of high scores in NA and EC domains were specifically predictive of the co-occurring group. The findings support the need for an early temperament measure to identify a high-risk phenotype that is specifically associated with an increased likelihood of developing traits ranging both ASD and ADHD and to provide us with information about who is at an increased risk for potentially greater clinical challenges later in life.

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Declarations

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