LONGITUDINAL DATA ANALYSIS IN CHILD AND ADOLESCENT MENTAL HEALTH

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Editorial: Longitudinal data analysis in child and adolescent mental health

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Editorial on the Research Topic
Longitudinal data analysis in child and adolescent mental health

Compared to adults, children and adolescents undergo rapid and dynamic changes in social, emotional, behavioral, and cognitive development and functioning (1, 2). As such, studies that track continuities and discontinuities of individual development, and that elucidate factors influencing different patterns of individual development, are essential in child and adolescent mental health research. Critical questions in this area include: which problems do children continue to exhibit over time; are there measurable characteristics specific to those children; what factors predict future psychopathologies; and what are the effects of early interventions and treatment on mental health outcomes? These questions are also important in clinical medicine, given that many psychiatric disorders and problems, including depression, anxiety, attention deficit hyperactivity disorder, and behavioral problems, can have their onset in childhood and persist into adolescence and adulthood (3). However, cross-sectional designs, frequently used in research for the simplicity of the data acquisition and the practicality in terms of cost and time, cannot provide answers to research questions focused on functioning over the life course.

In contrast, longitudinal study designs that follow the same individuals over multiple waves of data collection can shed light on complex developmental processes (4), providing evidence that can address questions such as those posed above. Additionally, with the development of standardized and valid assessment tools suitable for repeated measurements, and advances in statistical modeling and analysis, longitudinal research has considerable power to elucidate causal mechanisms of mental health disorders and other disorders. A single-cohort design, where a sample of a defined age is recruited at one point in time and followed up at subsequent intervals, is the most commonly used longitudinal design. A longitudinal sequential design, where two or more cohorts of differing ages are selected at the start of the study and are followed forwards, is another strategy that overcomes limitations in the single cohort study design, such as

the inability to delineate age effects (developmental changes associated with age), period effects (variations in the time periods that affect all population regardless of age and cohort at the same time: war, infectious disease outbreaks, for example) and cohort effects (characteristics unique to the birth year of the cohort). To reflect this growing research area, we developed this Research Topic to present papers using longitudinal data analyses in child and adolescent mental health.

Several articles published in this collection provided findings related to predictive factors for future mental health problems through their longitudinal study designs. In a Korean community-based longitudinal study, 1,760 seventh-grade adolescents in Korea were followed for 2 years to examine the effects of exposure to online games before entering elementary school on Internet Gaming Disorder (IGD) occurrence during the secondary school years (Jeong et al.). The authors employed generalized-estimating-equation model and identified exposures to online games during preschool years as predictors for the high risk of IGD during the two-year study follow-up period (adjusted relative risk:1.69; 95%confidence interval:1.08–2.66). In another study conducted in the Netherland, the authors utilized longitudinal data prospectively collected from 2,523 individuals between 13 and 26 years of age in the Dutch Tracking Adolescents' Individual Lives Survey (Melo et al.). In this study, they examined whether reward sensitivity measured at age 13 predicted the course of multiple psychopathology domains over five measurement waves during the 14-year follow-up period, and found that reward sensitivity had a stable main effect on some psychopathology domains (anxiety, aggression), but that its effect increased over time on some domains (alcohol and cannabis use), indicating the transdiagnostic role of reward sensitivity in the course of the development of psychopathology between adolescence and adulthood. In addition to these two articles, Japanese researchers reported the positive influence of praise for the child's prosocial behaviors at 10 years of age on the child's depressive symptoms at age 12, and the impact of maternal stress related to child rearing during the first 3 years following birth on the child's ADHD symptoms at 12 years of age using data from the Tokyo Teen Cohort study, a population-based prospective study targeting adolescents (Nagaoka et al., Endo et al.). Adequate sample sizes in this cohort study (3,171 households for the first wave of data collection) allowed the researchers to identify statistically significant associations between the variables tested. In the second study from this research group, the researchers utilized data from the Maternal and Child Health Handbook, a home health book distributed by Japanese municipalities to all pregnant women who are expected to prospectively record their pregnancy and delivery and monitor the child's development, minimizing recall bias related to child-rearing stress.

In two articles, researchers employed cross-lagged analysis, an analytical strategy used to describe reciprocal relationships or directional influences between variables over time, to examine the association between family functioning and adolescents' depressive symptoms in China (Wang et al.), and between maternal internalizing problems (anxiety and depression) and the child's tics in early adolescence in Japan (Yagi et al.). In the first article, 1,301 Chinese middle school students underwent assessment for family functioning and depressive symptoms three times over 3 years. This study revealed the negative influence of the family function in the 7th grade on the child's depressive symptoms in the 8th grade, while the child's depressive symptoms in the 8th grade negatively impacted the family function a year after, suggesting a circular effect between family function and adolescent depressive symptoms. In the other article using data from the above-mentioned cohort study established in Tokyo, researchers identified bidirectional relationships between maternal depressive and anxious symptoms and the frequency of adolescents' tics, measured at ages 10 and 12. Findings from these two articles underscore the importance of advancing family-centered care in this field.

Longitudinal research also enables researchers to distinguish different trajectory patterns of the child's development. The researchers from Japan using the birth cohort data in Hamamatsu city employed parallel process multigroup latent class growth analysis to identify distinct trajectory patterns of three different domains of adaptive behaviors (communication, daily living skills, and socialization) and assessed sex differences in the trajectory structures and neurodevelopmental traits of children assigned to each trajectory class (Nishimura et al.). In this study, researchers identified four distinct trajectories and sex differences in the scale scores of adaptive behaviors and neurodevelopmental traits. In another study, researchers retrospectively collected data on healthcare utilization through medical chart review in children with neurodevelopmental disorders who presented to registered medical facilities in Japan (Aoki et al.). Data related to the number of outpatient consultations, history of hospitalization, and the use of multi-agency liaison over the last 5 years, repeatedly measured once every 6 months (i.e., 10-time points) were analyzed as longitudinal variables using cluster analysis. Findings revealed that while many children required consultations for a brief period, some needed continued support/consultations. In school-age children and adolescents, ADHD and other psychiatric comorbidities were associated with clusters indicating the continuous, longer use of healthcare.

This collection of articles demonstrates the scope and power of longitudinal research, and we hope that the findings are used to drive real change across a range of policy areas and intervention approaches. The selection of articles represents our collective belief that longitudinal research plays a vital role in understanding the social, environmental and family factors in early life that can affect health and wellbeing over the life course.

Author contributions

TH drafted the editorial. All authors reviewed and commented on the draft and contributed to the final version of the editorial.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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Study Protocol: Longitudinal Attention and Temperament Study

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Background: Attention processes may play a central role in shaping trajectories of socioemotional development. Individuals who are clinically anxious or have high levels of trait anxiety sometimes show attention biases to threat. There is emerging evidence that young children also demonstrate a link between attention bias to salient stimuli and broad socioemotional profiles. However, we do not have a systematic and comprehensive assessment of how attention biases, and associated neural and behavioral correlates, emerge and change from infancy through toddlerhood. This paper describes the Longitudinal Attention and Temperament study (LAnTs), which is designed to target these open questions.

Method: The current study examines core components of attention across the first 2 years of life, as well as measures of temperament, parental psychosocial functioning, and biological markers of emotion regulation and anxiety risk. The demographically diverse sample (N = 357) was recruited from the area surrounding State College, PA, Harrisburg, PA, and Newark, NJ. Infants and parents are assessed at 4, 8, 12, 18, and 24 months. Assessments include repeated measures of attention bias (via eye-tracking) in both infants and parents, and measures of temperament (reactivity, negative affect), parental traits (e.g., anxiety and depression), biological markers (electrophysiology, EEG, and respiratory sinus arrythmia, RSA), and the environment (geocoding, neighborhood characteristics, perceived stress). Outcomes include temperamental behavioral inhibition, social behavior, early symptom profiles, and cellular aging (e.g., telomere length).

Discussion: This multi-method study aims to identify biomarkers and behavioral indicators of attentional and socioemotional trajectories. The current study brought together innovative measurement techniques to capture the earliest mechanisms that may be causally linked to a pervasive set of problem behaviors. The analyses the emerge from the study will address important questions of socioemotional development and help shape future research. Analyses systematically assessing attention bias patterns, as well as socioemotional profiles, will allow us to delineate the time course of any emerging interrelations. Finally, this study is the first to directly assess competing models of the role attention may play in socioemotional development in the first years of life.

Keywords: attention, temperament, anxiety, eye-tracking, EEG, longitudinal, infancy

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BACKGROUND

The centrality of attention in development grows out of its role as a specific brain-based mechanism whose core function is to influence the operation of other mechanisms—by choosing the focus of attention for further processing, by maintaining this focus as needed, and by disengaging from the focus of attention when it no longer serves current goals (1). The earliest forms of self-regulation are rooted in the ability to disengage, shift gaze, and re-orient on a new focus of attention (2). In this way, attention mechanisms may play a pivotal role in shaping the individual's experienced environment from the first days of life (3). An emerging literature points to a potential causal association between attention (particularly attention bias to threat) and the presence of clinical and trait anxious behaviors in adults and children (4, 5). Attention bias refers to selective attention processes that preferentially select for and process specific categories of salient stimuli (6). There is some evidence that systematic biases toward and away from threat may play a causal or sustaining role in the emergence of disorder (7). In the anxiety literature, threat is often conveyed with the use of negative faces (e.g., angry or sad), particularly when examining social anxiety (7).

If this view is correct, individual differences in attention, first emerging in infancy, should be associated with diverging trajectories of socioemotional development. These trajectories may be potentiated among children at temperamental risk for anxiety (8) or children exposed to anxiogenic environments (9). In particular, the evident link between early temperamental negative affect and the later emergence of anxiety may be potentiated by the added presence of an attention bias to threat (10, 11). Although we are unable to follow the full emergence of anxiety in the first 2 years, we can capture the processes that may lay an initial developmental foundation. Understanding these early relations could thus provide avenues for (1) understanding mechanisms that lead to the emergence of social withdrawal and anxiety and (2) identifying individuals at risk for socioemotional difficulties. Taken together, this knowledge would help the field focus on specific windows of intervention, targeting causal mechanisms while the system is still plastic and malleable.

However, the literature to date cannot directly provide the needed data because it has focused on older children and adults when examining the relation between attention, affect, and socioemotional functioning. In addition, the data generated are from predominantly single-session, cross-sectional designs focusing on individuals already presenting with clear signs of clinical anxiety or trait-level distress (12, 13). Much of the developmentally-informed research on anxiety has focused on the classification and treatment of disorder (14). Although there is increasingly more data available with child samples, we have scant knowledge of normative or maladaptive developmental trajectories in infancy (15, 16). As such, it is not clear how attention patterns come to be associated with affect and how these constructs, together, underlie the emergence of anxiety.

Field and Lester (17) suggested three potential developmental models of attention bias (**Figure 1** illustrates the models using temperament as the potential developmental moderator). The integral bias model (18) suggests that the magnitude of any information processing is determined by individual factors (e.g., anxiety, temperament) and should be evident and fairly stable across the lifespan, assuming that it is measured using a developmentally appropriate task (Figure 1A). As such, infants with early signs of negative affect would already show a more pronounced bias to threat relative to infants without this temperamental profile. Much of the current clinical literature makes this *implicit* assumption. The moderation model (17) suggests that development moderates the expression of an existing bias to threat (**Figure 1**B), such that under certain circumstances (e.g., in children at temperamental risk for anxiety) the initial normative bias may be linked to the later emergence of elevated fear and social withdrawal (6, 19, 20). In contrast, normative biases will decrease over time for children with low temperamental risk. Finally, the acquisition model (**Figure 1**C) suggests that developmental experiences shape the acquisition of an attention bias gradually over time (17), either in tandem or subsequent to the emergence of fear and anxiety.

Testing these models, and examining the broader assumptions regarding attention-emotion relations, requires systematic studies that examine individual differences (21) across multiple levels of analysis (22) over time. Our prior work has examined

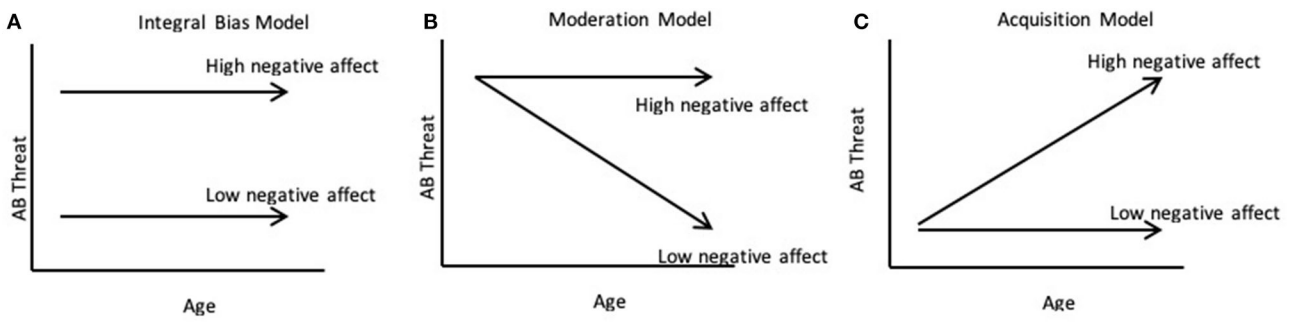

FIGURE 1 | Schematic illustration of the three models for the emergence of attention bias in the first years of life based on Field and Lester (17). The integral bias, moderation, and acquisition models differ in the timing, stability, and sensitivity to outside factors for attention processes.

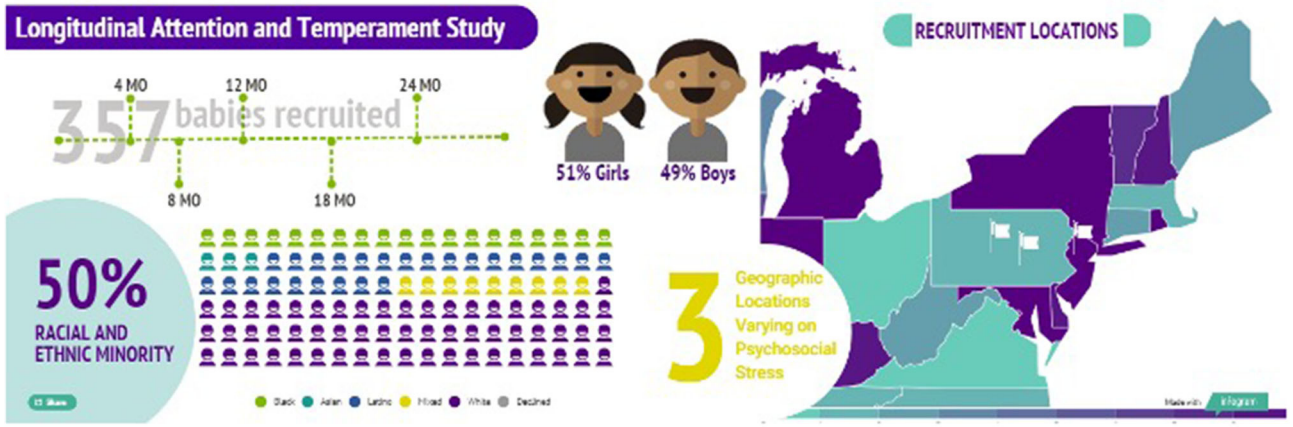

FIGURE 2 | Schematic of the LAnTs cohort. Families are recruited from areas surrounding three locations, State College, PA, Harrisburg, PA, and Newark, NJ. The sample was recruited primarily at 4 months of age, and then assessed again at 8, 12, 18, and 24 months.

associated questions in cross-sectional samples (23–27). The Longitudinal Attention and Temperament study (LAnTs; **Figure 2**) was designed to extend this work by bringing together three developmentally-appropriate tasks (dot-probe, overlap, vigilance) that can be used across the first 2 years of life (26). In addition, we assess early temperament using both observed behavior and parental reports. To identify endogenous factors that may modulate developmental risk, we assess resting electroencephalogram (EEG) to capture measures associated with emotion regulation and socioemotional risk, including frontal EEG alpha asymmetry (28), delta-beta coupling (29), and neural noise (30). We also capture respiratory sinus arrythmia (RSA) at rest and during our temperament battery (31) to examine peripheral markers of regulation (32). Given the central role parents play in shaping the daily experiences of children, contextual measures of parental attention bias, symptomatology, and psychosocial stress are assessed at every time point. Finally, we incorporate both objective (e.g., geocoding) and subjective (e.g., perceived violence and support) measures of the child's broader environment (33). Across levels of analysis the protocol generates a multidimensional profile of the individual and nested layers of development from the micro- through the mesosystem over time (34). LAnTs was designed to examine two core aims:

First, we will test the integral bias, moderation, and acquisition models outlined by Field and Lester (17). The first step will be to quantify the developmental trajectory (i.e., growth curve) of attention to threat. Each developmental model makes a unique prediction regarding how individual, biological, and environmental moderators will affect the size and direction of the developmental trajectory of attentional bias over time. Therefore, we will quantify the extent to which individual differences in negative affect moderate attention trajectories. We will then do the same analysis incorporating individual biomarkers (EEG and RSA). Finally, we will turn our focus on contextual factors (parental attention bias, symptomatology, psychosocial stress).

Second, we will examine the extent to which the gradient of individual attention growth curves predicts behavioral inhibition at age two. We will also capture potential behavioral, biological and contextual moderators of these individual gradients, particularly if the acquisition or moderation models are supported. As part of these outcome assessments, we will also examine early measures of psychopathology (35) and biological measures of chronic stress [e.g., telomere length (36)]. Greater detail regarding the larger analytic approach is provided in the **Supplementary Materials**.

The purpose of this paper is to provide a detailed description of the LAnTs protocol, measures, and sample. This will help place future analyses within the context of the full protocol. In addition, interested researchers may determine that the sample provides data needed for ancillary analyses.

METHODS

General Procedure

We collected data from infants ($N = 357$) longitudinally at 4, 8, 12, 18, and 24 months, using a multi-method approach (see **Table 1**). At all five time-points the infant protocol included 3 eye-tracking tasks and a behavioral temperament battery [reactivity (37) at 4 months and the Laboratory Temperament Assessment Battery (Lab-TAB) (38) at 8–24 months]. At these visits, parents also completed two eye-tracking tasks and questionnaires assessing infant temperament, their own psychological state and traits, and the sociodemographic features of their environment. Geocoding was used as an additional measure of the familial environment.

At the latter four time-points participants engaged in a structured parent-infant interaction. Infants also provided resting EEG and RSA. RSA data were also collected during the behavioral temperament battery and parent-child dyads. At 24 months, infants completed a behavioral inhibition (BI) protocol and engaged in an additional social dyad with an unfamiliar same-age peer. At this final visit, buccal swabs were collected from parents and infants for telomere length assays.

TABLE 1 | List of LAnTS measures by time point of data collection.

	Description	4-mo	8-mo	12-mo	18-mo	24-mo
Eye-tracking measures						
Baby dot-probe task (infant)	Attention bias task	X	X	X	X	X
Overlap task (infant)	Attention orienting	X	X	X	X	X
Vigilance task (infant)	Attention vigilance	X	X	X	X	X
Adult dot-probe task (parent)	Attention bias task	X	X	X	X	X
Adult vigilance task (parent)	Attention vigilance	X	X	X	X	X
Behavioral measures						
THISTLE reactivity coding	Infant reactivity to novelty	X				
Lab TAB	Infant temperament		X	X	X	X
Free play	Mother-child dyadic play		X	X	X	X
Parental-report infant measures						
Infant behavior questionnaire (IBQ-R)	Infant temperament	X	X	X		
Toddler behavior assessment questionnaire (TBAQ)	Toddler temperament			X	X	X
Infant-Toddler socioemotional assessment (ITSEA)	Toddler social-emotional problems			X	X	X
Child behavior checklist (CBCL)	Childhood anxiety				X	X
MacArthur-Bates communicative development inventory short form (MB-CDI-SF)	Child language development					X
Parental personality and symptomatology						
Adult temperament questionnaire (ATQ)	Parent temperament	X				
Eysenck personality questionnaire (EPQ)	Parent personality	X				
Check & buss shyness scale (CBSS)	Parent shyness	X				
Adult measure of behavioral inhibition (AMBI)	Parent behavioral inhibition	X				
Retrospective measure of behavioral inhibition (RMBI)	Parent behavioral inhibition	X				
Positive and negative affect scale (PANAS)	Parent emotionality	X	X	X	X	X
State-trait anxiety inventory (STAI)	Parent anxiety (trait)	X	X	X	X	X
Beck anxiety inventory (BAI)	Parent anxiety (state)	X	X	X	X	X
Beck depression inventory (BDI)	Parent depression	X	X	X	X	X
Parental psychosocial stressors						
ICPSR community survey	Environmental stress	X	X	X	X	X
Confusion, hubbub, and order scale (CHAOS)	Disorganization in the home	X	X	X	X	X
Parent daily hassle survey (PDHS-R)	Stressful life events	X	X	X	X	X
Geocoding	Environmental risk	X	X	X	X	X
Biomarkers of risk						
EEG at rest	EEG asymmetry & coherence		X	X	X	X
RSA during the lab TAB and dyad	Parasympathetic response		X	X	X	X
Telomere length assays	Aging and stress exposure					X
Behavioral inhibition						
Social dyad & individual protocol	Social behavior and novelty					X

For families enrolled after 4 months, the ATQ, EPQ, CBSS, AMBI, and RMBI were recorded at the first visit.

Data collection was generally completed in two, 2-h visits to the lab for the first four timepoints, although some families completed all tasks in a single visit, and a subset of families required three visits. During Visit 1, the infant and the primary caregiver typically completed the eye tracking tasks, with the infant first, followed by the caregiver. At 4 months, the eye-tracking and behavioral measures were usually all collected in a single day. For the 8- through 24-month time points, resting EEG was collected during Visit 2, followed by free play, and the Lab TAB episodes. RSA was collected throughout the behavioral tasks. The majority of visits followed this structure, but task orders sometimes varied based on the infant's needs. Most caregivers completed the online questionnaires at home prior to the visit, but in some cases, they were completed in the lab or over the phone. If questionnaires had to be completed in the lab, primary caregivers would do so while the infant was completing the eye tracking tasks or after data collection was completed. The social dyad was completed on a separate day, in a final visit to the lab at 24 months.

A detailed description of each measure (see also **Table 1**) can be found in the **Supplemental Materials**.

FIGURE 3 | LAnTs sample demographics, including racial/ethnic background (**left**) and income (**right**).

SAMPLE CHARACTERISTICS

Here we highlight core metrics that describe and characterize the sample at the time of enrollment. Data collection is still ongoing through Fall 2021.

Sample

Participants were recruited through local baby registries (40% families) and university-sponsored participant databases (13% families). In addition, we used a variety of community-level recruitment strategies, such as visiting local lactation/parenting classes, communicating with families at local community events, and talking to parents at local hospitals, health care centers, and Women's and Infant Centers (WIC). Community recruiting identified 38% of our families. The remaining 10% of families were recruited by word-of-mouth. Prospective families were contacted by letter, email, or phone explaining the motivations and methods of the study. The Institutional Review Boards at the Pennsylvania State University and Rutgers University approved all procedures and parents provided written consent and were compensated for their participation.

Infants and their caregivers were enrolled when the infants were 4 months of age ($N = 298$; 151 males, 147 females; $M_{age} = 4.80$ months; $SD_{age} = 0.80$, $Range_{age} = 3.27–7.60$ months), with an additional 46 participants enrolled at 8 months ($N = 46$; 19 males, 27 females; $M_{age} = 8.83$ months; $SD_{age} = 0.73$, $Range_{age} = 7.53–10.20$ months), and 13 participants at 12 months ($N = 13$; six males, seven females; $M_{age} = 12.73$ months; $SD_{age} = 1.12$, $Range_{age} = 10.63–14.90$ months), for a total enrollment of 357 infants in the full sample (176 males, 181 females). Participants were recruited from areas surrounding three sites: State College, PA ($N = 167$), Harrisburg, PA ($N = 81$), and Newark, NJ ($N = 109$).

Race and Ethnicity

Caregivers identified 58 of the infants (16%) as African American/Black, 9 (3%) as Asian, 78 (22%) as Latinx, 180 (50%) as white, and 27 (8%) as mixed race. Five (1%) additional caregivers declined to provide this information (see **Figure 3**, left).

Annual Household Income

Across the sample, 49 families (14%) reported a household income of $15,000 or less, 20 (6%) reported $16,000–20,000, 22 (6%) reported $21,000–30,000, 16 (5%) reported $31,000–40,000, 22 (6%) reported $41,000–50,000, 29 (8%) reported $51,000–60,000, and 140 (39%) reported an income above $60,000. Fifty-nine (17%) additional caregivers declined to provide this information (see **Figure 3**, right).

Parental Education

For mother's education, 11 (3%) completed grade school only, 17 (5%) had some high school, 36 (10%) graduated from high school, 57 (16%) had some college or trade/technical degree, 73 (20%) were college graduates, 58 (16%) had graduate training, and 66 (19%) had a graduate degree; 39 (11%) additional caregivers declined to provide this information. For fathers, 11 (3%) completed grade school only, 15 (4%) had some high school, 50 (14%) graduated from high school, 60 (17%) had some college or trade/technical degree, 70 (20%) were college graduates, 42 (12%) had graduate training, and 56 (16%) had a graduate degree; 53 (15%) additional caregivers declined to provide this information.

Infant Temperament

Of our enrolled families, 312 parents completed the Infant Behavior Questionnaire (39) (one parent did not provide data for the negative affect subscale). For high-order factors, infants were rated on negative affect ($M = 3.01$, $SD = 0.66$, Min = 1.00, Max = 5.08), surgency ($M = 4.50$, $SD = 7.84$, Min = 2.37, Max = 6.53), and orienting/regulation ($M = 5.08$, $SD = 6.09$, Min = 2.28, Max = 7.00; see **Figure 4**) at time of enrollment.

Parent Psychopathology

Parents completed the Beck Anxiety Inventory (BAI) (40) and the Beck Depression Inventory (BDI) (41) as measures of parental psychopathology (see **Figure 5**). Values were prorated to account for missing values, such that the denominator of the sum score

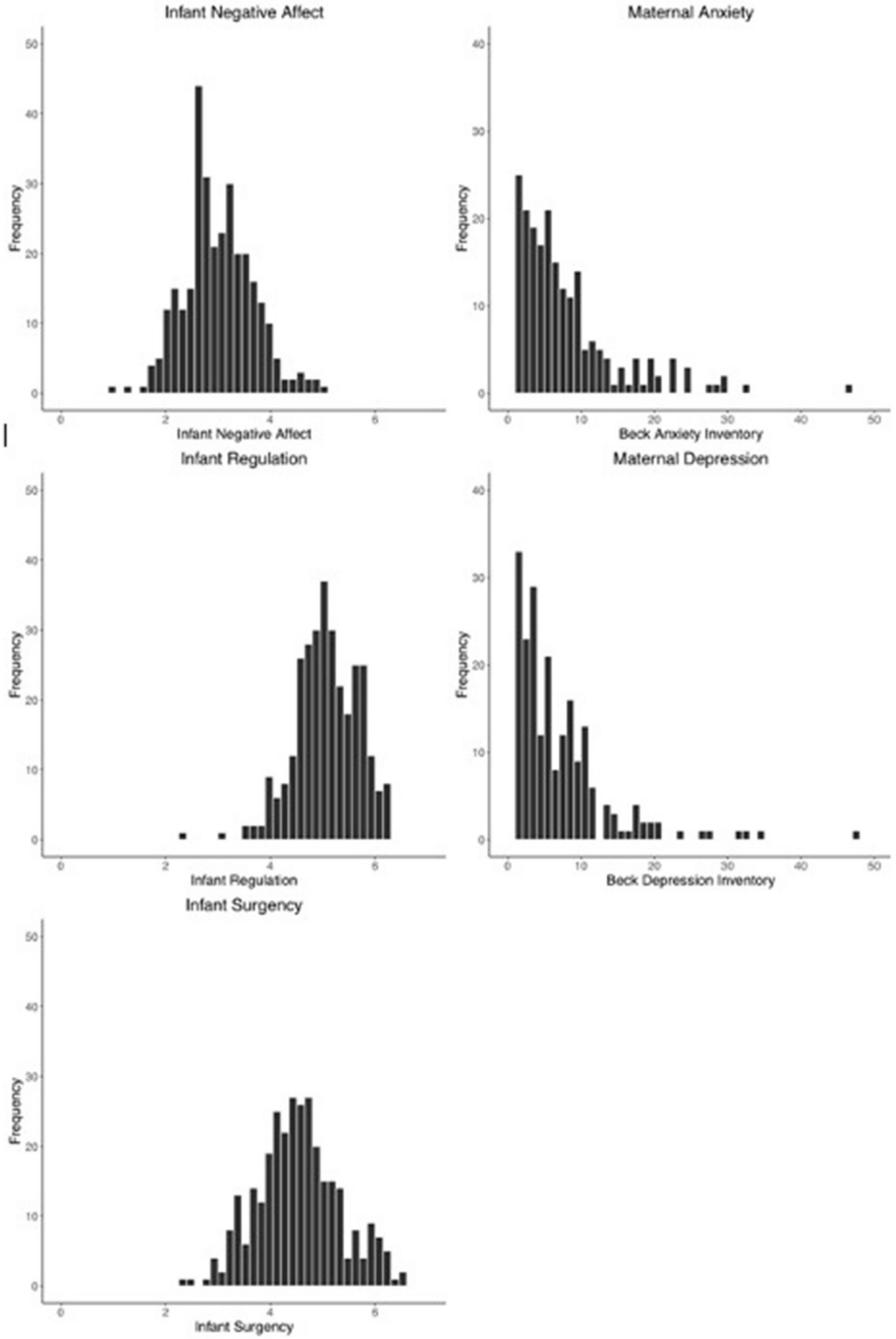

FIGURE 4 | Histograms noting the distribution of core measures of infant temperament for the higher-order scales of negative affect, regulation, and surgency from the Infant Behavior Questionnaire (**left column**) and maternal symptoms of anxiety and depression (**right column**) from the Beck Anxiety and Beck Depression Inventories, respectively, at the point of enrollment.

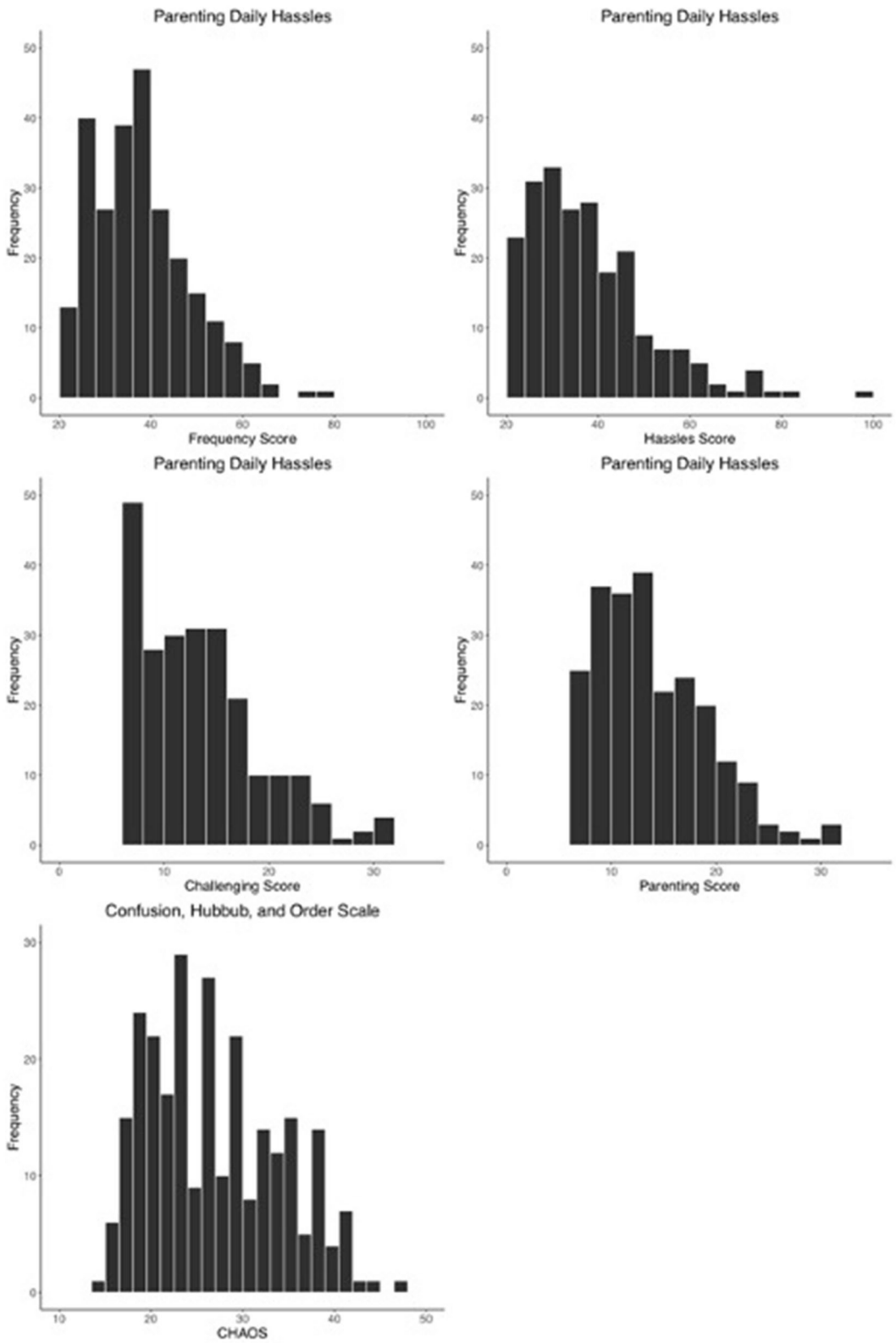

FIGURE 5 | Histograms noting the distribution of core measures of parental perception of the environment at the point of enrollment. The first two rows present scores from of Parenting Daily Hassles with the frequency, hassles intensity, challenging behaviors, and parenting subscales. The third row presents the distribution of scores from the Confusion, Hubbub, and Order Scale.

was adjusted for each item a parent did not complete on the questionnaire. Of our enrolled families, 272 parents completed the BAI at the time of enrollment ($M = 6.66$, $SD = 7.55$, Min = 0.00, Max = 53.00). The BDI was completed by 277 parents at the time of enrollment ($M = 5.80$, $SD = 6.49$, Min = 0.00, Max = 48.00).

Home Life and Parenting

As an assessment of environmental confusion in the home, 265 parents completed the Confusion, Hubbub, and Order Scale (CHAOS) (42) ($M = 27.18$, $SD = 7.25$, Min = 15.00, Max = 50.00; **Figure 5**). Parents also completed the Parent Daily Hassles Survey (PDHS-R), an assessment of the frequency and intensity of daily hassles (43). At enrollment, 263 parents completed the frequency of hassles scale ($M = 37.09$, $SD = 13.76$, Min = 20.00, Max = 100.00) and 235 parents completed the intensity of hassles scale ($M = 37.09$, $SD = 13.76$, Min = 20.00, Max = 100.00). The PDHS-R further provides a challenging behavior and parenting task intensity score. The challenging behavior total score is obtained by summing seven items from the intensity scale scores and the parenting tasks scale is obtained by summing eight items from the intensity scale. At enrollment, 234 completed the challenging behavior subscale ($M = 13.99$, $SD = 5.89$, Min =7, Max = 35.00) and 233 parents completed the parenting task intensity subscale ($M = 14.39$, $SD = 5.17$, Min = 8.00, Max = 32.00).

DISCUSSION

The LAnT study's multi-method approach aims to (1) test the three models proposed by Field and Lester (17) and (2) examine the association between early patterns of attention to threat and BI at age 2 (3). This work fills evident gaps in the literature since the attention-affect research (1) has focused on adult clinically-defined populations, (2) often does not systematically assess constructs across multiple tasks and contexts, and (3) rarely takes a *developmental* view that examines core mechanisms as they emerge in infancy in hopes of differentiating between normative patterns and patterns associated with specific risk trajectories. This line of research reflects calls from the National Institute of Mental Health (NIMH) to implement the Research Domain Criteria (RDoC) across processes and across time (44). Here, we integrate multilevel mechanisms by examining response to potential threat (negative valence systems), attention patterns (cognitive systems) and early patterns of affect across varying socioemotional contexts (negative valence systems and social processes). We also go to the heart of NIMH's Objective 2, by characterizing trajectories of neural and behavioral development in order to identify clinically useful indicators of change across illness trajectories. This approach also parallels emerging studies (45) that examine selective attention and responsiveness to emotional expression as a means of scaffolding the development of empathy and social cognition. The available data also suggest that attention patterns, and their associations with socioemotional functioning, may change over time (46–48). Thus, it will be important to continue longitudinal assessments beyond toddlerhood and into early childhood.

By capturing the earliest mechanisms that may be causally linked to a pervasive set of problem behaviors, the study applies innovative measurement techniques to central questions of socioemotional development and may shape future research. The systematic assessment of attention bias patterns, socioemotional profiles, and environmental characteristic will allow us to delineate the time course of any emerging interrelations. Finally, as outlined in the current paper, the measures generated through the protocol can serve as the foundation for numerous other questions of interest to the scientific community.

DATA AVAILABILITY STATEMENT

The datasets for this study will be shared in the National Institute of Mental Health Data Archive (NDA) and Databrary (49) as data are collected, processed, and curated. Inquiries regarding data sharing and the status of the data can be addressed to the study PIs.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Boards at Pennsylvania State University and Rutgers University, Newark. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KP-E, VL, KB, AF, and LAnTs team drafted the manuscript. KP-E, VL, KB, and AF conceptualized the study and wrote the grant funding the research. The LAnTs team designed the tasks, collected data, and wrote the protocol descriptions. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.656958/full#supplementary-material

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ORIGINAL RESEARCH
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Preschool Exposure to Online Games and Internet Gaming Disorder in Adolescents: A Cohort Study

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Objectives: Although considerable evidence has already been collected on the effects of early initiation of drug/alcohol consumption on addictive behaviors in adolescents, little is known about the impact of early exposure to online games during preschool ages on the risk of internet gaming disorder (IGD). We evaluated the effects of exposure to online games before entering elementary school on IGD occurrence during the secondary school years using a community-based longitudinal study.

Methods: Data from 1,760 adolescents (seventh grade), who were recruited from the iCURE study and followed for 2 years, were analyzed. A high risk of IGD (HRIGD) was assessed by the Internet Game Use Elicited Symptom Screen, a self-reported questionnaire based on the fifth version of DSM-5 IGD criteria. Early exposure to online gaming was defined as when adolescents played online games during their preschool years. A multivariate generalized-estimating-equation model was applied to examine the independent risk factor of the occurrence of HRIGD during the 2-year follow-up period.

Results: As compared with the later-exposure group, those with early exposure to online games showed an ∼1.7-fold greater incidence of HRIGD over the 2-year follow-ups after adjusting for potential confounders including baseline IGD scores (adjusted relative risk:1.69; 95%confidence interval:1.08–2.66). Pre-specified sensitivity analyses showed that the results were robust.

Conclusion: Exposure to online gaming during the preschool years increases the likelihood of occurrence of HRIGD in adolescence. Restricting exposure to online games during the preschool years should be examined as a way to reduce the risk of IGD in adolescents.

Clinical Trial Registration: www.clinicaltrials.gov, identifier: NCT02415322.

Keywords: preschool, online game, internet gaming disorder, adolescents, cohort

INTRODUCTION

Online gaming is a widespread recreational activity, irrespective of culture, age, and gender. However, concerns have been raised regarding whether early exposure to online games may lead to harmful effects on physical and mental health in adolescence (1–3). Among video gaming and various internet activities, online gaming appears to be associated with increased propensities for addiction (4), with much existing research focusing on negative consequences of gaming (5, 6).

Internet gaming disorder (IGD) has been conceptualized based on the theoretical frameworks of substance use disorders (SUDs) (7). These frameworks consider gaming behavior as potentially addictive (8). Early initiation of drug use has been associated with multiple problems later in life, such as negative health, social, and behavioral outcomes and increased likelihoods to develop SUDs (9).

DeWit et al. reported that the likelihood of developing lifetime alcohol dependence in those who start to drink at earlier ages was nearly 10 times that of those who started drinking later on (10). According to results from the New Zealand birth cohort, children who had been introduced to alcohol before the age of 6 years were 2.4 times more likely to report heavy or problem drinking at the age of 15 years than those who did not drink alcohol before the age of 13 years (11). Early age at gambling onset has also been linked to at-risk/problematic gambling during adolescence, particularly with respect to non-strategic forms of gambling involving assume luck without decision making any skill, gamblers cannot influence the outcome of the game (12). Addictive behaviors have been linked to sensation seeking in substance use behavior (6), and a sensation-seeking tendency has also been associated with problematic gaming in adolescents (5).

Although some studies have demonstrated beneficial effects of playing video games on psychological and physical health (13), there is evidence that if used in excess it can become an addictive behavior. Previous researches on video games has focused on the negative effects on gamers. It has been suggested that excessive video gaming is associated with attention problems, poor academic performance, anxiety, depressive symptoms, and deterioration of interpersonal relationships, family conflicts, youth violence or crimes (14). Since adolescence is typically viewed as a life stage where vulnerability to addiction is more pronounced, IGD may lead to particularly serious health problems in adolescents. More specifically, because of cognitive, social, hormonal, and neurobiological immaturities, adolescence is a period of increased risk of experiencing psychological disorders including addictive behaviors (15). Gaming disorder manifests as an impaired control over gaming and an increasing priority over other life interests and daily activities, leading to recurrent gaming despite increasing negative consequences (16, 17).

Although considerable evidence has already been produced on the effects of early initiation of drug or alcohol consumption on addictive behaviors in adolescents, little is known about the impact of early exposure to online games during the preschool ages on the risk of IGD. To fill this gap, we evaluated the relationship between exposure to online games before entering elementary school on the incidence of IGD during the secondary school years in a longitudinal, community-based cohort study.

Abbreviations: IGD, Internet gaming disorder; HRIGD, High risk of Internet gaming disorder; iCURE, Internet User Cohort for Unbiased Recognition of Gaming Disorder in Early Adolescence; IGUESS, Internet Game Use-Elicited Symptom Screen; DSM−5, The fifth version of the Diagnostic and Statistical Manual of Mental Disorders; ICD-11, The 11th revision of the International Classification of Diseases; SES, Socioeconomic status; GEE, Generalized estimating equation.

METHODS

Study Population

Our study population was derived from the internet user Cohort for Unbiased Recognition of gaming disorder in Early adolescence (iCURE) study, which is a Korean school-based prospective cohort study. A total of 2,319 students in the third, fourth, and seventh grades were enrolled between March 2015 and August 2017. Follow-up assessments were conducted at 12 and 24 months, with follow-up rates of 95% (n = 2,206) and 92% (n = 2,129), respectively. We included seventh grade adolescents at baseline (n = 1,920). Among them, 160 with confirmed high risk of IGD (HRIGD) at baseline were excluded; thus, the study sample included 1,760 normal game user in seventh grade students, who were evaluated with respect to the effects of early exposure to online games on the incidence of HRIGD in the eighth and ninth grades. Written informed consent was acquired from all participants and their parents or legal guardians after they received an explanation of the nature of the principles of research, including confidentiality and the freedom of choice to participate. The pre-registered study protocol has been described in detail elsewhere (18). This analytic study was fully reviewed and approved by the institutional review board of the Catholic University of Korea (MC21EISI0065).

Measurements

Data collection was performed at participants' schools during school hours during both baseline and follow-up time points. All participants completed questionnaires using self-administered web-based surveys, with a supervising research assistant available to answer questions.

Incidence of IGD Symptomatology

The incidence of IGD symptomatology was assessed by the Internet Game Use Elicited Symptom Screen (IGUESS). Originally, the IGUESS incorporated DSM-5 IGD diagnostic criteria into a brief self-reported assessment tool, asking questions on experiences regarding nine IGD symptoms during the past 12 months. IGUESS has 9-items. Each item in the IGUESS is rated on a four-point Likert scale (0 = not at all, 1 = occasionally, 2 = frequently, and 3 = always), scores ranged from 0 to 27 points. When comparing the clinician's diagnosis based on the DSM-5 IGD criteria, the sensitivity, specificity, and diagnostic accuracy of the IGUESS were 86.7, 80.0, and 86.8%, respectively, at a cutoff

score of 10 points to designate a respondent as HRIGD. Cronbach's alpha provided an index of reliability, and the value of the nine items on the IGUESS was 0.94 (19). IGD symptomatology was assessed at 12 and 24 months. Herein, this scale was deemed reliable, with a Cronbach's alpha of 0.85-0.87.

Exposure to Online Games

The following question was asked to assess the initial exposure to online games at baseline: "When did you first start playing online games?" Respondents were then asked to select from one of the following: preschool; first, second, third, fourth, fifth, sixth, or seventh grade; or never. Those who responded that they played online games during their preschool years were defined as having "early exposure" and those who started playing online games after entering elementary school were defined as having "later exposure" to online games, respectively.

Sociodemographic Factors

General characteristics of participants, including gender, family structure, and socioeconomic status (SES), were obtained from baseline data. Family structure was categorized as either intact or non-intact, with an intact family defined when the adolescent was living with both parents and a non-intact family defined as when the adolescent was living with only a mother or father or with neither parent due to divorce, death, or parental separation. SES was assessed using the following question posed to the parents: "Which of the following is your family's level of SES (with options ranging from 1 = *lowest* to 7 = *highest*; scores of 1–4 points were categorized as low to moderate and scores of 5–7 points were categorized as high)?

Depressive Symptoms

Depressive symptoms were assessed with the Children's Depression Inventory at baseline, which has 27-items, scores ranged from 0 to 54 points. We used the Korean version of the Children's Depression Inventory, which has demonstrated good reliability and validity for the assessment of depressive symptoms (20). A total score of 22 points or more was considered to indicate presence of depressive symptoms. The Cronbach's alpha value was 0.89 in this study.

Attachment to Parents at Baseline

The Inventory of Parent and Peer Attachment—Revised is a 25-item instrument that employs a five-point Likert scale. This instrument is used to assess adolescents' perceptions of relationships with their parents in terms of the degree of mutual trust, quality of communication, and alienation. Possible scores range from 25 to 125 points, with higher scores indicating a greater degree of attachment to the parents (21). The degree of attachment to parents was assessed at baseline. For descriptive purposes, we used median splits to define higher and lower levels of attachment to parents. The Cronbach's alpha value was 0.94 in this study.

Openness of Communication With Parents at Baseline

To measure the "openness of communication" between adolescents and their parents, we used subscale of the Parent–Adolescent Communication Inventory. It consists of 20-items and scores range from 0 to 60, with higher scores reflecting a greater degree of openness in parent–adolescent communication (22). The degree of openness of communication between adolescents and their parents was assessed at baseline. For descriptive purposes, we used median splits to define higher and lower levels of openness of communication between parents and adolescents. The Cronbach's alpha value was 0.71 in this study.

Social Relationship Factor: Perceived Social Support at Baseline

The Social Support Appraisals Scale is a 24-item self-report instrument that assesses perceived social support (23). Items are rated on a five-point Likert scale and higher scores reflecting stronger social support. The degree of social support was assessed at baseline. Although social support was considered a continuous predictor, for descriptive purposes, we utilized median splits to define higher and lower levels of social support. The Cronbach's alpha value was 0.94 in this study.

Online Gaming Activity at Baseline

Gaming time was assessed by questions that inquired about how many hours participants played online games on average weekdays at baseline. We categorized the average time spent playing online games as <60 min, 60-239 min, or 240 or more minutes per day based on data distribution—the median score was 60 min and the time corresponding to 95% was 240 min. Respondents were asked about the titles of the online games they most frequently had played during the past 12 months and we categorized games as either multiplayer or single-player online games based on the characteristics of their content. Also, in response to "Do you use a PC bang?" those who said "yes" were classified as using PC bangs. For reference, a PC bang (Korean Internet café) is a type of LAN gaming center in South Korea where patrons can play multiplayer computer games for an hourly fee.

Statistical Analysis

Descriptive statistics were characterized frequencies and numbers or mean ± SDs. The analyses incorporated both 12- and 24-month outcomes into a single model using longitudinal generalized-estimating-equation (GEE) regression methods. The incidence of IGD symptomatology was modeled using an IGUESS score of at least 10 points as the threshold score for HRIGD.

GEE was chosen for the analysis given that factors affecting the relationship are time-dependent measures, and it accounted for correlated data with multiple observations per individual (24). The goal is to make inferences about the population when accounting for the within-subject correlation. GEE tells us that preschool exposure to online game was related to incidence of HRIGD at the two different follow-up points (25). This method provides standard errors adjusted by multiple observations per

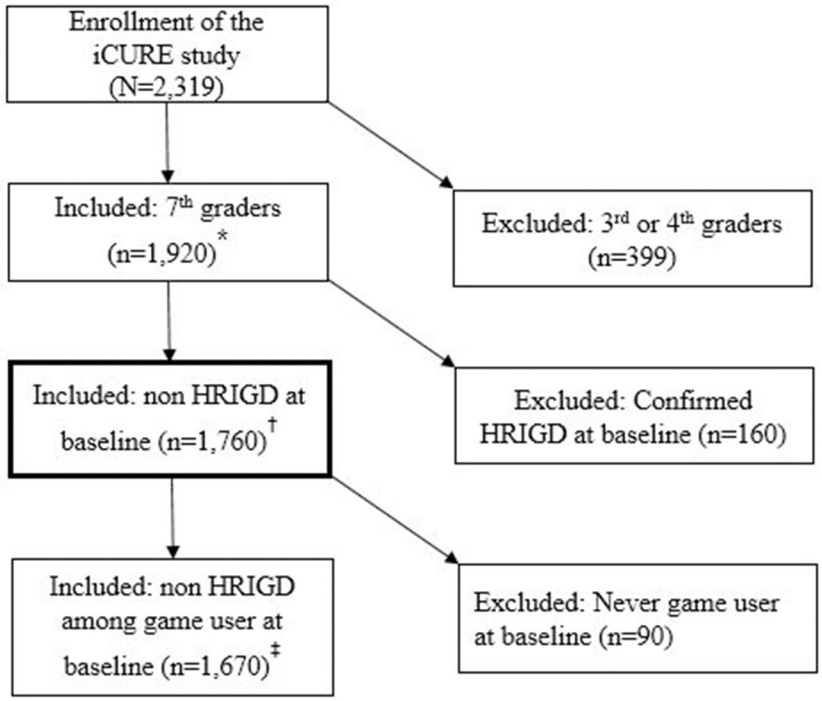

FIGURE 1 | Flow diagram of inclusion and exclusion criteria for the data analysis. *Sensitivity analysis set to evaluate effect of cumulative risk of early exposure to online game on HRIGD. †Main analysis set to evaluate the effect of early exposure to online game on incidence of HRIGD. ‡Sensitivity analysis set to evaluate effect of early exposure to online game on incidence of HRIGD among game users at baseline.

person using an exchangeable correlation structure, making it possible to consider data from every participant follow-up visit in this analysis (26).

GEE analysis was conducted using a binomial regression model with a logit link function. The working correlation matrix fit autoregressive, exchangeable, and unstructured, respectively, and we finally selected an unstructured correlation matrix for the analysis of correlated data based on the model with the minimum QIC statistic.

In the multivariable GEE model, we adjusted for potential confounding factors including, gender, family structure, SES, depressive symptoms, attachment to parents, openness of communication with parents, and social support as well as baseline IGD scores. Online game–related activities at baseline were not included in the multivariate model as confounders since gaming-related activities were considered to be an outcome of early exposure on online games. We used inverse probability of attrition weighting to address missing data due to participant dropout.

To test the robustness of our findings, we conducted pre-specified sensitivity analyses in terms of the definitions of the study population. First, we included all seventh graders regardless of their baseline IGD scores to evaluate the lifetime cumulative effect of early exposure to online games on IGD without adjusting for baseline IGD scores.

Second, we additionally excluded 90 adolescents classified as not using online games at baseline to obtain a conservative estimation of the effects of early exposure to games on the occurrence of IGD symptomatology during the secondary school years. The flow diagram of the data analyses set was depicted in **Figure 1**. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). All *p*-values were two-sided.

RESULTS

Among 1,760 participants, 253 (14.4%) were classified into the group with early exposure to online games and 1,507 (85.6%) were classified into the later-exposure group. The mean age of the participants was 13 years old. There were no between-group differences in gender, family structure, socioeconomic status, depressive symptoms, attachment to parents, openness of communication with parents, and social support (**Table 1**). However, there were significant differences in online-game–related activities between the two groups in the baseline assessments. As compared with the later-exposure group, adolescents included in the early-exposure group were more likely to use PC bangs, spend more time playing online games on weekdays, and have higher mean baseline IGD assessment scores (all $p < 0.05$) (**Table 2**).

TABLE 1 | Baseline characteristics according to early or later exposure to online games among 1,760 adolescents who have ever played online games.

Variables	Online game exposure		*P*-value
	Early (n = 253, 14.4%)	Late (n = 1,507, 85.6%)	
Age (mean ± SD)	13.0 ± 0.2	13.0 ± 0.2	0.263
Gender			0.279
Boy	135 (53.4)	859 (57.0)	
Girl	118 (46.6)	648 (43.0)	
Family structure			0.727
Intact family	230 (90.9)	1,380 (91.6)	
Non-intact family	23 (9.1)	127 (8.4)	
Socioeconomic status (middle or above)	162 (71.9)	1,048 (69.6)	0.455
Depressive symptoms	12 (4.7)	49 (3.3)	0.230
Lower attachment to parents	133 (52.6)	734 (48.7)	0.255
Lower openness of communication with parents	133 (52.8)	715 (47.5)	0.131
Lower social support	121 (47.8)	734 (48.7)	0.796

Early exposure was defined as having started to play online games during the preschool years.
Later exposure was defined as having started to play online games after entering elementary school.

TABLE 2 | Baseline gaming–related activity according to early or later exposure to online games among 1,760 adolescents who have ever played online games.

Variables	Online game exposure		*P*-value
	Early (n = 253, 14.4%)	Late (n = 1,507, 85.6%)	
PC bang use	61 (24.1)	269 (17.9)	0.018
Game time during weekday (min/day)			0.005
<60	123 (48.6)	749 (48.7)	
60–239	105 (41.5)	685 (45.5)	
≥240	25 (9.9)	73 (4.8)	
Most frequently played type of online game			0.082
None	87 (34.4)	614 (40.7)	
Single-player game	97 (38.3)	563 (37.4)	
Multiple-payer game	69 (27.2)	330 (21.9)	
IGD score (mean ± SD)	3.2 ± 2.7	2.7± 2.6	0.003

Baseline gaming–related activity was evaluated in the seventh grade (baseline).
IGD scores were evaluated using the IGUESS scale.
P-values were calculated by either the chi-squared test or t-test.

Among 1,760 non-HRIGD participants at baseline, the incidence of HRIGD in the early- and later-exposure groups were 8.8 and 4.2% ($p = 0.002$) at 12 months of follow-up, 6.9 and 4.2% ($p = 0.071$) at 24-months follow-up, and 4.3 and 1.2% ($p = 0.001$) at both 12- and 24-months follow-up (**Figure 2**).

In the multivariable GEE model, exposure to online games during the preschool years was revealed to be an independent risk factor associated with incidence of HRIGD during secondary school. As compared with in the later-exposure group, those with early exposure to online games showed a 1.69-fold higher incidence of HRIGD after adjusting for sociodemographic, psychological, family, and social relationship factors as well as baseline IGD scores (aRR: 1.69; 95%CI: 1.08–2.66 for model II) (**Table 3**).

The first sensitivity analysis included all of the participants to evaluate the cumulative effects of early exposure to online games on the incidence of IGD symptomatology during secondary school. As compared with in the later-exposure group, those with early exposure to online games showed a 2.2-fold increase in HRIGD (95%CI: 1.64–2.97) over the 2-year follow-up period after adjusting for possible confounders (**Supplementary Table 1**).

A total of 1,670 adolescents classified with current use of online games in the non-HRIGD population at baseline were included in the second sensitivity analysis to evaluate conservative effect estimates of the exposure to games during the preschool years on the incidence of IGD symptomatology. As compared with the later-exposure group, those with early exposure to online games showed an approximately 1.7-fold increase in HRIGD onset(95%CI: 1.07–2.64) over the 2-year follow-up period after adjusting for possible confounders as well as baseline IGD scores (**Supplementary Table 2**).

DISCUSSION

Online games have gained popularity since the start of the new millennium and have led to significant growth in the gaming industry (27). South Korea was ranked recently as one of the countries with the greatest percentage of smartphone owners and mobile games were the most popular form of gaming in a global survey (28).

The iCURE cohort was conducted as a baseline survey for seventh-grade students in 2015 and 2016. Most participants were adolescents born between 2002 and 2003. Since online games such as MMORPGs were developing at that time, it is possible that they have been exposed to online game during their preschool years. This population therefore might be a particularly relevant cohort in which to evaluate possible effects of early exposure to online games during the preschool years on the development of IGD symptomatology during adolescence.

In our cross-sectional analysis, no difference in sociodemographic characteristics between non-HRIGD adolescents in the early- and later-exposure groups was found. However, game-related factors differed between the two groups, suggesting possible cumulative effects of game exposure during the preschool years. Since the iCURE study is a school-based cohort, adolescents who had already experienced IGD before the time of cohort enrollment due to early exposure to online games may either had already moved to an alternative school system or refused to participate in the cohort study. Such possibilities may have influenced observed associations at baseline.

In order to estimate the occurrence of IGD risk during the 2-year follow-up period according to early exposure to online

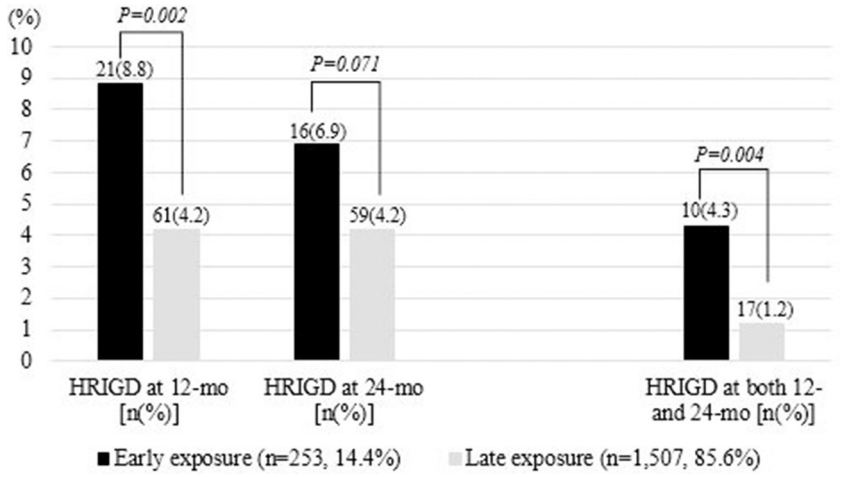

FIGURE 2 | Incidence of HRIGD in the early- and later-exposure groups at 12 and 24 months of follow-up. HRIGD, high risk of internet gaming disorder.

TABLE 3 | Univariable and multivariable GEE analyses using binomial models of the relative risks of incidence of HRIGD in the eighth and/or ninth grades among non-HRIGD adolescents in seventh grade (n = 1,760/5,280 observations).

	Model I	Model II
Online game exposure	**cRR (95% CI)**	**aRR (95% CI)**
Early (n = 253, 14.4%)	1.85 (1.18–2.90)	1.69 (1.08–2.66)
Later (n = 1,507, 85.6%)	1	1

Model I, Crude values.
Model II, Adjusted by demographic, psychological, family environment, and social relationship factors, including gender, family structure, socioeconomic status, depressive symptoms, attachment to parents, openness of communication with parents, and social support as well baseline IGD score (seventh grade).
cRR, crude relative risk; aRR, adjusted relative risk; HRIGD, high risk of Internet gaming disorder; CI, confidence interval.

games among youth with normal game use, the baseline IGD score was adjusted as a potential confounder. Our 2-year follow-up results suggested that exposure to online games during the preschool years was an independent risk factor for the onset of HRIGD during the secondary school years.

Of 1,760 students classified as non-HRIGD individuals at baseline, there were 253 adolescents who were exposed to online games during their preschool years, and 27 experienced HRIGD during the 2-year follow-up period. The incidence of HRIGD in the early-exposure group was 10.7%. On the other hand, there were 1,507 students who were exposed to online games after entering elementary school, of whom 103 experienced HRIGD during the 2-year follow-up period. The incidence of HRIGD in the later-exposure group was 6.8%. Our results showed that early exposure to online games yields a significant risk ratio of 1.69. The clinical implication is that if early exposure to online games led to an increased HRIGD incidence in adolescents and the early exposure rate was 10% in a group of 10,000 adolescents, then interventions for suppressing exposure to online games during preschool years might be able to prevent approximately 77 non-HRIGD secondary school students from transitioning to an HRIGD status.

Available studies indicate that individuals who begin using the internet at younger ages may exhibit an increased risk for internet addiction (29). Although IGD is considered a behavioral addiction, multiple similarities have been described between addictive gaming and other addictions, such as SUDs and gambling disorder. Excessive game use has been proposed to relate to reward deficiency that may involve reduced dopaminergic activity, similar to SUDs like cocaine-use disorder (30). In a small study, game-playing was found to induce dopamine release similar to that seen with cocaine use (31).

A recent study showed that increased screen-based media consumption was linked to reduced microstructural integrity of brain white-matter tracts, which are important in the early years of brain development, among 5-year-old preschool children (32). Early childhood is a time of rapid brain development; structural connections increase as brain networks become more segregated and specialized (1). These developments are related to a wide range of cognitive developments and are associated with self-regulatory processes. The American Academy of Pediatrics recommends no screen time for children until 18 to 24 months of age and an hour or less of screen time per day for preschool-aged children (33).

We evaluated the cumulative effects of early exposure to online games from the preschool years to the secondary school years and found that the risk score for incident HRIGD was not altered in the sensitivity analysis. Despite the possibility that a selection bias was introduced in this analysis, early exposure to online games was an independent risk factor that increased the risk of IGD symptomatology by 2.2-fold as compared with the later-exposure group.

Given potential debate regarding whether youth without use of online games at baseline carry considerable risk for IGD given absence of exposure, we conducted another sensitivity analysis including only adolescents who played online games

at baseline to assess for incident HRIGD. Children who were exposed to online games during their preschool years appeared still significantly at greater risk of HRIGD during their secondary school years. These pre-specified sensitivity analyses supported the robustness of the primary analysis.

There are study limitations. The initiation age of online games was assessed *via* self-report retrospectively and was not independently verified. Among adolescents who reported that they initiated online game-playing during their preschool years, even though the spectrum of game exposure may have varied, early exposure to online games was found to increase the likelihood of HRIGD during adolescence. Psychosocial factors such as depressive symptoms, attachment, and social support were measured in the seventh grade at the time of cohort registration, so they may not accurately reflect the psychosocial characteristics at the time of game exposure. If the psychosocial characteristics such as attachment or depressive symptoms were known at the time of exposure to games, the influence of various psychosocial factors between game exposure and the occurrence of game disorders could have been evaluated.

Since exposure was defined as a broad spectrum, the association between early exposure to online games and the development of HRIGD should be investigated further using finer assessments.

We used the cutoff value on a median split of psychosocial measurements, including attachment to parents, openness of communication with parents, and perceived social support. Compared with the original continuous measure, an artificially categorized variable can be less precise because it does not allow the researcher to discriminate between differently scoring members in the same group.

CONCLUSION

Early exposure to online games continues to increase the likelihood of incident HRIGD during the secondary school years among youth with normal game-playing in the seventh grade. Restricting exposure to online games during the preschool years should be investigated further as a possible way to reduce the risk of IGD in adolescents.

As a strategy to reduce the risk of IGD in adolescents, it is necessary to provide information to children and parents about the possibility that early exposure to online games can increase the risk of IGD. Because parent–child communication and parental monitoring regarded as one central parental skill to focus on prevention of IGD, interventions or counseling that focus on parental involvement can yield behavioral change in children.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was acquired from all participants and their parents or legal guardians after they received an explanation of the nature of the principles of research, including confidentiality and the freedom of choice to participate. This study was fully reviewed and approved by the Institutional Review Board of the Catholic University of Korea (MC21EISI0065). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HJ conceptualized and designed the study, designed the data collection instruments, developed data analysis plan, carried out the initial analyses, interpreted the data for the work, drafted the initial manuscript, and reviewed and revised the manuscript. HY conceptualized and designed the study, designed the data collection instruments, interpreted the data for the work, guided and supervised the writing of the manuscript, and reviewed and revised the manuscript. S-YL and HL designed the data collection instruments, coordinated and supervised data collection, and reviewed and revised the manuscript. MP and YS interpreted the data for the work and reviewed critically the manuscript for important intellectual content, and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.760348/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Longitudinal Bidirectional Relationships Between Maternal Depressive/Anxious Symptoms and Children's Tic Frequency in Early Adolescence

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Background: Previous studies have revealed an association between maternal depressive/anxious symptoms and children's tics. However, the longitudinal relationships between these symptoms remain unclear. We examined the longitudinal relationships between maternal depressive/anxious symptoms and children's tic frequency in early adolescence with a population-based sample.

Methods: The participants consisted of 3,171 children and their mothers from the Tokyo Teen Cohort (TTC) study, a population-representative longitudinal study that was launched in Tokyo in 2012. Maternal depressive/anxious symptoms and children's tics were examined using self-report questionnaires at the ages of 10 (time 1, T1) and 12 (time 2, T2). A cross-lagged model was used to explore the relationships between maternal depressive/anxious symptoms and children's tic frequency.

Results: Higher levels of maternal depressive/anxious symptoms at T1 were related to an increased children's tic frequency at T2 ($\beta = 0.06$, $p < 0.001$). Furthermore, more frequent children's tics at T1 were positively related to maternal depressive/anxious symptoms at T2 ($\beta = 0.06$, $p < 0.001$).

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Conclusions: These findings suggest a longitudinal bidirectional relationship between maternal depressive/anxious symptoms and children's tic frequency in early adolescence that may exacerbate each other over time and possibly create a vicious cycle. When an early adolescent has tics, it might be important to identify and treat related maternal depressive/anxious symptoms.

Keywords: tics, tic frequency, maternal depressive/anxious symptoms, longitudinal study, general population study, early adolescence

INTRODUCTION

Tics are sudden, rapid, recurrent, and non-rhythmic motor movements or vocalizations. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) includes three tic disorders (1). Tourette syndrome (TS) is defined by the presence of at least two motor tic behaviors and one vocal tic behavior for a minimum period of a year, manifesting before the age of 18. Chronic tic disorder (CT) is defined by the presence of either motor or vocal tics for at least 1 year, while provisional tic disorder is defined as tics that have been present for less than a year. Recent population-based studies have demonstrated that tics are more common than previously recognized (2–5). According to the International Classification of Diseases 10th Revision (ICD-10), which is an international diagnostic classification developed by the World Health Organization (WHO), one in five to ten children has experienced tics (6). Tic disorders impose a psychosocial burden on children and their families because tics are characterized by the visibility of symptoms, which can cause stigma and prejudice (7–10). Attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are common comorbidities of tic disorders (7, 11, 12). Tic disorders tend to be remitted with age through adolescence (7, 13, 14). The overall similarity in these patterns of comorbidity and natural history among tic disorders suggests that tic disorders have etiological continuity (15–17), and a recent diagnosis of "tic spectrum disorders" has been suggested (18). Many clinical studies and experimental studies historically use tic frequency on measures to assess severity at outcome (19–24).

Tic disorders consist of a complex involvement of both multiple genes and environmental factors (25, 26). Little is known about the exact brain mechanisms associated with tic development and expression (27, 28), although preliminary evidence from neurochemical and neuroimaging investigations suggests a primary role for dysfunction of the dopaminergic pathways within the cortico-striato-cortico-frontal circuitry (29–31). Environmental factors for tics include infection and autoimmune dysfunction, maternal environment during pregnancy, and psychosocial stress (11, 28). It has been suggested that psychosocial factors such as trauma and intense daily psychological stress may be risk factors in individuals with genetic vulnerabilities to TS (11, 32).

The identification of parental psychopathology could be informative in the evaluation of risk factors for the development of tic disorders in children (33). Previous research has shown that there is an association between maternal psychiatric symptoms and children's tic disorders. Chronic maternal anxious symptoms and prenatal maternal depressive symptoms have been associated with increased odds of children having TS/CT at age 13 (34). In another study, a maternal history of non-specific psychiatric disorders, including anxiety disorders and depressive disorders, was shown to increase odds of children having TS/CT during childhood and adolescence (35). It is presumed that maternal depressive/anxious symptoms are associated with the occurrence of children's TS/CT *via* maternal-specific environmental and/or genetic factors (34, 35).

Although the association between maternal mental health and children's tic disorders has been proved (34, 35), it is not clear whether maternal psychiatric symptoms are associated with the subsequent course of children's tic disorders. If maternal psychiatric symptoms predict the subsequent course of children's tic disorders, then maternal psychiatric symptoms could possibly be a prognostic factor or an intervention target of tic disorders. To examine this point, we investigated the relationship between maternal depressive/anxious symptoms and children's tic frequency in early adolescence with a longitudinal design.

In addition, we speculated that maternal depressive/anxious symptoms and children's tic frequency influence each other bidirectionally. Some studies have shown bidirectional influences on maternal and children's psychiatric symptoms. For example, depression in mothers increases the risk of emotional and behavioral problems in their children and vice versa (36, 37). However, no study has investigated the bidirectional relationship between maternal psychiatric symptoms and children's tics. Research on the longitudinal bidirectional relationship between maternal depressive/anxious symptoms and children's tics would be helpful in advancing the research and practices related to tics.

Our aim was therefore to examine the relationships between maternal depressive/anxious symptoms and child's tic frequency in a longitudinal study design using a general population of early adolescent samples. In this population-based study, we referred to a tic or tics instead of the diagnostic term "tic disorders" because we did not make clinical diagnoses of the participants.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CFI, comparative fit index; CI, confidence interval; CT, chronic tic disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th edition; GHQ-28, General Health Questionnaire-28; K6, Kessler Psychological Distress Scale; OCD, obsessive-compulsive disorder; RMSEA, root mean square error of approximation; SD, standard deviation; TS, Tourette syndrome; TTC, Tokyo Teen Cohort.

Our hypotheses were as follows: (1) maternal depressive/anxious symptoms predict children's tic frequency 2 years later, and (2) maternal depressive/anxious symptoms and children's tic frequency influence each other bidirectionally over time.

MATERIALS AND METHODS

Participants

This study used data from the Tokyo Teen Cohort (TTC) study (http://ttcp.umin.jp/), a population-based longitudinal survey focusing on children's health from biopsychosocial multidisciplinary viewpoints (38). The TTC study has started from October 2012 and is currently being conducted. The participants were recruited from three municipalities in Tokyo (Setagaya, Mitaka, and Chofu) using the Basic Resident Register. The candidate participants were 14,553 children born between September 1, 2002, and August 31, 2004 (**Figure 1**). Invitation letters were sent to the primary parents of those children around their 10th birthday. Of these children, 10,234 were successfully contacted, and these children were invited to participate in the cohort study. Of these 10,234 children, 4,478 children participated in the baseline survey named the Tokyo Early Adolescence Survey (T-EAS). This baseline survey was conducted from October 2012 to January 2015, when the participants were approximately 10 years old (time 1, T1). Among the 4,478 participants in the T-EAS, candidates were chosen as participants for the second wave of the TTC study. For the sake of cohort management, the target number of participants to be included in the second wave of the TTC was 3,000 children. When choosing these TTC participants, an oversampling method was used instead of inclusion criteria, considering the low follow-up rate of families with low annual household incomes. Among children who participated in T-EAS and were interested in participating in the cohort study, all 620 children whose household annual income was lower than 4,990 thousand yen were invited. From the remaining 3,858 children, 2,551 children were randomly invited to the second wave of TTC. Thus, 3,171 participants were extracted as targets for the second wave of the TTC study. The second wave of the TTC study was carried out from August 2014 to December 2016, at the time when the participants were approximately 12 years old (time 2, T2). Of the 3,171 children who were invited, 3,007 individuals participated in the second wave of the TTC study (follow-up rate 94.8%). In each wave of the data collection, trained interviewers visited the participants' homes. They distributed questionnaires to the children and primary parents (mostly mothers), and they conducted psychological tests on the children.

Ethical Approval

Ethical approval for this study was obtained from the research ethics committees of the Tokyo Metropolitan Institute of Medical Science (Approval Number: 12-35), The Graduate University for Advanced Studies, SOKENDAI (2012002), and the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (10057). We obtained informed assent from the children and written informed consent from their primary parents.

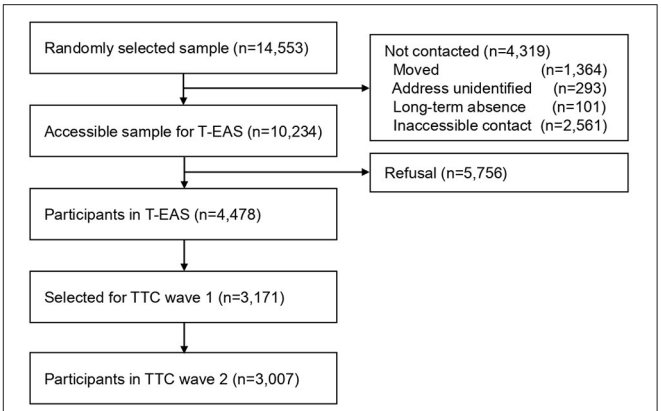

FIGURE 1 | Flowchart of participant recruitment.

Measures

Tic Frequency

We evaluated tic frequency at T1 and T2. The participants' primary parents answered a questionnaire about the children's tics; this questionnaire has been used in a previous study (5). The questionnaire includes a section with the following five questions about specific motor and vocal tics in the past year: "Q1: Has your child had any repeated movements of parts of the face and head (e.g., eye blinking, grimacing, sticking tongue out, licking lips, spitting)?"; "Q2: Has your child had repeated movements of the neck, shoulder or trunk (e.g., twisting around, shoulder shrugging, bending over, nodding)?"; "Q3: Has your child had repeated movements of the arms, hands, legs, or feet?"; "Q4: Has your child had repeated noises and sounds (e.g., coughing, clearing throat, grunting, gurgling, and hissing)?"; and "Q5: Has your child had repeated words or phrases?" Each question is answered as either "definitely," "probably," or "not at all" present. Furthermore, we asked the following question about the frequency of these repetitive behaviors: "Q6: About how often does/did this happen in the last year?" This question was answered on the following 5-point Likert scale: "1: less than once a month, 2: 1–3 times a month, 3: about once a week, 4: more than once a week, 5: every day." We defined the participants who responded "definitely" or "probably" to any of Q1, Q2, and Q4 as having tics. The participants who only endorsed repeated movements of the arms, hands, legs or feet (Q3) or repeated words or phrases (Q5) in the absence of a positive response to the other questions about the types of tics (Q1, Q2, Q4) were excluded from a case definition to remove non-tic movements such as stereotypy or isolated echolalia. We defined as tics all responses of "definitely" or "probably" to questions concerning motor and/or vocal tics regardless of their frequency because there is no condition of frequency in the diagnostic criteria of tic disorders (1) and because we aimed to exhaustively find tics in the general population. For those without tics, the frequency of tics was regarded as 0, and for those with tics, the frequency of tics was evaluated on a 5-point scale from the answer in Q6.

Maternal Depressive/Anxious Symptoms

We employed the Kessler Psychological Distress Scale (K6) (39–41) for T1 and the General Health Questionnaire-28 (GHQ-28) (42, 43) for T2. The K6 and the GHQ-28 are both widely used self-report questionnaires that were developed to evaluate depressive/anxious symptoms. We used different scales between T1 and T2 in the current study because the TTC study also switched the scale used for maternal depressive/anxious symptoms from the K6 to the GHQ-28 starting at T2. The K6 is a short questionnaire consisting of 6 questions about the subjective mental distress of the respondent over the past 30 days that are answered on a 5-point scale, and the scores of the 6 items are added together (0–24 points). The GHQ-28 consists of 28 questions about the respondent's subjective physical and mental states over the past few weeks, with a total score being calculated for each item by giving 0 points each for the right two responses and 1 point each for the left two responses (0–28 points). Cutoff values are often used to screen for anxiety disorders and depression when assessing the K6 and the GHQ-28. However, in this study, we used raw values of the K6 and the GHQ-28 as continuous scales instead of screening scales, for the purpose of evaluating the severity of depressive/anxious symptoms, including the normal range in the general population. The Cronbach's alpha value was 0.84 for the K6 and 0.88 for the GHQ-28. We found that the distributions of the K6 and the GHQ-28 were similar based on the graphing cumulative distribution of their *Z* scores (**Supplementary Figure 1**). If a primary parent other than a mother answered the K6 or the GHQ-28, we regarded those responses as missing values.

Other Variables

Sex (5, 7, 44), age (32, 45, 46), maternal age (35, 47–49), socioeconomic status (50), and maternal alcohol use during pregnancy (51) were included in the analyses since previous studies have reported that these factors influence the occurrence of TS/CT. The data for these variables were obtained from the responses to the questionnaires completed by caregivers. To assess socioeconomic status, family income was evaluated on an 11-point scale, which ranged from "0–990,000 yen" to "more than 10,000,000 yen." Information on maternal alcohol use during pregnancy was obtained from maternity record books that were provided for almost all mothers by local public organizations in Japan.

Statistical Analysis

Longitudinal relationships between maternal depressive/anxious symptoms and children's tic frequency were studied with structural equation modeling. We used SPSS® (Statistical Package for Social Science; IBM Corp., Armonk, N.Y. USA) version 21.0 for the characteristics of the study participants and Amos ver. 22.0 (IBM Corp, New York) for the structural equation modeling. We used the following two cross-lagged design models. The first model analyzed the longitudinal relationships between maternal depressive/anxious symptoms and children's tic frequency without adjusting for covariates (unadjusted model). The second model adjusted for sex, age in months, family income, maternal age, and maternal alcohol use during pregnancy (adjusted model).

Missing values in the categories of tics, maternal depressive/anxious symptoms, and the covariates were accounted for by full information maximum likelihood procedures available in Amos. This method estimates model parameters and standard errors using all available data while adjusting for the uncertainty associated with missing data (52).

The threshold for statistical significance was set to $p < 0.05$ (two-sided) for all analyses. We evaluated the fit of our models by using the comparative fit index (CFI) and the root mean square error of approximation (RMSEA). A good model fit was indicated by an RMSEA value smaller than 0.05 and a CFI value larger than 0.95 (53, 54).

TABLE 1 | Demographic characteristics of the participants.

Variables	T1 (10 years of age)		T2 (12 years of age)	
	n/*Mean*	(%)/*SD*	n/*Mean*	(%)/*SD*
Sex, male	1,684	(53.1%)		
Age in months	*122.1*	*3.3*	*146.0*	*3.7*
Maternal age	*42.0*	*4.2*		
Family income[a]				
<5 million yen	620	(20.4%)	448	(16.5%)
≥5 million yen, <8 million yen	941	(31.0%)	782	(28.8%)
≥8 million yen, <10 million yen	568	(18.6%)	518	(19.1%)
≥10 million yen	917	(30.1%)	970	(35.7%)
Maternal alcohol use during pregnancy	748	(27.2%)		
Tic frequency				
No tics	2,365	(76.7%)	2,042	(76.5%)
With tics	720	(23.3%)	626	(23.5%)
Less than once a month	138	(4.5%)	122	(4.6%)
1–3 times a month	114	(3.7%)	115	(4.3%)
About once a week	37	(1.2%)	66	(2.5%)
More than once a week	206	(6.7%)	161	(6.0%)
Every day	225	(7.3%)	162	(6.1%)
Maternal depressive/anxious symptoms				
T1, K6	*2.9*	*3.3*		
T2, GHQ-28			*5.4*	*4.9*

[a] *Family income was evaluated on the 11-point scale described in section Materials and Method and categorized into the four groups in this table.*

SD, standard deviation; K6, Kessler Psychological Distress Scale; GHQ-28, General Health Questionnaire-28.

RESULTS

Characteristics of the Study Participants

Table 1 shows the demographic characteristics of the 3,171 study participants. Of the 3,171 included children, 2,601 children (82.0%) had complete data about tics across both time points; 67 (2.1%) and 484 (15.3%) children had missing data about tics in

either T1 or T2, respectively, and 19 (0.6%) children had missing data about tics in both T1 and T2. Across both time points, data about maternal depressive/anxious symptoms were complete for 2,683 mothers (84.6%); 24 (0.8%) and 309 (9.7%) mothers had missing scores in either T1 or T2, respectively; and 155 mothers (4.9%) had missing data about maternal depressive/anxious symptoms in both T1 and T2.

Of the participants, 23.3% children (720 of 3,085 available data) at T1 and 23.5% children (626 of 2,668 available data) at T2 had tics. These prevalence rates are consistent with previous studies that have estimated the point prevalence of tics in childhood to be approximately 20–29% (2–4). Of the 2,601 people whose data on the presence of tics were obtained in both T1 and T2, 332 participants endorsed tics at both T1 and T2, 280 participants endorsed tics only for T1, 265 participants endorsed tics for only T2, and 1,724 did not endorse tics at either time point.

Longitudinal Relationships Between Maternal Depressive/Anxious Symptoms and Children's Tic Frequency in Early Adolescence

We investigated the relationships between maternal depressive/anxious symptoms and children's tic frequency in a cross-lagged model analysis (**Figure 2**, **Table 2**). There was a cross-sectional association between maternal depressive/anxious symptoms and child's tic frequency at T1 and T2. Higher levels of maternal depressive/anxious symptoms at T1 significantly increased children's tic frequency at T2 (adjusted model: $\beta = 0.06$, $p < 0.001$). In contrast, higher frequency of children's tics at T1 was related to higher levels of maternal depressive/anxious symptoms at T2 (adjusted model: $\beta = 0.06$, $p < 0.001$). All of these models indicated good model fit to the data (adjusted model: CFI = 0.950, RMSEA = 0.046). These results revealed that maternal depressive/anxious symptoms and children's tic frequency had longitudinal, bidirectional relationships with each other.

DISCUSSION

This was the first study to examine the longitudinal relationships between maternal depressive/anxious symptoms and children's tic frequency in a population-based early adolescent sample. The following two findings were obtained. First, when more severe maternal depressive/anxious symptoms are present, children are likely to present more frequent tics 2 years later. Second, the severity of maternal depressive/anxious symptoms and children's tic frequency are longitudinally associated with each other.

The present results showed cross-sectional relationship between maternal anxiety/depressive symptoms and children's tic frequency and small but significant longitudinal bidirectional relationship between them. Previous studies showed relationship between past maternal mental symptoms and children's TS/CT, and presumed that maternal mental symptoms are associated with the occurrence of children's TS/CT *via* maternal-specific environmental and/or genetic factors (34, 35). The present results is consistent with those previous studies and provided a new perspective that suggests longitudinal bidirectional relationship between maternal anxiety/depressive symptoms and children's tic frequency.

Several explanations may be possible for the significant magnitude-response relationship between maternal depressive/anxious symptoms and children's later tic frequency. First, maternal depressive/anxious symptoms may affect the occurrence, persistence, and exacerbation of children's tics as an environmental factor because environmental factors such as psychosocial stresses are known to exacerbate tics (55–59). In addition, several studies have shown that tic frequency can be influenced by antecedent environmental events and social consequences although they referred relatively immediate and short term reaction. For example, some activities reduce tic frequency such as focusing attention away from tics (60), aerobic exercise training (61) and participation in musical activity (62). There are no reports of an association between maternal psychiatric symptoms and the course of children's tics. However, some studies have shown an association between maternal psychiatric symptoms and the course of children's psychiatric symptoms. For example, maternal depression has been shown to be associated with increased psychiatric diagnoses and emotional and behavioral problems in children, and when maternal depression is remitted, the children's problems are more likely to also be in remission (63). Furthermore, improvement in parental depression has a positive impact on the health, emotional, cognitive, academic and overall functioning of children (64). Thus, similar to these reports, maternal depressive/anxious symptoms might affect the course of children's tics as an environmental factor. Second, there might be genetic relationships between maternal depressive/anxious symptoms and the occurrence, persistence, and exacerbation of tics. Family studies of TS have suggested that TS has genetic correlations with depressive disorders and anxiety disorders (65, 66), although these correlations are possibly mediated through ADHD and OCD (66). There has been no research examining the genetic relationships between maternal depressive/anxious symptoms and the persistence or exacerbation of tics, but the results of this research could not rule out these possibilities. Furthermore, there is also a possibility that an interaction of genetic and environmental factors is involved in the relationships between maternal depressive/anxious symptoms and children's tics. The results of this study could not distinguish genetic and environmental contributors to the relationships between maternal depressive/anxious symptoms and children's tics.

Our findings on the association between children's tic frequency and increased maternal depressive/anxious symptoms 2 years later can be explained by several potential mechanisms. One of the possible mechanisms is that the parenting stress associated with bringing up children with tics might influence maternal depressive/anxious symptoms. Parents of children with TS experience increased levels of caregiver burdens and parenting stress compared to parents of children without TS (67, 68). The visible nature of tics can have an impact on the parent-child relationship, with parents becoming overprotective

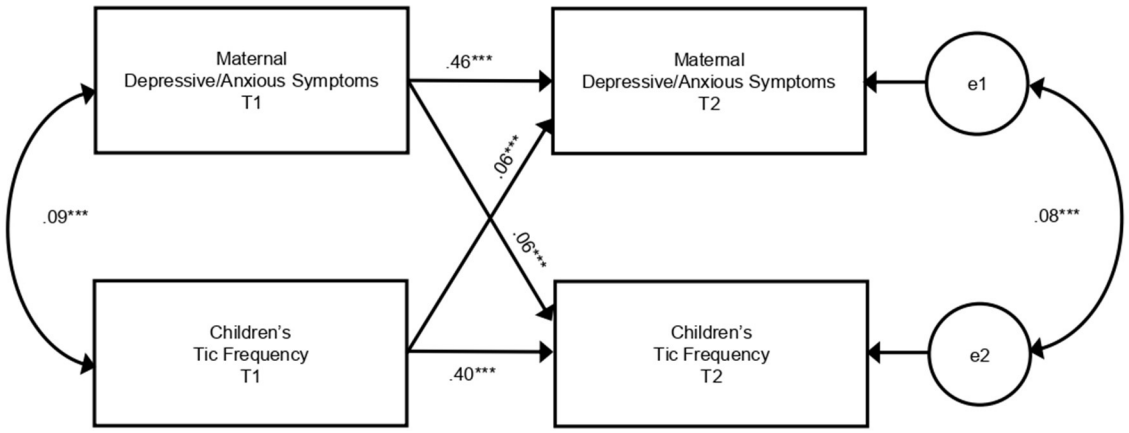

FIGURE 2 | Cross-lagged model of relationships between maternal depressive/anxious symptoms and children's tic frequency. This figure shows the results of the adjusted model in **Table 2**. Paths from covariates are omitted from the figure. e, error variable; T1, 10 years of age; T2, 12 years of age. ***$p < 0.001$.

TABLE 2 | Relationships between maternal depressive/anxious symptoms and children's tic frequency (n = 3,171).

	Unadjusted model					Adjusted model				
Path	**β**	**B**	**SE**	**95% CI**	***p*-value**	**β**	**B**	**SE**	**95% CI**	***p*-value**
Maternal depressive/anxious symptoms T1 ⇔ Children's tic frequency T1	0.10	0.50	0.10	0.31–0.70	<0.001	0.09	0.49	0.10	0.30–0.69	<0.001
Maternal depressive/anxious symptoms T2 ⇔ Children's tic frequency T2	0.09	0.52	0.12	0.28–0.75	<0.001	0.08	0.50	0.12	0.26–0.73	<0.001
Maternal depressive/anxious symptoms T1 → Maternal depressive/anxious symptoms T2	0.47	0.69	0.03	0.09–0.74	<0.001	0.46	0.68	0.03	0.63–0.73	<0.001
Children's tic frequency t1 → Children's tic frequency T2	0.41	0.39	0.02	0.35–0.42	<0.001	0.40	0.38	0.02	0.35–0.41	<0.001
Maternal depressive/anxious symptoms T1 → Children's tic frequency T2	0.06	0.03	0.01	0.01–0.05	<0.001	0.06	0.03	0.01	0.01–0.04	<0.001
Children's tic frequency T1 → Maternal depressive/anxious symptoms T2	0.07	0.20	0.05	0.10–0.30	<0.001	0.06	0.19	0.05	0.09–0.30	<0.001
	$\chi^2 = 0$, Degrees of freedom = 0, p = -, CFI = 1.0, RMSEA = 0 (saturated model)					$\chi^2 = 77.834$, Degrees of freedom = 10, $p < 0.001$, CFI = 0.950, RMSEA = 0.046				

T1, 10 years of age; T2, 12 years of age; β, standardized coefficient; B, coefficient; SE, standard error; CI, confidence interval; CFI, comparative fit index; RMSEA, root mean square error of approximation.

of, worrying about, struggling to accept or trying to control children's tics, which can lead to family conflicts, poor parent-child relationships and increased frustrations in parenting (7, 9, 10, 69, 70). Parenting stress in parents of children with tics could also occur due to children's comorbidities, such as ADHD, OCD, and behavioral problems (67, 68). In a previous population-based study, 21.2% of children had tics, and children with tics were more affected by psychopathologies, including ADHD and OCD, than were children without tics (12). In addition to these environmental factors, both genetic factors and genetic/environmental interactions might have an effect of children's tics on maternal depressive/anxious symptoms.

The implications of this study were that the longitudinal bidirectional relationships between maternal depressive/anxious symptoms and children's tic frequency may suggest a vicious cycle in which maternal depressive/anxious symptoms make tic frequency increased, and children's tic frequency make maternal depressive/anxious symptoms worse. This study also suggested that not only intervention in children's tics but also intervention in maternal depressive/anxious symptoms might be important for the treatment of tics. However, the present study was unable to separate genetic and environmental factors in the association between children's tic frequency and maternal depressive/anxious symptoms; therefore, further research is needed to determine the effect of intervention on maternal anxiety/depressive symptoms.

While there has been a consensus on the importance of family psychoeducation in the treatment of tics (7, 27), it is not known whether maternal psychiatric problems influence the course of children's tics. This study provides new insights for future research and practice.

The strength of this study was that, for the first time, it was shown that higher levels of maternal depressive/anxious symptoms are related to an increased children's tic frequency 2 years later and that there are longitudinal relationships between maternal depressive/anxious symptoms and children's tic frequency. Other strengths were the large sample size, the high follow-up rate of the study, and the inclusion of non-clinical tics. In contrast, this study also had several limitations. First, we used different measures of maternal depressive/anxious symptoms for T1 and T2. We found that the distributions of the K6 and the GHQ-28 were similar by graphing the cumulative distribution of the *Z* scores of the K6 and the GHQ-28 (**Supplementary Figure 1**). Additionally, this limitation did not influence the course from maternal depressive/anxious symptoms to children's tic frequency. Second, in this study, children's tics were evaluated not by direct clinical assessments but by questionnaires to caregivers. However, we deliberately chose rigorous tic definitions and sought to exclude participants with non-tic movement disorders (e.g., stereotypies associated with autism or an intellectual disability, repetitive arm/leg movements that could be better explained by tremor, or motor restlessness) (5). In this study, the prevalence of tics was 23.3% at age 10 and 23.5% at age 12. These prevalence rates could be considered reasonable based on the following evidence. Point prevalence depends strongly on age; the highest rate is estimated to be approximately 20% at age 5–10, and the lifetime prevalence is much higher (3). In previous studies that have directly observed children, tics were found in 29.2% of fourth-grade children in an elementary school in Washington D.C. (2) and in 21.2% of children aged 9–17 years old (mean 13.1 years old) in Monroe County, Rochester, New York (4). The prevalence rates of tics in the present study were consistent with those found in these previous studies. Third, the data analysis in this study could not adjust for ADHD and OCD, which are frequently comorbid with tics. That may be because of the strong association of tics with ADHD and OCD. Future studies are needed to examine the effects of ADHD and OCD on the bidirectional relationships between maternal depressive/anxious symptoms and children's tic frequency. The fourth limitation was that the research interval in this longitudinal study was relatively short. Typically, tics improve gradually during adolescence, with repeated periods of remission and exacerbation. Thus, it might be difficult to capture change in the short research period of 2 years. Longer-term follow-up periods are needed in the future. The fifth limitation was that we did not collect information about the maternal history of tics. Given the low rate of medical consultation for tics (5, 12, 65) and the clinical outcome that tics often improve or disappear after adolescence (7, 13, 14), it is probably not possible to obtain accurate information on the maternal history of tics. Finally, there were also some limitations inherent to the cross-lagged model (71); i.e., there is a possibility that there are multiple potential additional factors (not included in the model) that influence the bidirectional relationship over time.

The following two studies would be helpful in testing the viability of the relationships between maternal depressive/anxious symptoms and children's tic frequency and in advancing research and practice. First, if the course of children's tic frequency could be observed at three or more time points, it would be possible to confirm the vicious cycle that develops between maternal depressive/anxious symptoms and children's tics and to investigate the mediating factors. For example, children's anxiety/depression symptoms might mediate the relationships between maternal depressive/anxious symptoms and children's tic frequency. In addition, comorbidities or poor quality of life might mediate the relationships between children's tic frequency and maternal depressive/anxious symptoms. Second, intervention studies could examine whether improvements in maternal depressive/anxious symptoms improve children's tics.

This study was the first to show the relationship between preceding maternal depressive/anxious symptoms and an increased children's tic frequency 2 years later in early adolescence. Furthermore, we found longitudinal bidirectional relationships between maternal depressive/anxious symptoms and children's tic frequency. Although we could not separate environmental factors and genetic factors in this research, the findings implied that it may be important to care not only for children with tics but also for their mothers' depressive/anxious symptoms when tics are treated in early adolescence.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Tokyo Metropolitan Institute of Medical Science (Approval Number: 12-35), the Graduate University for Advanced Studies, SOKENDAI (2012002), the Graduate School of Medicine and Faculty of Medicine, the University of Tokyo (10057). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TY conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript, and being supervised by SA. AN, SY, YK, and KK critically reviewed the manuscript for important intellectual content and contributed to the discussion. SU supervised the statistical analysis. All authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.767571/full#supplementary-material

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The Association Between Family Function and Adolescents' Depressive Symptoms in China: A Longitudinal Cross-Lagged Analysis

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The complex interrelationships between family function and adolescents' depressive symptoms are not yet fully clarified, especially in China. Based on the family systems theory, this study explored the relationships between family function and Chinese adolescents' depressive symptoms by a 3-year longitudinal study design. Three waves of data were collected from 1,301 Chinese middle school students in Grade 7 to Grade 9. All participants completed the Chinese Family Assessment Instrument (CFAI) and the Center for Epidemiologic Studies Depression Scale (CES-D) once a year during the junior middle school period. Our results showed that both family function and adolescent depressive symptoms were stable in Grade 7 and Grade 8, but in Grade 9, family function increased and depressive symptoms declined. Furthermore, we found that the family function in Grade 7 negatively influenced depressive symptoms of adolescents in Grade 8, while adolescent depressive symptoms in Grade 8 negatively impacted subsequent family function in Grade 9, namely there was a circular effect between family function and adolescent depressive symptoms. These findings suggest that the associations between family function and adolescents' depressive symptoms are dynamic and time-dependent. Our study contributes to the intervention aimed at the reduction of adolescent depressive symptoms from the family perspective.

Keywords: adolescents, family function, depressive symptom, cross-lagged analysis, circular effect

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INTRODUCTION

Depression has become an alarming health issue among adolescents, with typical symptoms such as feelings of sadness, decreased interest, and suicidal thoughts (1, 2). In China, previous reports from the National Health Commission (3) pointed that, ∼30 million teenagers exhibited varied degrees of emotional disorders, with depressive symptoms the most common. A recent study showed that the prevalence rates of depressive symptoms among early adolescents are rising rapidly, up to an astonishing incidence rate of 24.3% (4). As a prevalent psychological disorder, adolescent depression was significantly associated with a series of impairments in cognitive, psychological and social functioning, such as academic failure (5), interpersonal problems (6), and even self-injury and suicide (7, 8). Evidence from the Scar Hypothesis of depression had also assumed

that depressive symptoms had a long-lasting deleterious effect on adolescents' self-concept and personality, leaving a "scar" on an individual's self-esteem (9–11). Furthermore, going through depression during early adolescence could even result in an increased risk of other health issues in adulthood (12–14).

Given these negative effects of adolescent depression, substantial researches have addressed which factors are implicated in the deterioration of depressive symptoms. Existing evidence suggests that both individual and environmental characteristics have made their contributions to adolescents' depressive symptoms (15, 16). Among these factors, the family function has drawn substantial attention due to its vitally important role in adolescent development (17–19). However, previous studies focused more on the unidirectional effect of family function on adolescents' depressive symptoms (16, 20), giving less consideration to the potential negative effect of adolescent depressive symptoms on the whole family system and the potential bidirectional relations between them. Additionally, the majority of them adopted cross-sectional data (21, 22), or short-term longitudinal data (23), from which the dynamic interaction between family functioning and adolescent depressive symptoms could not be well-demonstrated. Therefore, it is particularly necessary to conduct a longitudinal study to clarify the possible dynamic association between family function and adolescent depressive symptoms, especially in the Chinese context, where people take the family of great importance.

The family function generally indicates the quality of family life involving a family's competence, wellness, as well as strengths and weaknesses (24). Taking the family system as a whole, this concept is above and beyond both the dual parent-child relationship and the binary conjugal relationship (25). Family function encompasses three core dimensions: mutuality, communication, and harmony (26), which have been extensively employed in the related studies of the family domain (27, 28). A large body of studies has revealed that family function plays a critical role in an individual's healthy development. For example, one prospective study showed that harmonious family relationships and good parent-child communication could significantly promote positive developmental attributes (28), which is expected to be beneficial for the academic achievement of adolescents (29). On the contrary, teenagers who live in an impaired family are more likely to experience internalizing problems such as depression, anxiety, and withdrawal (30), and show externalizing problems such as antisocial, aggressive and disobedient behaviors (31).

To date, numerous studies have been conducted to investigate the relationship between family function and adolescent depressive symptoms, in which scholars found that these two factors were negatively correlated (32, 33). As for the direction of the association between them, the majority of extant studies supported the family-driven effect (family function influences adolescent depressive symptoms), in which researchers regard family function as an important predictor of adolescent depressive symptoms. For example, some scholars found that adolescents living in highly dysfunctional families were prone to have negative self-cognition, which was a key trigger to the emergence of depressive symptoms in adolescents (34, 35). Similar results were found among teenagers in China (36, 37). A recent Chinese study, using a sample of 11,865 adolescents, has also found that impaired family function might increase the risk of adolescent internalizing problems like depression, and researchers further point out that the influence of family function on adolescent depression was partly mediated by positive youth development attributes (28). With the awareness of the dynamic development of adolescent depressive symptoms, some scholars began to pay attention to the longitudinal influence of family factors (e.g., family relationships, family social support, and family functioning) on depressive symptoms (38, 39). For instance, one current research found that poor family functioning at baseline could significantly predict depressive symptoms of junior high school students 1 year later (16). Nonetheless, the above studies have the common point of treating family function as a static antecedent variable, failing to address the potential reverse influence from the adolescent depressive symptoms to the whole family.

According to the family systems theory (40, 41), the plight of the family systems could induce the occurrence of individual psychological problems, individual mental health problems might also put the family at risk, resulting in poorer communication, worse cohesion, and more conflicts and arguments (23). Thus, apart from the family-driven effect, there might be still two possible effects: the child-driven effect (adolescent depressive symptoms influence family function), and the potential reciprocal effect (reciprocal influence of family function and adolescent depressive symptoms). Although early studies have demonstrated the destructive effects of individual mental distress on the family, most of them used clinical samples. For example, a study using 424 depressed patients indicated that more severe depressive symptoms were positively related to subsequent more family arguments for both men and women (42). In fact, for depressed adolescents, their emotional problems might also damage the family function. The "below" pressure hypothesis also provides some insight into this child-driven effect (43). It assumes that adolescent maladjustment such as depressive symptoms could serve as the "below" pressure, putting a huge strain on their parents. Thus, family conflict might be introduced (44), and the negative emotions would further spread through the whole family (45), hindering the family system from functioning well. However, as far, empirical researches examining the child-driven effect among the subclinical adolescent samples were relatively rare. From childhood to adolescence, early adolescents experienced great change on cognitive, emotional, and social levels. During this special turning period, the development risk of internalization or externalization of adolescents greatly increased (46, 47), which will undoubtedly put the whole family under pressure (48, 49). Especially when adolescents experienced emotional problems, the function and satisfaction of the family were threatened (23, 50).

Theoretically, the relationship of family factors and individual emotional distress was likely bidirectional in nature. In fact, a handful of studies have supported the reciprocal effect. For example, in a 3-year longitudinal study that involved 451 early adolescents and their families, researchers found a reciprocally interrelated association of marital conflict and

adolescent depressive symptoms (51). Likewise, other scholars also found a significant cross-lagged relationship between parent-child hostility and adolescent depression for mother and daughter (52). However, those studies were mainly conducted in particular dyadic or family subsystems. Empirical evidence on the reciprocal linkage between family function (on the whole family system level) and adolescent depressive symptoms is insufficient and inconsistent. Based on both Victoria and Washington samples in America, Kelly et al. (50) found that family conflict and adolescent depressed mood were bidirectionally linked over time, which was independent of the factors outside the family, such as school bullying or academic performance. Whereas, in a more recent study, Mastrotheodoros et al. (23) fail to certify the reciprocal model, with results in the cross-lagged panel models showing a unidirectional association from internalized problem to family functioning at the 6-month time interval. Since these studies were carried out based on the context of Western culture, we still know little about the cause or effects of family function on Chinese teenagers' depressive symptoms. As a country emphasizing collectivism, Chinese youth are deeply influenced by family (53). The role of the family in the development of adolescents is particularly prominent, and different from that of western culture in many respects (54, 55). Therefore, it is certainly worthy to reveal the longitudinal relationship between family function and Chinese adolescent depressive symptoms in a relatively long period of time.

Guided by the family system theory, the present study adopts a 3-year longitudinal tracking design, attempting to investigate the possible longitudinal associations between family function and adolescent depressive symptoms in the context of Chinese culture. The current study is anticipated to offer some implications for the intervention to interrupt the progression of adolescents' depressive symptoms, as well as the improvement of their family function. The hypotheses of this study are as follows: (i) family function and depressive symptoms would change during the three junior high school years; (ii) family function significantly affect adolescent depressive symptoms; (iii) adolescent depressive symptoms significantly influence family function; (iv) family function and adolescent depressive symptoms might have a reciprocal relationship.

MATERIALS AND METHODS

Participants

Data for the current study were based on three measurement waves, which were collected in October 2016 (T1; when adolescents just entered into junior school), 1 year later (T2; when adolescents had spent 1 year in junior school) and 2 years later (T3; when adolescents were in junior grade three). We conducted surveys in five middle schools from nine districts in Shenzhen, Guangdong Province, China by random selection. At the first wave, 1,544 adolescents with a mean age of 12.46 years old (SD = 0.63) participated in the initial study. At the subsequent waves, the sample sizes of participates were 1,511 for T2, and 1,480 for T3, respectively. Non-response at T2 and T3 was mainly for the reason that these students were absent during the survey days or they had moved to other schools. Therefore, our final analytical sample included a total of 1,301 students who completed all the items of two main study variables at three measurement waves.

Procedure

Adolescents were invited to attend a paper-and-pencil test in classroom settings during regular school hours. Before each measurement, research assistants introduced the aim of the study, the procedures of the test, as well as the confidentiality safeguards. After receiving this information, students decided to participate in or withdraw from the study. If they agreed upon participation, adolescents and their parents should provide informed consent. At all measurements, written informed consent was obtained. The research assistants were present during the 20-min test to supervise the whole data collection, and answer students' questions about the test at every wave of surveys. No compensation was offered to the participants. Both the Human Research Ethics Committee of the affiliated institution and the administrative committees of the surveyed schools approved the questionnaires and procedures.

Instruments

Chinese Family Assessment Instrument

The refined version of the Chinese Family Assessment Instrument was used to measure adolescents' family function (26). This scale contains 9 items, with each of the three items measuring mutuality, communication, harmony and conflicts, respectively. A sample item for mutuality sub-scale is "My family lives in harmony," for communication sub-scale is "In general, parents and children often have conversations," and for harmony and conflicts sub-scale is "We have a lot of friction." Participants were instructed to rate each item from 1 ("very dissimilar") to 5 ("very similar"). After reversing the conflict sub-scale scores, the means of the nine items were computed, with a higher score representing a healthier family function. In this study, the Cronbach's alpha coefficient of the CFAI was 0.86 at Time 1, 0.85 at Time 2, and 0.89 at Time 3.

Center for Epidemiologic Studies Depression Scale

Adolescent depressive symptoms were assessed using the Chinese version of the Center for Epidemiological Studies Depression Scale (56, 57). It consists of 20 items, with a Likert rating scale from 0 to 3, representing "rarely or none of the time," "sometimes [1–2 days]," "often [3–4 days]," "most or all of the time [5–7 days]," respectively. An example is "I was bothered by things that usually don't bother me." Participants make choices on each statement to assess the frequency they had experienced these depressive symptoms in the last week. Participants who scored higher in the CES-D were considered to have a higher level of depressive symptoms. In the current study, the Cronbach's alpha coefficients for the CES-D at Time 1, Time 2, and Time 3 were 0.85, 0.85, and 0.88, respectively.

Demographic Variable

Adolescents' demographic information were measured by a questionnaire including the adolescents' gender (1 = boy and

TABLE 1 | Demographic characteristics of participants.

	n (%)/ mean (SD)	
Age (years)	12.46	0.63
Sex		
Male	666	51.19%
Female	621	47.73%
Missing	14	1.08%
Only child		
Yes	499	38.36%
No	799	61.41%
Missing	3	0.23%
Place of birth		
City	1,141	87.70%
Rural	158	12.14%
Missing	2	0.15%
Father's education level		
Junior school and below	404	31.05%
Senior school	451	34.67%
Bachelor's degree	226	17.37%
Above a bachelor's degree	120	9.22%
Missing	100	7.69%
Mother's education level		
Junior school and below	492	37.82%
Senior school	427	32.82%
Bachelor's degree	217	16.68%
Above a bachelor's degree	74	5.69%
Missing	91	6.99%
Per capita monthly family income (CNY)		
<1,000	27	2.08%
1,000∼1,999	81	6.23%
2,000∼2,999	135	10.38%
3,000∼3,999	169	12.09%
4,000∼4,999	121	9.30%
5,000∼5,999	127	9.76%
6,000 or above	439	33.74%
Missing	202	15.53%

2 = girl), age, place of birth (1 = rural area, 2 = Shenzhen, and 3 = other cities), only child or not (1 = only-child, 2 = non-only child), parents' education level (1 = middle school or below, 2 = high school or vocational college, 3 = university, and 4 = above university), and per capita monthly family income (CNY) (1 = <1,000, 2 = 1,000∼1,999, 3 = 2,000∼2,999, 4 = 3,000∼3,999, 5 = 4,000∼4,999, 6 = 5,000∼5,999, 7 = 6,000 or above). **Table 1** summarizes the demographic characteristics of participants.

Data Analysis

As usual, we input all data into the SPSS25.0. Then, the means and standard deviations of the two main study variables were computed, and one-way repeated measures ANOVA was applied to examine the changes in family function and depressive symptoms across the three-time points. We also calculated correlations between family function and depressive symptoms. Next, since the current study adopted a repeated-measure design, measurement invariance testing was conducted to examine if the constructs of family function and depressive symptoms kept invariant over 3 years. After doing this, we performed an auto-regressive cross-lagged (ARCL) model to check the effects of family function and adolescent depressive symptoms in Mplus 8.3. ARCL analyses contained both cross-lagged effects and autoregressive effects. It allowed us to examine the potential influence of one construct (e.g., family function) on another (e.g., depressive symptoms) at a later time point (cross-lagged effects), controlling for the regression of both constructs on themselves assessed at the previous time points (auto-regressive effects). In ARCL analysis, demographic variables were taken as covariates. Due to the non-response on several demographic variables for some adolescents, the full information maximum likelihood (FILM) estimation for unbiased estimates was used to handle the missing demographic data (58).

To examine the goodness of model fit, a series of criteria were estimated, including chi-squared index, comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA) with 95% confidence intervals (95% CI), and standardized root mean square residual (SRMR). We considered the model fit acceptable if 1) normed chi-square (χ^2/df) was <5; 2) the values of CFI and TLI were more than 0.90; 3) the values of RMSEA and SRMR were <0.08 (59). Additionally, because that family function and depressive symptoms were self-reported by the adolescents themselves, there might exist common method biases in the present study. Thus, we conducted Harman's single-factor test to examine the possible common method variance (60).

RESULTS

Testing of Common Method Variance

The Harman's single-factor analysis was for the test of the common method variance effect. The results showed that 6, 5, and 5 factors had eigenvalues >1 for the three time-point assessments, and that the rates of the first factors accounting for the amount of variation were all below 40% (25.36, 24.87, 32.46%, respectively). These results indicated that the common method biases could be ignored in this study.

The Development Trend of Family Function and Adolescent Depressive Symptoms Over 3 Years

One-way repeated measures ANOVA was used for the difference of family function and adolescent depressive symptoms among the three measurement times, respectively (see **Table 2**). For family function, a significant time effect was observed, $F_{(1.93,\ 2510.36)} = 14.47$, $p < 0.001$. Pairwise comparisons indicated that the difference of family function scores was not significant between T1 and T2 ($p > 0.05$), but the scores of family function at T3 were significantly higher than T1 ($p < 0.001$) and T2 ($p <$

TABLE 2 | Descriptive statistics for family function and depressive symptoms.

Time	Family function		Depressive symptoms	
	M	SD	M	SD
T1	4.07	0.77	13.66	9.15
T2	4.04	0.79	13.76	9.33
T3	4.17	0.77	12.40	9.31

T1, Time 1 (first year); T2, Time 2 (second year); T3, Time 3 (third year).

0.001). For adolescent depressive symptoms, a significant effect of time was observed, $F_{(1.94,\ 2525.51)} = 12.53$, $p < 0.001$. Further analyses showed that the difference of adolescent depressive symptoms scores was not significant between T1 and T2 ($p > 0.05$), while the scores of adolescent depressive symptoms at T3 were significantly lower than T1 ($p < 0.001$) and T2 ($p < 0.001$).

Analysis of Correlation Between Family Function and Adolescent Depressive Symptoms

Table 3 showed the correlation coefficient between family function and adolescent depressive symptoms in the three surveys. The results revealed that family function significantly negatively correlated with adolescent depressive symptoms both synchronously and longitudinally. The synchronous correlation coefficient ranged from −0.30 to −0.47, and the longitudinal correlation coefficient ranged from −0.13 to −0.30. The preliminary findings suggested that the adolescent depressive symptoms arise as the family function declined, and vice versa. Additionally, adolescent depressive symptoms were positively associated with each other during 3 years, with the correlation coefficient ranged from 0.25 and 0.42. Meanwhile, family functions were positively to each other over the 3 years, with the correlation coefficient ranged from 0.26 to 0.43.

Measurement Invariance of Family Function and Depressive Symptoms

Measurement invariance of the two main study variables at three-time points was examined. The configural invariance model (M0), factor loading invariance model (M1) and residual invariance model (M2) of family function and depressive symptoms were established, respectively. For family function and depressive symptoms, the fitting indexes of each model were all met the criteria (see **Table 4**). On the advice of Cheung and Rensvold (61), compared with chi-square values, ΔCFI was a more stable indicator for model comparison since it is less influenced by model parameters and sample size. Therefore, this study used the Δ CFI index for model comparison. If Δ CFI is >0.01, we declined to the hypothesis of measurement invariance (61). In this study, model comparison results suggested that both family function and depressive symptoms showed measurement invariance across three-time points (Δ CFI < 0.01). Thus, the cross-lagged analysis could be carried out in the next step.

Autoregressive Cross-Lagged Analysis of Family Function and Adolescent Depressive Symptoms

First, adopting the unique information method (62), we packaged family functions into three observed items (mutual relationship, communication and adaptation, conflict and harmony), and depressive symptoms into four observed items (depression, positive emotion, somatic symptoms, and interpersonal problems). Then, we employed structural equation modeling (SEM) with latent variables to analyze the cross-lagged relationship between family function and adolescent depressive symptoms. Since previous studies have shown that demographic variables such as gender, age, place of birth, only child or not, parents' education level, and per capita monthly family income were highly correlated with family function and adolescent depressive symptoms (16, 63, 64). In this study, those variables were put in the model as control variables, thus we could exclude the potential influence on them. In the autoregressive cross-lagged model, we also allowed the synchronous correlations among the two latent variables, and the error correlation of the same observed variables at the three measurements. The model fitted data well: $\chi^2/df = 4.07$, $p < 0.001$, CFI = 0.93, TLI = 0.91, RMSEA = 0.05 (90% CI = [0.046, 0.052]), SRMR = 0.08. **Figure 1** showed the standardized path coefficients. To simplify the model, the predictive pathways of the control variables for the family function and adolescent depressive symptoms at the three-time points are not shown in **Figure 1**.

The results suggested that gender (β = 0.06, $p < 0.05$), father's education level (β = 0.11, $p < 0.05$), and per capita monthly family income (β = 0.08, $p < 0.05$) had a significant predictive effect on T1 family function. The predictive coefficient of gender for T1 and T3 adolescent depressive symptoms was significant (β = 0.08, $p < 0.05$; β = 0.15, $p < 0.001$, respectively). Father's education level had a significant predictive effect on T2 adolescent depressive symptoms (β = −0.09, $p < 0.05$), and only child or not also had a significant predictive effect on T3 adolescent depressive symptoms (β = −0.08, $p < 0.01$). After controlling for the influence of demographic variables, the autoregressive path coefficients of family function were 0.29 and 0.25, respectively; and the autoregressive path coefficients of adolescent depressive symptoms were 0.24 and 0.23, respectively. These results indicated relatively strong autoregressive effects for both family function and adolescent depressive symptoms over 3 years. As for the cross-lagged effects, family function at T1 significantly and negatively predicted adolescent depressive symptoms at T2 (β = −0.09, $p < 0.01$), and adolescent depressive symptoms at T2 significantly and negatively predicted family function at T3 (β = −0.07, $p < 0.05$). However, the prediction of adolescent depressive symptoms at T1 on family function at T2 was not significant, and the prediction of family function at T2 on adolescent depressive symptoms at T3 was also not significant.

DISCUSSION

From the perspective of family system theory, the current study adopted three waves of longitudinal data with a 3-year time lag to

TABLE 3 | Correlations of family function with adolescent depressive symptoms.

Variables	T1 FF	T2 FF	T3 FF	T1 Dep	T2 Dep	T3 Dep
T1 FF	1					
T2 FF	0.26**	1				
T3 FF	0.43**	0.24**	1			
T1 Dep	−0.37**	−0.13**	−0.30**	1		
T2 Dep	−0.19**	−0.30**	−0.16**	0.25**	1	
T3 Dep	−0.29**	−0.13**	−0.47**	0.42**	0.25**	1

*T1, Time 1 (first year); T2, Time 2 (second year); T3, Time 3 (third year); FF, Family Function; Dep, Depressive symptoms. **$p < 0.01$.*

TABLE 4 | Model fitting results of measurement invariance for family function and depressive symptoms.

	χ^2	df	*p*	CFI	TLI	RMSEA (90% CI)	SRMR	ΔCFI
FF								
M0	36.388	15	<0.001	0.995	0.989	0.033 (0.019, 0.047)	0.027	
M1	65.291	19	<0.001	0.990	0.981	0.043 (0.032, 0.055)	0.046	0.005
M2	69.999	23	<0.001	0.990	0.984	0.040 (0.029, 0.050)	0.046	0.000
Dep								
M0	81.748	39	<0.001	0.993	0.988	0.029 (0.020, 0.038)	0.029	
M1	98.411	45	<0.001	0.991	0.987	0.030 (0.022, 0.038)	0.032	0.002
M2	153.583	51	<0.001	0.984	0.979	0.039 (0.032, 0.047)	0.034	0.007

FF, Family Function; Dep, Depressive symptoms; M0, configural invariance model; M1, factor loading invariance model; M2, residual invariance model.

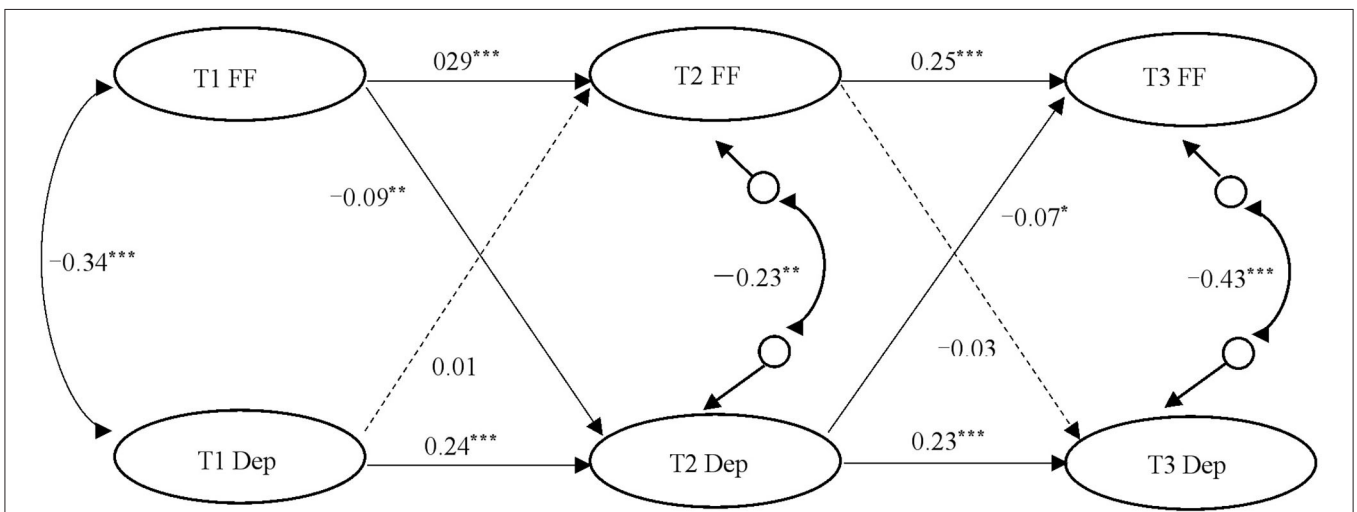

FIGURE 1 | The ARCL model of family function and adolescent depressive symptoms. T1, Time 1 (first year); T2, Time 2 (second year); T3, Time 3 (third year); FF, Family Function; Dep, Depressive symptoms. Solid line = significant coefficient; Dotted line = non-significant coefficient. All coefficients were standardized. Control variable was not exhibited in the figure for the simplicity of the model. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

examine the relationship between family function and depressive symptoms among Chinese middle school-aged adolescents. Our study found that both family function and depressive symptoms in adolescents were stable in Grade 7 and Grade 8. However, in Grade 9, there was a significant increase in family function, but a significant decline for adolescent depressive symptoms. The results of the cross-lagged analysis reveal that the associations between family function and adolescent depressive symptoms are dynamic and time-dependent: the family function in Grade 7 negatively influences depressive symptoms of adolescents in Grade 8, after being affected, adolescent depressive symptoms in Grade 8 could also negatively impact subsequent family function in Grade 9. In other words, there is a circular effect between family function and adolescent depressive symptoms.

In our study, we found a slight decrease in family function and a subtle increase in adolescent depressive symptoms between

Grade 7 and Grade 8, but neither of them was significant. However, compared to the first 2 years, there were significant changes in family function and adolescent depressive symptoms in Grade 9. In the last year of junior high school, adolescent depressive symptoms significantly declined and their family functioning significantly increased. These findings supported our hypothesis (i). Our results were not consistent with previous studies based on western samples (23, 50), but they were in line with recent researches conducted in China (65, 66). For example, Sun et al. (65) followed 1,419 Chinese junior high school students from thirteen junior middle schools in Beijing for 3 years and found that depressive symptoms in junior high school students was relatively stable from the first to the second year but declined significantly in the third year. Another study, using Chinese rural junior middle school students, also found that family functioning was significantly higher in the third year than in the first and second years (66). Our findings indicate that both family function and adolescent depressive symptoms have their unique developmental characteristics in China.

Regarding the change of family function, possible explanations are that families have to adapt to the children's transition from primary school to secondary school, and they also need to accommodate to students' growing needs for independence and autonomy (48). These may lead to comparatively low family functioning during Grade 7 to Grade 8. At Grade 9, the preparation for senior high school entrance examination in China may enhance autonomy support from parents, promote family harmony, and reduce conflict in the family, thereby making the entire family function more properly. Several reasons for the development trend of adolescent depressive symptoms are as follows. During Grade 7 to Grade 8, students have to adapt to the new peers and new teachers as well as confront the challenges of self-development tasks like self-identity confusion (67), so the depressive symptoms are relatively high. After entering Grade 9, apart from the special attention on entrance examination that makes adolescents regulate their mood to concentrate on learning, the matures of physical and mental development may also contribute to the natural decrease of mild or moderate depressive symptoms in adolescents (68). In addition, our study also showed that family function was significantly and negatively associated with adolescents' depressive symptoms at the same measuring point during three school years. The significantly negative correlation between them also suggests that the two variables share many common changes and have a close linkage.

The results of cross-lagged analysis showed that the impaired family function significantly predicted adolescent depressive symptoms from Grade 7 to Grade 8, which supports our hypothesis (ii). This result is consistent with most previous studies showing that family dysfunction, including more family conflict, lower levels of interactions with parents, and poor family relationships, is a risk factor for adolescents' internalizing problems (28, 37, 69). Early adolescence is a susceptible period for individuals to develop anxiety, depression, and other psychological problems (70). Adolescents who living in an unhealthy family have to cope with various negative life events, which would trigger a series of stress that negatively influencing their cognitive style, leading them slide into depression (71). Meanwhile, a poor family function is also a hazard factor that hampers the development of positive psychological resources (e.g., resilience, cognitive ability, emotional regulation ability) in adolescents (28). These resources are considered as strengths to help adolescents overcome adverse situations and stay away from depression (72, 73). Furthermore, emotional security theory also contends that family instability and interparental conflict could induce the emotional insecurity of children in the family, lead to boosted fear, vigilance and distress, and further contribute to a greater likelihood of emotional problems, including depressive symptoms (74, 75).

Interestingly, our study found no significant effect of family function at Grade 8 on adolescent depression at Grade 9. We speculate that, in early middle school years, family functioning may have a strong effect on adolescent internalizing problems. As adolescents become mature, its influence on adolescents might gradually diminish due to the growing demand for autonomy and independence, as well as the increasing importance of peer relation (76, 77). Furthermore, in the current study, we discovered the opposite direction of predictive effect from adolescent depressive symptoms to family function, supporting our hypothesis (iii). The late appearance of the child effect is in agreement with several longitudinal studies showing that adolescents play a stronger role in the development of their families as children grow older (77). For instance, Georgiou and Fanti (78) found that the relationship between child's behavior problems and mother-child conflict was bidirectional at early ages. But, as time passed by, "child effects" become stronger compared to "parent effects." Two possible explanations might help us understand the emergence of the child effect. On one hand, in contrast to "upper" pressure from the social environment, adolescent depressive symptoms, as a source of "below" pressure from children's behavior problems, may elicit more intrusive parenting and produce more parenting stress (79, 80). Thus, adolescent depressive symptoms would influence the parent-child relationship and even damaging the communication among family members (48, 49), making the whole family system get into dysfunctional states (48, 49). On the other hand, emotional problems (such as anxiety, depression, etc.) are easily contagious among households' members (45), which may change the whole atmosphere of the family and reduce the cohesion and adaptability of the family. Therefore, during the later middle school years, when the influence of adolescent depressive symptoms on the family has accumulated to a certain degree after a period of time, adolescent depressive symptoms turn to "erode" and "damage" family function.

Although the cross-lagged analysis results indicate that both family function and adolescent depression can serve as a cause and a consequence, the direction of associations between family function and adolescent depression depend on time. That is to say, during the early middle school year, adolescents are easier to get depressed because of impaired family function. But in the later middle school year, adolescents who experienced more depression are more likely to get a decline in their family function. Thus, the results suggest that there is an unexpected circular effect rather than the hypothetical reciprocal effects, thus

hypothesis (iv) is not verified. Our findings are not in line with the earlier research finding bidirectional effects between family conflict and adolescent depressive mood (50), as well as the previous research of western adolescents that only discovered a significant effect of childhood behavior problems on family functioning, but not vice versa (23). Our study has unfolded a more comprehensive picture of the dynamic reciprocity between family function and adolescent depressive symptoms, consistent with developmental contextualism emphasizing the interaction between organism and context on development (81). Differences, such as the interval of tracking (i.e., 6 vs. 12 months) and considered covariates (i.e., exclude vs. include of transition) may offer explanations for these inconsistencies between our results and those studies conducted on western culture (23, 50). Of note, in the current study, we found significant predictive effects of family function on adolescent depressive symptoms from Grade 7 to Grade 8, as well as adolescent depressive symptoms on family function from Grade 8 to Grade 9, both with relatively small coefficients (−0.09 and −0.07). Indeed, in longitudinal studies, since the medium predictive effects of a predictor on the outcome are greatly attenuated by the strong stability in the outcome, it is not at all surprising that even the small effect sizes were not trivial, but still meaningful after controlling for the stability effects (82).

Several limitations should be cautiously taken into consideration in this study. First, the results of this study relied on adolescent self-report. This may result in biased outcomes, considering that depressed mood could affect adolescents' perceptions of family conflict and mutual relationships (83). Future studies may take other assessment methods such as observer-rating (e.g., McMaster Clinical Rating Scale) to provide a more objective understanding of family functioning (84). Second, our study only tracked three waves from Grade 7 to Grade 9, thus we may not capture the school transition, such as from primary school to middle school or from middle school to high school, during which great change occurs both for adolescents and the family (85, 86). Future research is necessary to explore the relationship patterns between family function and adolescent depressive symptoms using more data waves including the critical school transition period. Third, the present study has only examined the dynamic interplay between family function and adolescent depressive symptoms. In future studies, it is worthwhile to see if these associations would change due to some socio-demographic factors such as gender (girl vs. boy) or socioeconomic status (economic advantage vs. economic disadvantage). Positive traits of individuals (e.g., resilience) or contextual variables (e.g., peer support) also need to be examined to identify possible buffers between family functioning and adolescent depressive symptoms. Last but not the least, our results were based on a sample of middle school students in China belonging to a collectivistic culture, which may show the influence of cultural differences (54). More data are needed from other cultures to verify the cultural uniqueness of the development trend of family functioning and adolescent depressive symptoms and the interrelationships between them. Additionally, we also need to notice that the auto-regressive cross-lagged models introduce an inherent problem of between- and within-person associations not being disaggregated, which would influence the interpretability of our results.

Despite these limitations, our study contributes to the family-child relations literature by supporting an intertwined developmental relationship of family function and adolescent depressive symptoms. This research also provides an important addition of how such relationships could depend on time, which implying that researchers and practitioners should emphasize different points in different periods when it comes to practice. In the early middle school year, considering the protective impact of family function on adolescent mental health, it is particularly crucial that families should try their best to create an enabling and harmonious environment to prevent their children from mental disorders. While at the late stage of middle school, given the influence of adolescent depressive symptoms on the family system, it is urgently demanded for parents and other family members to understand depression and its effects fully and deeply, thus avoiding excessive erosion of adolescent depressive mood on the whole family. Meanwhile, in view of the interrelated nature of family and adolescents, the role of school and government must not be ignored. For those adolescents living in dysfunctional families, schools should try to reduce the harm caused by adverse family environments via a variety of methods. For instance, schools could educate teenagers on emotional regulation strategies, guide them to adjust negative self-cognition and self-evaluation, cultivate their positive traits. While the government should take supportive policies for healthy family function and promote family education to maximize these adolescents' welfare. For example, the government could encourage or implement the family-based prevention or intervention programs targeting both children and their families at risk, which may contribute to the virtuous circle between family and adolescents and produce long-last beneficial effects.

CONCLUSION

In conclusion, the present study found that both family function and depressive symptoms underwent a certain change during the three junior high school years. But the negative cross-sectional correlation between family function and adolescent depressive symptoms remained significant and stable across three academic years. Moreover, during the early middle school year, poor family function significantly affected subsequent adolescent depressive symptoms. While in the later middle school year, adolescent depressive symptoms significantly influenced subsequent family function. Given the intertwined nature of the family function and adolescent depressive symptoms, family-based intervention should be a promising method both for adolescents and their families.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Research Ethics Committee of Shen Zheng University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EW and JZ designed the study and directed its implementation, did the literature search, and wrote the manuscript. EW, SP, and BZ reviewed the manuscript and revised it critically. All authors contributed to and have approved the final manuscript.

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Trajectories of Healthcare Utilization Among Children and Adolescents With Autism Spectrum Disorder and/or Attention-Deficit/Hyperactivity Disorder in Japan

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Background: Early intervention and prevention of psychiatric comorbidities of children with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are urgent issues. However, the differences in the diagnoses of ASD and ADHD and psychiatric comorbidities associated with age, long-term healthcare utilization trajectories, and its associated diagnostic features have not been fully elucidated in Japan.

Method: We conducted a retrospective observational study using the medical records. Member hospitals of three major consortiums of hospitals providing child and adolescent psychiatric services in Japan were recruited for the study. Children who accessed the psychiatry services of the participating hospitals in April 2015 were followed up for 5 years, and data on their clinical diagnoses, consultation numbers, and hospitalizations were collected. Non-hierarchical clustering was performed using two 10-timepoint longitudinal variables: consultation numbers and hospitalization. Among the major clusters, the differences in the prevalence of ASD, ADHD, comorbid intellectual disability, neurotic disorders, and other psychiatric disorders were assessed.

Results: A total of 44 facilities participated in the study (59.5%), and 1,003 participants were enrolled. Among them, 591 diagnosed with ASD and/or ADHD (58.9%) and 589 without missing data were assessed. The mean age was 10.1 years, and 363 (70.9%) were boys. Compared with the pre-schoolers, the school-aged children and adolescents had fewer ASD, more ADHD, and fewer comorbid intellectual disability diagnoses, as well as more diagnoses of other psychiatric disorders. A total of 309 participants (54.7%) continued consultation for 2 years, and 207 (35.1%) continued for 5 years. Clustering

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analysis identified three, two, and three major clusters among pre-schoolers, school-aged children, and adolescents, respectively. The largest cluster was characterized by early termination of the consultation and accounted for 55.4, 70.6, and 73.4% of pre-schoolers, school-aged children, and adolescents, respectively. Among the school-aged children, the diagnosis of ADHD was associated with a cluster that required longer periods of consultations. Among the adolescents, comorbid psychiatric disorders other than intellectual disability and neurotic disorders were associated with clusters that required hospitalization.

Conclusion: Continuous healthcare needs were common and psychiatric comorbidities were associated with complex trajectory among adolescents. The promotion of early intervention and prevention of comorbidities are important.

Keywords: child and adolescent psychiatry, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), healthcare utilization, longitudinal analysis, early identification and intervention, Japan, neurodevelopmental disorders

INTRODUCTION

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are two common mental disorders in children and adolescents categorized as neurodevelopmental disorders (NDDs). ASD is characterized by social interaction and communication problems and restricted and repetitive patterns of behaviors, interests, or activities. ADHD is characterized by inattention, hyperactivity, and impulsivity (1). As high as 25.7–65.0% of people with ASD had comorbid ADHD (2). Based on the evidence that both are disorders with onset during the developmental phase and have considerable co-occurrence (3, 4), Diagnostic and Statistical Manual of Mental Disorders (DSM-5) allocates ASD and ADHD to the same category of NDDs (1). Previous studies have reported that the prevalence of ASD is ∼1%, and the prevalence of ADHD is ∼5% (5–7). As a reflection of the change in diagnostic criteria from the disease to the spectrum level and the increase in public awareness, in some countries, the reported prevalence of ASD and ADHD have been further increasing (8–12). In addition to their high prevalence, ASD and ADHD are important disorders, as ASD and ADHD often require continuous psychosocial and medical support.

The burden of ASD and ADHD on individuals, families, and society is huge (13–15). Children and adolescents with ASD or ADHD often experience psychiatric symptoms in addition to the core symptoms of ASD or ADHD (2, 16). Previous studies demonstrated that as high as 70% of adolescents with ASD and one-half of children and adolescents with ADHD have at least one psychiatric comorbidity (17, 18). To reduce the high burden of individuals with ASD and ADHD, early identification and support, including early developmental intervention and parental support, have been promoted in several high-income countries, such as the United States and the United Kingdom (19, 20). Early intervention is considered to reduce difficulties faced by individuals and help them improve their daily functioning and prevent the co-occurrence of psychiatric symptoms (13, 20, 21). However, some barriers against getting diagnosis of ASD and ADHD are known to exist such as lack of knowledge, stima, and poor service access (22, 23). In Japan, a large-scale school survey among primary and secondary school students demonstrated that 3.1% of students had inattention or hyperactivity problems and 1.1% had social interaction problems and restricted and repetitive patterns of behaviors, and they needed specialist assessment for suspicions of neurodevelopmental disorders in 2012. However, 40% of the participants did not receive any special support (24). There is an urgent need to promote early identification and intervention and prevent psychiatric comorbidities in children with ASD or ADHD in Japan (25).

Understanding the current healthcare utilization by children with ASD or ADHD is essential. However, the healthcare use trajectories have not been fully investigated in many countries including Japan. Instead, there had been some previous studies analyzing treatment dropout and hospitalization. Previous studies in the US identified that 30% of children with past ASD diagnosis and one fourth of children with past ADHD diagnosis did not receive current treatment (26, 27). Another study demonstrated that approximately 10% of children and young people with ASD require hospitalization during their treatment course and late diagnosis and comorbid psychiatric problems such as depression were risk factors for hospitalization (28). The evidence regarding the period of consultation, frequency of consultation over time and hospitalization and these patterns is still lacking.

In Japan, psychosocial development in children is assessed at health checkups at 1.5 and 3 years of age, as stipulated in the Maternal and Child Health Act (29). Children with developmental concerns were identified, followed up, and advised to get specialist assessment if necessary. Those who are overlooked in the screening process later visit specialists for assessment when they have greater concerns.

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; ASD, Autism spectrum disorder; ICD, International Classification of Diseases; NDD, Neurodevelopmental disorder.

Therefore, the purpose of this study was to investigate age-related patterns of presentations, typical healthcare utilization trajectories, and associated diagnostic characteristics among children and adolescents with ASD and/or ADHD. It is essential to identify the clinical features of children with ASD and ADHD at these hospitals to improve their medical care and support in Japan.

METHODS

Study Design

This was a retrospective medical record data analysis. The data were derived from the medical records of the patients. Children and adolescents who accessed the child and adolescent psychiatry outpatient services at participating hospitals for the first time in April 2015 were included in the survey. Healthcare utilization was followed up until March 2020; the 5 years were divided into 10 half-year periods. Participants with a primary or secondary diagnosis of ASD or ADHD were included in the analysis.

Study Settings

The participating hospitals were members of the three major consortiums of hospitals providing child and adolescent psychiatric services in Japan. The three major consortiums are the child mental health network development program, the Japanese Association of Children's Hospitals and Related Institutions, and the Japanese Council of Child and Adolescent Mental Institution (30–32). The total number of hospital members was 74.

Data Collection

The study data were collected and managed using the Research Electronic Data Capture hosted at National Center for Child Health and Development (33, 34). Research Electronic Data Capture is a secure web-based software platform designed to support data capture for research studies; it provides (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

Measures

Age, sex, and psychiatric diagnoses were collected. For each half-year, the number of outpatient consultations (continuous variable), the existence of hospitalization (binary variable), and the existence of multi-agency liaison (binary variable), such as educational or social welfare institutions, were collected. The duration of consultation was calculated using the first and last consultation dates during the study period. Psychiatric diagnoses were collected using the Tenth Revision of the International Classification of Diseases (ICD-10) (35). Regarding psychiatric disorders, pervasive developmental disorder (ICD-10: F84) was treated as an equivalent of ASD, and hyperkinetic disorder (ICD-10: F90) was treated as an equivalent of ADHD in the DSM-5 (36). Regarding psychiatric diagnoses other than ASD and ADHD, three categories were derived: (1) intellectual disabilities (ICD-10: F7), (2) neurotic, stress-related, and somatoform disorders (ICD-10: F4) as neurotic disorders, and (3) other psychiatric disorders other than intellectual disabilities and neurotic disorders as other psychiatric disorders. The diagnosis given prior to the visit to the participating hospitals and its age were not collected in this study.

Statistical Analysis

The data were stratified by the three age groups according to the age of the first consultation: pre-school (<6 years old), school-aged (6 years old and more/<10 years old), and adolescents [10 years old and more (37)]. A descriptive analysis was performed for each age group. The differences in the prevalence of ASD and ADHD and the three comorbidity categories for the three age groups were determined. Chi-squared test or Fisher's exact test was performed. Bonferroni adjustment for multiple comparisons was applied, and the statistical significance threshold was set at $p = 0.016$ (0.05/3).

Cluster Analysis and Discriminant Analysis

Non-hierarchical clustering was performed on longitudinal data of two indicators: the number of consultations at the psychiatric outpatient service and the existence of hospitalization due to psychiatric problems. Although, psychiatric hospitalization rate was assumed low, children's psychiatric hospitalization implies high healthcare needs. Thus, hospitalization was also analyzed. The k-means method specifically designed for the longitudinal data was adopted as the clustering method (38). The number of clusters was set between 2 and 6, and the number of redraws was 50 for each cluster number. The clustering analysis is non-supervised learning and there is no gold standard method to determin the cluster number. In the present study, the number of clusters was determined using the cluster validity index (Calinski-Harabasz Score) and expert opinions. The stability of the model was assessed based on the consistency of the results of the complete dataset and the 80% subsample of the dataset. The subsample was randomly chosen 20 times. Analysis was conducted using R 3.6.2, klm3d package (39). Missing values were not imputed but the participants with missing values were excluded from the analysis. To examine the difference in diagnostic characteristics between the clusters, the difference between the major clusters that accounted for 5% or more of each age group was examined. Small clusters that accounted for <5% of each age group were removed from the statistical comparison, as the variability was not ignored. Differences in the prevalence of ASD, ADHD, comorbid intellectual disability, neurotic disorders, and other psychiatric disorders across the major clusters were examined using the chi-squared test or Fisher's exact test. Bonferroni adjustment was performed for multiple comparisons and set at $p = 0.01$ (0.05/5). Descriptive analysis was performed to demonstrate the clinical characteristics, such as 2-year consultation continuation, 5-year consultation continuation, consultation duration, hospitalization, and multi-agency liaison during the follow-up.

Ethical Consideration

The opt-out procedure was performed before the data collection. This study was approved by the ethical committee of the National Center for Child Health and Development in Japan (2020-252).

TABLE 1 | Demographic and clinical background of participants in each age-group.

	Pre-school (<6 years old)	School-aged (6 years old and more/<10 years old)	Adolescent (10 years old and more)	*P*-value
n	121	160	308	
Age Mean (SD)	4.1 (1.1)	8.1 (1.1)	13.5 (2.3)	
Male *n* (%)	91 (75.2%)	122 (76.3%)	210 (68.2%)	Pre-school vs. school-aged: $P = 0.95$ School-aged vs. adolescent: $P = 0.09$ Pre-school vs. adolescent: $P = 0.19$
Diagnosis				
ASD *n* (%)	109 (90.1%)	118 (73.8%)	243 (78.9%)	Pre-school vs. school-aged: $P = 0.001$ School-aged vs. adolescent: $P = 0.25$ Pre-school vs. adolescent: $P = 0.01$
ADHD *n* (%)	19 (15.7%)	72 (45.0%)	116 (37.7%)	Pre-school vs. school-aged: $P < 0.001$ School-aged vs. adolescent: $P = 0.15$ Pre-school vs. adolescent: $P < 0.001$
Psychiatric comorbidities				
At least one comorbidity *n* (%)	53 (44.2%)	94 (59.1%)	182 (59.3%)	Pre-school vs. school-aged: $P = 0.04$ School-aged vs. adolescent: $P = 1$ Pre-school vs. adolescent: $P = 0.02$
2 and more comorbidities *n* (%)	14 (11.6%)	22 (13.8%)	35 (11.4%)	Pre-school vs. school-aged: $P = 1$ School-aged vs. adolescent: $P = 1$ Pre-school vs. adolescent: $P = 1$
Intellectual disabilities *n* (%)	38 (31.4%)	23 (14.4%)	34 (11.0%)	Pre-school vs. school-aged: $P = 0.001$ School-aged vs. adolescent: $P = 0.37$ Pre-school vs. adolescent: $P < 0.001$
Neurotic disorders *n* (%)	18 (14.9%)	28 (17.5%)	75 (24.4%)	Pre-school vs. school-aged: $P = 0.67$ School-aged vs. adolescent: $P = 0.11$ Pre-school vs. adolescent: $P = 0.04$
Other psychiatric disorders *n* (%)	2 (1.7%)	18 (11.3%)	43 (14.0%)	Pre-school vs. school-aged: $P = 0.002$ School-aged vs. adolescent: $P = 0.50$ Pre-school vs. adolescent: $P < 0.001$

P-values are differences between age-groups were examined using the chi-squared test or Fisher's exact test.

RESULTS

Participating Facilities and Participants

Forty-four facilities participated in this study (59.5%). A total of 1,003 participants visited the child and adolescent mental health services at the facilities for the first time in April 2015 and were eligible for the study. None of them refused to participate in the opt-out procedure, and all were included in the study. Among them, 591 were diagnosed with ASD and/or ADHD (58.9% of participants), and the data of 589 without missing values among the number of outpatient consultations and the existence of hospitalization were analyzed (99.7%). The mean age was 10.1 years (SD 4.2, pre-schoolers: 121; school-age, 160; adolescent, 308), and 363 (70.9%) were boys. A total of 470 (79.8%) and 207 (35.1%) participants were diagnosed with ASD and ADHD, respectively.

Differences in Diagnosis Stratified by Age-Group

Of the pre-schoolers, 109 (90.1%) had ASD and 19 (15.7%) had ADHD. Of the school-aged children, 118 (73.8%) had ASD and 72 (45.0%) had ADHD. Of the adolescents, 243 (78.9%) had ASD and 116 (37.7%) had ADHD. There were statistically significant differences between the prevalence of ASD and ADHD among the pre-schoolers and older age groups (ASD pre-school vs. school-aged $P = 0.001$, pre-school vs. adolescent $P = 0.01$, ADHD pre-school vs. school-aged $P < 0.001$, pre-school vs. adolescent $P < 0.001$). The prevalence of intellectual disabilities was significantly lower among the school-aged children and adolescents than among the pre-schoolers (pre-school vs. school-aged $P < 0.001$, pre-school vs. adolescent $P < 0.001$), and that of other psychiatric disorders was significantly greater among school-aged children than among pre-schoolers (pre-school vs. school-aged $P < 0.01$, pre-school vs. adolescent $P < 0.001$); as high as 44.2, 59.1, and 59.3% of the pre-schoolers, school-aged children, and adolescents had at least one psychiatric comorbidity, respectively. Approximately 10% of patients had two or more psychiatric comorbidities (**Table 1**).

Clinical Features of Each Age-Group

Consultations were continued for 319 participants (54.7%) for two or more years and 207 participants (35.1%) for 5 years. More than half of the participants continued consultations for two or more years. A total of 46 participants (7.8%) required

TABLE 2 | Clinical features of participants in each age-group.

	Pre-school (<6 years old)	School-Age 6 years old and more/<10 years old)	Adolescent (10 years old and more)
n	121	160	308
2-year consultation continuation *n* (%)	68 (57.1%)	96 (60.8%)	155 (50.7%)
5-year consultation continuation *n* (%)	43 (35.5%)	75 (46.9%)	89 (28.9%)
Hospitalization during the study period *n* (%)	2 (1.7%)	12 (7.5%)	32(10.4%)
Multi-Agency liaison			
Any agent *n* (%)	46 (38%)	89 (55.6%)	162 (52.6%)
Educational agent *n* (%)	21 (17.4%)	61 (38.1%)	86 (27.9%)
Social agent *n* (%)	28 (23.1%)	29 (18.1%)	70 (22.7%)
Abuse related *n* (%)	0 (0%)	5 (3.1%)	5 (1.6%)

hospitalization during the follow up period. Hospitalization rate was higher in older age groups.

Of these, 297 participants required any kind of multi-agency liaison at least once during the study period (50.4%). The most frequently collaborated agency was educational agency (n = 168, 28.5%), followed by social agencies (n = 127, 21.6%). The consultation duration, hospitalization and multi-agency liaison by age group were summarized in **Table 2**.

Results of Clustering

Clustering of healthcare utilization trajectories of pre-schoolers identified three major clusters and three small clusters. The first cluster (cluster 1) was characterized by early discontinuation of consultation after the first visit with an average length of consultation period of 1.2 years (SD 1.5) (n = 67, 55.4%). The second cluster (cluster 2) was characterized by stable continuous consultations at approximately once every 6 months (n = 39, 32.2%). The third cluster (cluster 3) was characterized by frequent consultations that increased over time (n = 10, 8.3%). During later periods, Cluster 2 required monthly consultations. No diagnosis was discriminative among the three clusters. Compared to Cluster 1, there was a trend that more participants in clusters 2 and 3 required multi-agency liaison. Small clusters were clusters that required intensive consultations at the beginning and clusters that required hospitalizations at some point during the follow-up [five participants (4.1%) in three small clusters, (**Supplementary Tables 1, 2**)] (**Tables 3**, **4**, **Figure 1**).

Among school-aged children, two major clusters and three small clusters were identified. The first cluster (cluster 1) was characterized by early discontinuation of consultation after the first visit with an average length of consultation period of 2.4 years (SD 2.1) (n = 113, 70.6%), and the second cluster (cluster 2) was characterized by stable continuous consultations at the monthly level (n = 38, 23.8%). Compared with Cluster 1, Cluster 2 had significantly more participants with ADHD (37.2 vs. 65.8%,

TABLE 3 | Clinical features of major clusters.

Cluster	Participants	Duration of consultation (Years)	2-year continuation	5-year continuation	Hospitalization during study period	Outcome		Multi-Agency liaison			
						Agreed termination of the consultation	Referral to other health facilities	Any agent	Educational agent	Social agent	Abuse related
	n (%)	Mean (SD)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Pre-school (<6 years old)											
Cluster 1	67 (55.4%)	1.2 (1.5)	17 (25.8%)	6 (9.0%)	0 (0%)	25 (37.3%)	6 (9.0%)	20 (29.9%)	8 (11.9%)	13 (19.4%)	0 (0%)
Cluster 2	39 (32.2%)	4.2 (1.0)	36 (94.7%)	27 (69.2%)	0 (0%)	3 (7.7%)	4 (10.3%)	16 (41.0%)	8 (20.5%)	8 (20.5%)	0 (0%)
Cluster 3	10 (8.3%)	4.9 (0.0)	10 (100%)	9 (90.0%)	0 (0%)	0 (0%)	1 (10.0%)	6 (60.0%)	3 (30.0%)	5 (50.0%)	0 (0%)
School-Aged (6 years old and more/<10 years old)											
Cluster 1	113 (70.6%)	2.4 (2.1)	55 (48.7%)	38 (33.6%)	0 (0%)	24 (21.2%)	13 (11.5%)	53 (46.9%)	34 (30.1%)	13 (11.5%)	0 (0%)
Cluster 2	38 (23.8%)	4.9 (0.1)	36 (100%)	33 (86.8%)	3 (7.9%)	0 (0%)	4 (10.5%)	27 (71.1%)	21 (55.3%)	10 (26.3%)	3 (7.9%)
Adolescent (10 years old and more)											
Cluster 1	223 (72.4%)	1.7 (1.9)	79 (35.6%)	37 (16.6%)	2 (0.9%)	62 (27.8%)	51 (22.9%)	99 (44.4%)	47 (21.1%)	37 (16.6%)	1 (0.4%)
Cluster 2	58 (18.8%)	4.5 (0.7)	57 (100%)	42 (72.4%)	3 (5.2%)	5 (8.6%)	10 (17.2%)	41 (70.7%)	25 (43.1%)	19 (32.8%)	2 (3.4%)
Cluster 3	18 (5.8%)	2.7 (2.0)	11 (61.1%)	5 (27.8%)	18 (100%)	2 (11.1%)	9 (50.0%)	16 (88.9%)	9 (50.0%)	9 (50.0%)	2 (11.1%)

TABLE 4 | Diagnostic features of major clusters.

	Demographics				Diagnosis									
	Age		Male		ASD		ADHD		Intellectual disabilities		Neurotic disorders		Other psychiatric disorders	
Cluster	Mean (SD)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value
Pre-school (<6 years old)														
Cluster 1	4.2 (1.1)	0.74	53 (79.1%)	0.37	60 (89.6%)	0.24	10 (14.9%)	0.39	19 (28.4%)	0.72	14 (20.9%)	0.18	0 (0%)	0.28
Cluster 2	4.0 (1.1)		27 (69.2%)		37 (94.9%)		5 (12.8%)		14 (35.9%)		3 (7.7%)		2 (5.1%)	
Cluster 3	4.3 (1.2)		9 (90.0%)		8 (80.0%)		3 (30.0%)		3 (30.0%)		1 (10.0%)		0 (0%)	
School-Aged (6 years old and more/ < 10 years old)														
Cluster 1	8.1 (1.1)	0.98	82 (72.6%)	0.37	89 (78.8%)	0.04	42 (37.2%)	0.004	18 (15.9%)	0.60	20 (17.7%)	0.98	12 (10.6%)	0.77
Cluster 2	8.1 (1.1)		31 (81.6%)		23 (60.5%)		25 (65.8%)		4 (10.5%)		6 (15.8%)		5 (13.2%)	
Adolescent (10 years old and more)														
Cluster 1	13.5 (2.3)	0.71	156 (70.0%)	0.49	176 (78.9%)	0.64	84 (37.7%)	0.93	26 (11.7%)	0.80	51 (22.9%)	0.28	26 (11.7%)	0.005
Cluster 2	13.1 (2.3)		36 (62.1%)		45 (77.6%)		22 (37.9%)		5 (8.6%)		19 (32.8%)		7 (12.1%)	
Cluster 3	14.3 (2.5)		13 (72.2%)		16 (88.9%)		6 (33.3%)		2 (11.1%)		4 (22.2%)		7 (38.9%)	

P-values are differences in the prevalence of ASD, ADHD, comorbid intellectual disability, neurotic disorders, and other psychiatric disorders across the major clusters were examined using the chi-squared test or Fisher's exact test.

$p = 0.004$). Compared with Cluster 1, more participants required multi-agency liaison, including abuse-related liaison, in Cluster 2 during the study period. Small clusters were clusters that required hospitalization at the beginning and during the follow-up and required frequent hospitalizations [nine subjects (5.6%) in three small clusters, (**Supplementary Tables 1, 2**)] (**Tables 3**, **4**, **Figure 1**).

Among the adolescents, three major clusters and two small clusters were identified. The first cluster (cluster 1) was characterized by early discontinuation of consultation after the first visit with an average length of consultation of 1.7 years (SD 1.9) ($n = 223$, 72.4%). The second cluster (cluster 2) was characterized by continuous consultation ($n = 58$, 18.8%). The third cluster (cluster 3) was characterized by hospitalizations during the first 6 months after the first visit ($n = 18$, 5.8%). There was a significant difference in the prevalence of comorbid other psychiatric disorders among the major clusters (cluster 1 11.7%; cluster 2, 12.1%; cluster 3, 38.9%; $p = 0.005$). Compared to Cluster 1, more participants in Clusters 2 and 3 required multi-agency liaison. A higher proportion of participants in cluster 3 required multi-agency liaison because of child abuse. Small clusters were clusters that required hospitalization during the follow-up and frequent hospitalizations [nine participants (2.9%) in two small clusters, (**Supplementary Tables 1, 2**)] (**Tables 3**, **4**, **Figure 1**).

Stability of the Model

The stability of the clusters was assessed based on the stability of the results of 20 random sampling of 80% of the samples. The consistency was 97.4% for pre-schoolers, 98.4% for school-aged children, and 97.4% for adolescents.

DISCUSSION

Summary of the Results

This study demonstrated that there are age-related diagnostic patterns among children with ASD or/and ADHD: ASD was dominant among pre-schoolers, while ADHD increased among school-aged children and adolescents. Regarding psychiatric comorbidities, intellectual disabilities decreased among children in older age groups, while neurotic disorders and other psychiatric disorders increased as they grew. A high prevalence of psychiatric comorbidities was observed. More than half of the study participants continued consultation for 2 years, and approximately one-third continued for 5 years. Approximately half of the participants required multi-agency liaison. For each age group, the largest cluster was a cluster that followed the simplest trajectories with features such as fewer consultations, shorter duration of consultation, and fewer to no hospitalizations. The largest cluster comprised approximately half of the pre-schoolers and 3/4 of the older age groups. Among the school-aged children, a more complex trajectory with long-lasting and frequent consultations was associated with the diagnosis of ADHD. Among adolescents, a more complex trajectory that required hospitalization was associated with comorbid psychiatric disorders other than intellectual disabilities and neurotic disorders. The proportion of participants who

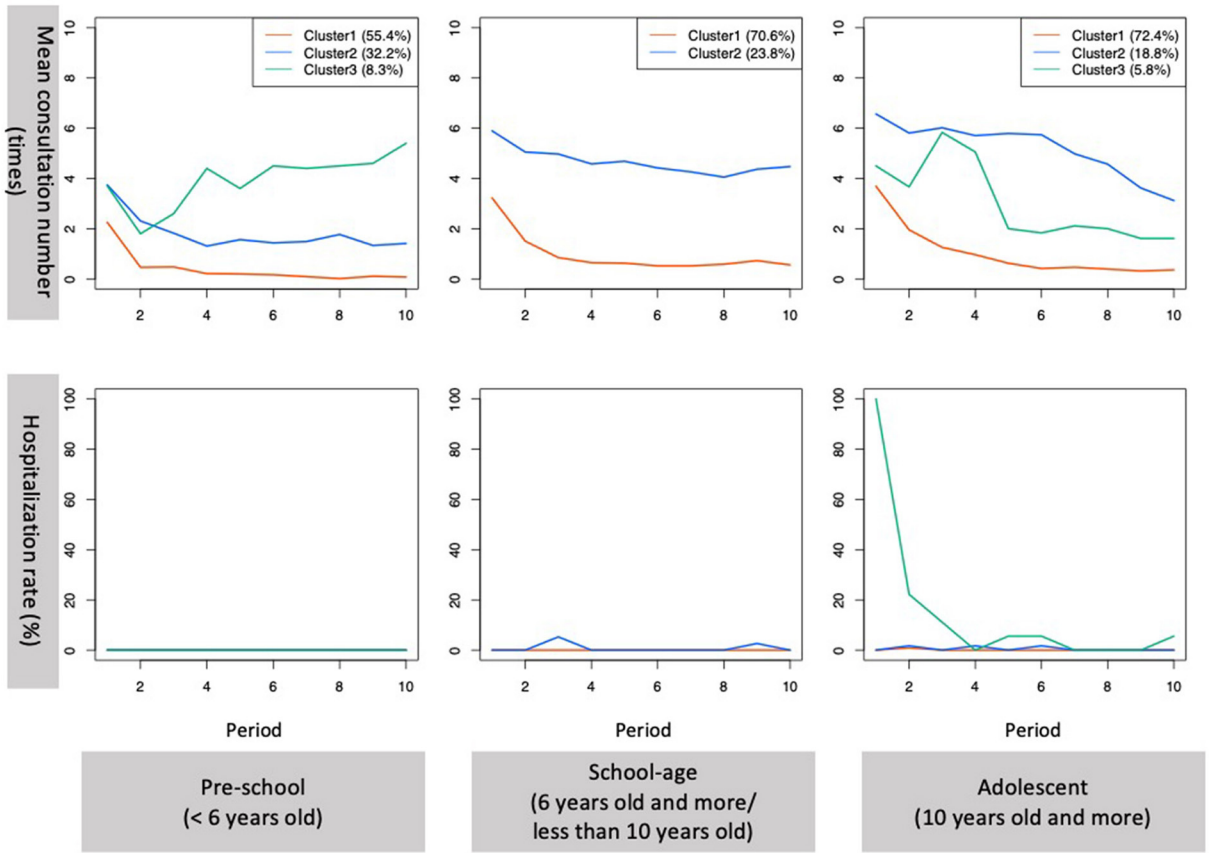

FIGURE 1 | Mean consultation number and hospitalization rate per period for the major clusters. Period 1–10 indicate 10 consecutive half-year periods. Period 1 is April 2015 to September 2015 and period 10 is October 2019–March 2020. Only the trajectories of the major clusters in each age group are presented. Red, blue, and green lines indicate clusters 1, 2, and 3 for each group, respectively.

required multi-agency liaison during the treatment course was higher among children grouped into more complex healthcare use trajectory clusters.

Our results demonstrated that comorbid intellectual disability decreased in the older age groups. This is consistent with the evidence that neurodevelopmental problems in children without intellectual disabilities tend to be overlooked and diagnosed late (40). To support children with ASD and/or ADHD who manifest problems after entering primary school, strengthening school capacity and better collaboration between the health and education sectors is important. In Japan, this is promoted by allocating school nurses or other mental health specialists to counsel psychosocial and behavioral problems and collaborate with school doctors (41). To promote early identification, further screening for ASD and ADHD is important.

Regarding the features of clusters, our results demonstrated that the proportion of the largest cluster which was characterized by shorter duration of consultation and fewer to no hospitalization were larger among school-aged children and adolescents compared to pre-schoolers. This might reflect several points. First is that children with higher disability tend to visit hospital earlier so that pre-schoolers included more children with continuous medical needs. Second is that adolescents start to be referred to adult psychiatry services. In addition, there are other factors that associate with short duration of consultation such as parental parental compliance. However, our study did not investigate these points. Although 10–20% of children in the largest clusters were referred to other health facilities, majority of them terminated consultation. This result is consistent with the previous findings from the US that high proportion of children with past ASD or ADHD diagnosis did not receive current treatment (26, 27).

More participants in more complex healthcare use trajectories required multi-agency liaison. This implies that children with higher healthcare needs cannot be supported by medical services alone. Healthcare providers' recognition of the needs and health system's support for the promotion of multi-agency liaison is necessary. More complex healthcare use trajectories often involved hospitalization. The hospitalization rate among all participants (7.8%) was comparable to the previous findings about the hospitalization rate among children and young people with ASD from the US (10.8%) (28).

In our study, there was an age-associated increasing trend in psychiatric comorbidities other than intellectual disabilities.

This is consistent with the results of a systematic review that demonstrated that the prevalence of various comorbid disorders increased with older age compared with the prevalence of ASD among adolescents and a review that demonstrated that the prevalence of comorbid depression increased in older children with ASD (2, 16, 42). The clustering analysis demonstrated that psychiatric comorbidities were associated with a more complex trajectory that required hospitalization among adolescents. This result implies that adolescents with ASD and/or ADHD with psychiatric comorbidities other than intellectual disability and neurotic disorder tend to have more healthcare needs, and there is a need to promote early identification and ensure service access in order to prevent children with ASD and ADHD from developing psychiatric comorbidities.

Limitations

First, this was a retrospective observational study that used medical records. Thus, our dataset does not include any clinical severity variables or socioeconomic variables associated with healthcare utilization. Nor, our study did not collect data on the changes in diagnosis during the treatment course. The results serve as a foundation for future research to investigate the factors that identify the target of early intervention or intensive intervention, and prospective longitudinal research is needed in this field in the future.

Second, the sample size was not sufficient to capture less frequent trajectories or differences in diagnostic patterns between the age groups. From our results, the less frequent trajectories involved frequent consultations and hospitalizations and were considered more complex. With a larger sample size, the association between less frequent trajectories and diagnosis may be significant. The difference in the proportion of comorbidities between school-aged children and adolescents may be considered significant with a larger sample size.

Third, this study could not follow healthcare utilization in health facilities other than the enrolled hospitals. However, child and adolescent psychiatry service is relatively centralized in Japan. The hospitals enrolled in the current study play a central role in child and adolescent psychiatry within their catchment areas. It could be assumed that participants with high healthcare needs had continued consultations at the same hospital.

Finally, as our study enrolled hospitals belonging to three major consortiums, the participation rate was ∼60%, and population representativeness was not high. However, as this was a retrospective medical record survey, there was no drop-out or refusal to participate in the opt-out procedure, which contributed to better data quality.

CONCLUSION

This study demonstrated age-related changes in diagnostic patterns among children with ASD or ADHD and their typical healthcare use trajectories. Future research investigating the factors associated with complex trajectories is necessary. The results imply that early identification, intervention, and prevention of psychiatric comorbidities and support involving multi-agency liaison are crucial, and they need to be promoted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of the National Center for Child Health and Development in Japan. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AA, TKa, KT, JI, TO, TKu, KN, KO, MO, TKo, and TI developed the concept of the study. JI, TO, TKu, KN, KO, MO, TKo, and TI coordinated the logistics, including the recruitment of the participating hospitals. MN created a data collection platform and supervised the data collection. The collaborative group members coordinated the logistics at each hospital and conducted data collection. AA, MN, TKa, and KT analyzed the data. AA drafted the manuscript. All authors critically reviewed the manuscript and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.812347/full#supplementary-material

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Reward Sensitivity at Age 13 Predicts the Future Course of Psychopathology Symptoms

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Background: There are numerous observations of reward sensitivity being associated with different psychiatric disorders. Nonetheless, most studies investigating this relationship have been cross-sectional. Additionally, current knowledge is fragmentary as studies often investigate only one disorder at a time. The present study addresses these gaps by investigating whether reward sensitivity at age 13 predicts the course of nine psychopathology domains (attention and hyperactivity, autism spectrum, reactive aggression, proactive aggression, mood, anxiety, smoking, alcohol use, and cannabis use) over a 14-year follow-up period.

Methods: We used dimensional outcomes on 2,523 individuals over five measurement waves between ages 13 and 26 of the Dutch Tracking Adolescents' Individual Lives Survey (TRAILS). Reward sensitivity was measured with the Behavioral Activation System (BAS) scale. The longitudinal associations between reward sensitivity and psychopathology were examined using growth curve analysis within a multilevel framework.

Results: Reward sensitivity at age 13 was associated with changes in psychopathology over time. Reward sensitivity had a stable main effect on the future course of reactive and proactive aggression problems and anxiety problems. The effect of reward sensitivity increased over time for alcohol and cannabis use. *Post-hoc* analyses showed that reward sensitivity also had a stable effect on attention problems and hyperactivity and smoking when based on the fun-seeking subscale for both domains and when changing the informant who reported on attention problems and hyperactivity. No evidence was found for a longitudinal association between reward sensitivity and autism spectrum problems and mood problems.

Conclusion: The current study provides evidence for the long-lasting effects of reward sensitivity on the course of different domains of psychopathology.

Keywords: reward, Behavioral Activation System (BAS), transdiagnostic, psychopathology, longitudinal studies, development, adolescence

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INTRODUCTION

Rewards are essential for human behavior because they guarantee our survival (e.g., by eating and drinking water) and influence our positive emotional experiences, motivation, and learning processes (1). Nonetheless, people with high or low reward sensitivity might be more vulnerable to developing psychiatric disorders. This is based on numerous observations that individual differences in reward sensitivity are associated with a wide range of psychiatric disorders. Examples include attention deficit and hyperactivity disorder (ADHD), autism spectrum disorder (ASD), disruptive behavior disorders (DBD), major depressive disorder (MDD), anxiety disorders, and substance use disorders (SUD) (2–9). Still, it is unclear whether extreme levels of reward sensitivity are merely part of the symptoms of psychopathology or play a role in the onset and course of psychiatric disorders.

One way of conceptualizing individual differences in reward sensitivity is based on Gray's reinforcement sensitivity model of personality (10). Gray proposes brain-behavioral systems that control behavioral activity. One of these systems is the Behavioral Activation System (BAS), which regulates approach motivation to attain rewards (10). The BAS has been largely used as a framework for understanding individual differences in reward sensitivity that are associated with psychopathology as measured by questionnaires. In this paper, we will use this framework and use reward sensitivity and BAS as interchangeable terms. The most common conceptualizations divide the BAS into three aspects/subscales that are all related to reward approach behavior but differ in what motivates the approach. Responsiveness relates to approach behavior that is motivated by the reward. Drive relates to the perseverance in pursuing a reward once selected. The last aspect, fun-seeking, relates to the motivation to seek new and intense rewards. Prior research showed some evidence for high reward sensitivity in ADHD, DBD, SUD, and anxiety disorders (2–5, 9). In contrast, MDD has been associated with low reward sensitivity (6). Even though research on reward sensitivity measured by questionnaires in ASD is scarce, some studies have described low reward sensitivity in ASD (7, 8).

Although extreme levels of reward sensitivity have been associated with many different psychiatric disorders, studies often investigated only one disorder at a time. As a result, methodological differences across these studies (e.g., design, sample characteristics, statistical approach) make our current knowledge fragmentary. Careful mapping of reward sensitivity to various psychiatric disorders might aid in filling this knowledge gap, elucidating shared and specific alterations associated with the onset and course of these disorders. Additionally, it is important to note that most research on the relationship between reward sensitivity and psychopathology has been cross-sectional, meaning that reward sensitivity and psychopathology were assessed during the same occasion. Therefore, it is not possible to draw any conclusions on a potential mechanistic role of extreme levels of reward sensitivity in psychopathology. One first step to further the field is to study the potential predictive role of reward sensitivity on the course of psychopathology over time.

Considering such a developmental perspective is also relevant because many psychiatric disorders have an onset in youth and are often chronic (11). Among all life phases, adolescence and the transition into adulthood stand out as an important period to study changes in psychopathology. Adolescence is a sensitive period of development that involves significant physical, sexual, cognitive, social, and emotional changes. Many psychiatric disorders have their onset during this period, such as MDD, anxiety disorders, and SUD. Other disorders may or may not remit, such as ADHD or DBD, or potentially slightly improve, such as ASD. Thus, in this period of considerable individual differences in change, symptoms of any of these disorders may improve or exacerbate into adulthood as a function of reward sensitivity.

This study investigated whether reward sensitivity at age 13 predicted the course of different psychopathology domains longitudinally from age 13 to 26. We focused on the following nine domains of psychopathology: attention and hyperactivity, autism spectrum, reactive aggression, proactive aggression, mood, anxiety, smoking, alcohol use, and cannabis use. Although most research on the relationship between reward sensitivity and psychopathology has focused on discrete categorical psychiatric diagnosis, we used dimensional measures that are closer to the observed continuous nature of severity of psychopathology symptoms and are therefore optimal to study developmental change.

Based on the current literature, we hypothesized that reward sensitivity would significantly predict the course of the psychopathology domains included in the study. Specifically, we expected (1) a positive association between reward sensitivity and the course of attention problems and hyperactivity, reactive and proactive aggression problems, anxiety problems[1], and substance use problems (i.e., smoking, alcohol use, and cannabis use) in two forms:

a) Less improvement over time in individuals with higher levels of reward sensitivity in problem domains with a normative decreasing course (attention problems and hyperactivity, and aggression problems).
b) More worsening over time in individuals with higher levels of reward sensitivity in problem domains with a normative increasing course (anxiety and substance use problems).

By contrast, we expected (2) a negative association between reward sensitivity and the course of autism spectrum and mood problems. This negative association may take two forms:

a) More improvement over time in those with higher levels of reward sensitivity in problem domains with a (slightly) normative decreasing course (autism spectrum problems).
b) Less worsening over time in those with higher levels of reward sensitivity in problem domains with a normative increasing course (mood problems).

[1]Please note that this is a deviation from our preregistration. We previously hypothesized that reward sensitivity would be negatively associated with anxiety problems based on the strong association between anxiety and depression. However, we had missed highly relevant literature supporting a positive association. Further details are provided in **Supplementary Data Sheet S1**.

MATERIALS AND METHODS

This study's aims, hypotheses, and analyses were preregistered on the Open Science Framework (https://osf.io/47qwk).

Sample and Design

We used data from the Tracking Adolescents' Individual Lives Survey (TRAILS). TRAILS is a Dutch longitudinal study designed to track development from preadolescence into adulthood, starting at 11 years old. Adolescents were recruited from primary schools of five municipalities in the North of the Netherlands. TRAILS comprises a general population cohort (N = 2,230) and a clinical cohort (TRAILS-CC; N = 543). TRAILS-CC was designed to selectively sample individuals at heightened risk for mental illness within the TRAILS cohort study. This clinical cohort consists of individuals referred to child psychiatric outpatient clinics before 11 years old. TRAILS has relatively high retention rates, ranging between 73 and 96% for the general population cohort and 73 and 85% for TRAILS-CC. An extensive description of the sampling procedures for TRAILS has been published elsewhere (12). The ethics committee of the University Medical Center Groningen approved TRAILS, and informed consent was obtained from parents and subsequently from the adolescents for the different measurement waves.

From age 11 onwards, participants were assessed every two to three years. At the second measurement wave (T2; 13 years old), reward sensitivity was assessed, which we use as the starting point in this study. Therefore, we used data from five measurement waves (T2–T6). From the baseline measurement (T1), we only used information on sex, parental socioeconomic status (SES), and intelligence quotient (IQ) as covariates in the analyses. We selected all participants for whom data on reward sensitivity at T2 was available. This amounted to 2,523 participants in the study at age 13, of which 48.3% were female. Although attrition is relatively low in TRAILS, data was imputed to maximize the number of complete cases per scale (see **Supplementary Data Sheet S2**). After imputation, over 90% of the cases were complete at baseline (T2). Additionally, we imputed data for attention problems and hyperactivity, reactive aggression problems, and autism spectrum problems at specific waves. Details are given below in the measurements section. Participants were ∼13 years at baseline (T2), 16 years at T3, 19 years at T4, 22 years at T5, and 26 years at T6 [M_{ageT2} (SD) = 13.44 (0.61); M_{ageT3} (SD) = 16.20 (0.71); M_{ageT4} (SD) = 19.07 (0.62); M_{ageT5} (SD) = 22.22 (0.67); M_{ageT6} (SD) = 25.72 (0.64)]. Most participants had an average SES (50.2%), and smaller groups had low (24.0%) and high SES (25.8%). Mean (SD) IQ at baseline was 95.57 (15.02).

Measurements

Behavioral Activation Scale (BAS)

Reward sensitivity was assessed at age 13 (T2) with the parent-rated BAS scale from the Behavioral Inhibition and Activation Scales (BIS/BAS Scales) (13). The questionnaire consists of 13 items divided into three subscales (i.e., responsiveness, drive, and fun-seeking). The total BAS scale was calculated as the mean score of the three BAS subscales. Items were scored on a 4-point scale, coded as 1–4 (1 "very untrue"; 4 "very true"). Internal consistency of the total scale was satisfactory (α = 0.75). In *post-hoc* exploratory analyses, we used the subscales with α = 0.64, α = 0.65, α = 0.44 for, respectively, responsiveness, drive, and fun-seeking.

Child/Adult Behavior Checklist

Attention problems and hyperactivity and reactive aggression problems were assessed with the parent-rated Child and the Adult Behavior Checklists (CBCL; ABCL) (14, 15) at waves T2, T3, and T5. Data were imputed at T4 and T6 (see **Supplementary Data Sheet S2**). The scale measuring attention problems and hyperactivity consists of seven items in the CBCL and 13 items in the ABCL, while the one measuring reactive aggression problems consists of 18 items in the CBCL and 16 items in the ABCL. We measured them as mean scores, and items were scored on a 3-point scale, coded as 0–2 (0 "not at all"; 2 "clearly or often"). Internal consistency was satisfactory across waves for both attention problems and hyperactivity (α between 0.82 and 0.88) and reactive aggression problems (α between 0.76 and 0.88). In sensitivity analyses, we used the overlapping items between childhood and adult versions which were 6 items for attention problems and hyperactivity (α between 0.74 and 0.80), and 16 items for reactive aggression problems (α between 0.84 and 0.90).

Youth/Adult Self Report

Mood and anxiety problems were assessed with the self-rated Youth and Adult Self Report (YSR; ASR) (14, 15) at T2, T3, T4, T5, and T6. The scale measuring mood problems consists of 13 items in the YSR and 14 items in the ASR, and the one measuring anxiety problems consists of six items in the YSR and seven items in the ASR. We measured them as mean scores, and items were scored on a 3-point scale, coded as 0–2 (0 "not at all"; 2 "clearly or often"). Internal consistency was satisfactory across waves for both mood (α between 0.76 and 0.87) and anxiety problems (α between 0.63 and 0.80). In sensitivity analyses, we used the overlapping items between childhood and adult versions which were 12 items for mood problems (α between 0.74 and 0.85), and five items for anxiety problems (α between 0.63 and 0.79).

Child/Adult Social Behavior Questionnaire

Autism spectrum problems were assessed with the parent-rated Child and the Adult Social Behavior Questionnaires (CSBQ; ASBQ) (16, 17) at waves T2, T3, T4, and T6. Data were imputed at T5 (see **Supplementary Data Sheet S2**). We used the four comparable subscales across instrument versions (i.e., reduced contact, reduced social insight, resistance to changes, and stereotyped behavior). In total, 30 items were used from the CSBQ and 28 items from the ASBQ, and we measured these problems as a mean score of all items. Items were scored on a 3-point scale, coded as 0–2 (0 "not at all"; 2 "clearly or often"). Internal consistency was satisfactory across waves (α between 0.92 and 0.93). In sensitivity analyses, we used the 20 overlapping items between childhood and adult versions (α between 0.88 and 0.89).

Antisocial Behavior Questionnaire

Proactive aggression problems were assessed with the self-rated Antisocial Behavior Questionnaire (ASBQ) (18) at T2, T3, T4, T5, and T6. The ASBQ included a slightly different number of items at each wave: 26, 28, 29, 29, and 26 items at waves T2, T3, T4, T5, and T6, respectively. We measured these problems as a mean score, and items were scored on a 5-point scale, coded as 0–4 (0 "no/never"; 4 "seven times or more"). Internal consistency was satisfactory across waves (α between 0.69 and 0.86). In sensitivity analyses, we used the 18 overlapping items between all versions (α between 0.69 and 0.84)."

Self-Rated Substance Use Problems

Smoking, alcohol use, and cannabis use were assessed through a self-rating survey at T2, T3, T4, T5, and T6. For smoking, we measured the self-rated frequency of cigarette smoking in the past month on a 7-point scale (coded as 0 "no cigarettes" /6 "more than 20 cigarettes"). We calculated a mean score for alcohol use, reflecting the average number of alcoholic beverages consumed during a regular day that could range from zero to 20 beverages. For cannabis use, we measured the self-rated frequency of monthly cannabis use that could go from zero to 40 times. Further details are provided in **Supplementary Data Sheet S3**.

Covariates

Baseline psychopathology, baseline age, IQ, parental SES, and sex were used to adjust for potential confounding. These variables are known to be linked to developmental course of psychopathology and could potentially be linked to reward sensitivity as well (19–22). Adjustment for these covariates thus aids the interpretation of the associations that we may find between reward sensitivity and psychopathology. Baseline psychopathology was computed as the score for each psychopathology domain at T2. Baseline age was computed as the age of each participant at T2. IQ was assessed at T1 with the shortened version of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (23). IQ was estimated for each person using the Vocabulary and Block Design subtests of the WISC-R (23–25). Parental socioeconomic status (SES) was based on a combined score of five Z-transformed indicators, i.e., educational attainment (both parents), profession (both parents) and household income. Next, we split parental SES into three categories (lowest 25% "low," middle 50% "average," highest 25% "high"), but only for descriptive purposes (i.e., SES was a continuous variable in the growth curve analyses). Finally, sex was assessed at T1 and coded as a binary variable (0 "female" /1 "male").

Please note that we used different informants for different problem domains. This distinction is based on previous literature that has shown that parents are generally better at reporting on ADHD and externalizing behavior problems, but less valid reporters of internalizing behavior problems (26–28). The only exception was proactive aggression problems, for which we used self-reported data. This was done because the ASBQ uses only self-report of proactive antisocial behaviors.

Statistical Analyses

We calculated, first, cross-sectional correlations of the total BAS scale and subscales with psychopathology at baseline[2]. These allow for comparison with the (mostly) cross-sectional literature and exploration of possible stronger associations with psychopathology at the subscale level compared to the total scale level. Second, for descriptive purposes, we provided the mean scores on the nine domains of psychopathology at T2, T3, T4, T5, and T6, illustrating the overall developmental change over time.

Next, we modeled the course of psychopathology over time, using growth curve analyses within a multilevel framework. This was done for each psychopathology domain separately. Psychopathology and time were person-centered at baseline. For the time variable, this meant that the age of each participant at baseline was subtracted from the ages at T2, T3, T4, T5, and T6, thus representing the follow-up time in the study. For psychopathology, this meant that the starting scores of each participant on the nine psychopathology domains were subtracted from the scores at T2, T3, T4, T5, and T6, as such representing the course relative to T2 (i.e., an intercept of zero at T2). This approach allows baseline psychopathology to be added as a covariate, thus disentangling the starting level of psychopathology from the effect of reward sensitivity on the *change* of psychopathology, which is the focus of our study (29). First, we calculated the intraclass correlation coefficients (ICC) from the unconditional means models. Next, the growth curve was modeled with a fixed intercept representing the starting point (T2) and a random time effect representing the course over time (T2–T6). The total BAS scale was subsequently added as main effect, indicating the association with the rate of change of the outcome, and in interaction with time, indicating the stability of the association over time. We adjusted for the level of psychopathology at baseline and in interaction with time (e.g., when modeling the course of mood problems, we adjusted for mood problems at baseline and in interaction with time) (29). Baseline age, IQ, and SES (all mean-centered), and sex were additional covariates. Finally, we rescaled all outcome variables to a 0–100 points scale for comparability across the different findings when visualizing the results. Given that this is a linear transformation, rescaling is fully compatible with the standardized regression coefficients.

Sensitivity Analyses

Three sensitivity analyses were performed. First, our main analysis used the original scales from the different measurement instruments. However, these scales include different items over time because different developmental periods require different behaviors. For example, "being expelled from class" is only appropriate when schooling is relevant for everyone; after that, this item is no longer included, but other items become relevant, such as "misinforming tax authorities" and "selling drugs." Therefore, our first sensitivity analyses involved re-running

[2]Please note that this is a deviation from our preregistration. Correlation analyses using the BAS subscales were added to explore whether the different aspects of reward sensitivity would be differently associated with the psychopathology domains. Further details are provided in **Supplementary Data Sheet S1**.

TABLE 1 | Correlations between total BAS and subscale mean scores and psychopathology domain scores at baseline.

	Attention problems and hyperactivity	Autism spectrum problems	Proactive aggression problems	Reactive aggression problems	Mood problems	Anxiety problems	Alcohol use	Smoking	Cannabis use
Total BAS	**0.13****	**0.05****	**0.14****	**0.15****	**0.11****	**0.11****	**0.04***	**0.04***	0.04
Responsiveness	0.02	0.03	−0.01	0.04	**0.10****	**0.17****	**−0.05****	−0.02	−0.03
Drive	**0.13****	**0.08****	**0.16****	**0.17****	**0.07****	0.03	**0.08****	**0.05****	**0.06****
Fun-seeking	**0.17****	0.04	**0.17****	**0.15****	**0.10****	**0.06****	**0.08****	**0.10****	**0.08****

*The bold values indicates that are statistically significant. The * symbol indicates the value $p < 0.05$ and ** symbol indicates the values $p < 0.001$.*

TABLE 2 | Mean scores for psychopathology domains over time.

	T2	T3	T4	T5	T6
Attention problems and hyperactivity	0.52 (0.47)	0.47 (0.45)	0.44 (0.33)	0.37 (0.36)	0.32 (0.30)
Autism spectrum problems	0.23 (0.26)	0.23 (0.26)	0.21 (0.25)	0.22 (0.23)	0.21 (0.26)
Reactive aggression problems	0.29 (0.30)	0.26 (0.30)	0.25 (0.21)	0.19 (0.25)	0.19 (0.21)
Proactive aggression problems	0.28 (0.32)	0.23 (0.30)	0.08 (0.18)	0.06 (0.13)	0.05 (0.11)
Mood problems	0.28 (0.26)	0.30 (0.27)	0.31 (0.31)	0.33 (0.32)	0.40 (0.36)
Anxiety problems	0.37 (0.32)	0.34 (0.31)	0.40 (0.36)	0.42 (0.38)	0.52 (0.42)
Smoking	0.27 (1.04)	1.01 (1.84)	1.40 (2.04)	1.48 (2.05)	1.20 (1.89)
Alcohol use	0.18 (0.43)	0.89 (1.26)	1.37 (1.57)	1.39 (1.55)	1.33 (1.66)
Cannabis use	0.11 (1.26)	1.08 (5.07)	1.82 (6.54)	1.85 (6.59)	2.20 (8.53)

Mean scores are presented in their original scales. Attention problems and hyperactivity, autism spectrum problems, reactive aggression problems, mood problems, and anxiety problems are on a 3-point scale. Proactive aggression problems are on a 5-point scale. Smoking is on a 7-point scale. Alcohol use is on a 21-point scale. Cannabis use is on a 41-point scale.

our models to check whether our results were influenced by these different developmentally appropriate items at different waves using only the fully overlapping items across the waves. We did this for attention problems and hyperactivity, autism spectrum problems, proactive and reactive aggression problems, mood problems, and anxiety problems. For substance use, all items used were already comparable across the waves. A second sensitivity analysis pertained specifically to the reactive and proactive aggression problems scales. These came from different instruments and had some items with similar content. Therefore, we re-ran the two models without the overlapping items to test whether overlapping items explained potential overlap in findings for these two domains. Finally, we re-ran our models adjusting for psychotropic medication use over time[3]. This was done to check whether our results were influenced by medication use.

RESULTS

Descriptive Statistics

The total BAS mean score (SD) was 2.91 (0.41). BAS subscales responsiveness, drive, and fun-seeking had mean scores (SD) of 3.22 (0.49), 2.74 (0.61), 2.70 (0.50), respectively. **Table 1** shows the cross-sectional associations between the total BAS and subscale mean scores and psychopathology at baseline. Specific BAS subscales had a somewhat higher cross-sectional correlation with some psychopathology domains than the total BAS score used in our main analyses. That is, compared to the overall mean score, attention problems and hyperactivity, proactive and reactive aggression problems, and substance use problems were somewhat more strongly correlated with drive and fun-seeking, while for anxiety, this was the case with responsiveness. On the other hand, autism spectrum problems were slightly more strongly correlated with drive. Although relatively small differences, these findings prompted additional exploratory *post-hoc* analyses to determine if targeted subscale analyses based on these correlational patterns would alter our main conclusions, as described in section *Post-hoc* Exploratory Analyses below.

Table 2 presents the mean scores on the nine psychopathology domains at T2, T3, T4, T5, and T6. These normative developmental patterns are in line with expectation, i.e., increasing over time for mood problems, anxiety problems, smoking, alcohol use, and cannabis use, decreasing over time for attention problems and hyperactivity, reactive aggression problems, and proactive aggression problems, and remaining stable (with only a slight decrease) for autism spectrum problems.

Intraclass Correlations

We first calculated the intraclass correlations (ICC). An ICC of at least 10% is considered appropriate to account for clustering effects over time with a multilevel model (30). The ICC was 0.47 for attention problems and hyperactivity, 0.41 for autism

[3]Please note that this is a deviation from our preregistration. These sensitivity analyses were added to explore whether our results were influenced by psychotropic medication use, which we had accidentally not considered upon pre-registration. Further details are provided in **Supplementary Data Sheet S1**.

TABLE 3 | Multilevel growth curve model estimates for all psychopathology domains.

	Attention and hyperactivity	Autism spectrum	Reactive aggression	Proactive aggression	Mood	Anxiety	Smoking	Alcohol	Cannabis
	Est (SE)	Est (SE)	Est (SE)	Est (SE)	Est (SE)	Est (SE)	Est (SE)	Est (SE)	Est (SE)
Fixed Effects									
(Intercept)	−0.16 (0.18)	−0.06 (0.13)	0.14 (0.13)	**−0.77 (0.08)****	**0.72 (0.19)****	−0.04 (0.22)	**4.66 (0.40)****	**0.49 (0.10)****	−0.11 (0.21)
Follow-up time	**−0.75 (0.03)****	−0.04 (0.02)	**−0.38 (0.02)****	**−0.54 (0.01)****	**0.39 (0.04)****	**0.62 (0.05)****	**1.95 (0.09)****	**0.56 (0.02)****	**0.54 (0.05)****
Reward sensitivity	0.24 (0.13)	0.07 (0.10)	**0.22 (0.10)***	**0.20 (0.07)***	0.23 (0.15)	**0.38 (0.16)***	0.04 (0.30)	−0.01 (0.08)	0.14 (0.15)
Reward sensitivity*Time	0.03 (0.03)	0.02 (0.02)	0.01 (0.02)	−0.00 (0.01)	0.01 (0.04)	0.00 (0.05)	0.18 (0.09)	**0.06 (0.02)***	**0.09 (0.05)***
Baseline psychopathology	**−2.29 (0.14)****	**−1.18 (0.10)****	**−1.54 (0.10)****	**−1.46 (0.07)****	**−2.13 (0.15)****	**−3.34 (0.16)****	**−1.17 (0.31)****	0.00 (0.08)	**−0.44 (0.17)***
Baseline psychopathology *Time	**−1.00 (0.03)****	**−0.39 (0.02)****	**−0.64 (0.02)****	**−0.64 (0.01)****	**−0.60 (0.04)****	**−0.79 (0.05)****	**−0.96 (0.10)****	**−0.14 (0.02)****	**−0.19 (0.06)***
Baseline age	**−0.47 (0.12)****	**−0.29 (0.09)***	**−0.37 (0.08)****	**−0.22 (0.04)****	0.07 (0.13)	0.07 (0.14)	−0.18 (0.27)	**0.28 (0.07)****	**0.36 (0.14)***
Sex	**0.57 (0.23)***	0.23 (0.17)	−0.32 (0.17)	**1.02 (0.09)****	**−2.27 (0.26)****	**−2.79 (0.30)****	−0.43 (0.54)	**1.48 (0.14)****	**1.36 (0.28)****
SES	**−0.27 (0.12)***	**−0.27 (0.09)***	**−0.23 (0.09)***	**−0.19 (0.05)****	−0.18 (0.14)	−0.12 (0.16)	**−1.20 (0.29)****	0.14 (0.07)	0.11 (0.15)
IQ	−0.02 (0.13)	**−0.24 (0.09)***	**−0.21 (0.09)***	**−0.19 (0.05)****	0.13 (0.14)	**−0.47 (0.16)***	**−0.93 (0.29)***	0.01 (0.07)	0.07 (0.15)
Random effects									
Variance	1.03	0.71	0.60	0.01	1.64	3.22	11.45	0.44	3.02
Residual variance	62.12	31.59	32.78	17.07	80.21	96.08	337.23	23.38	88.36
ICC	0.46	0.52	0.48	0.02	0.48	0.60	0.61	0.46	0.61

*Est, estimate; SE, standard error. The bold values indicates that are statistically significant. The * symbol indicates the value $p < 0.05$ and ** symbol indicates the values $p < 0.001$.*

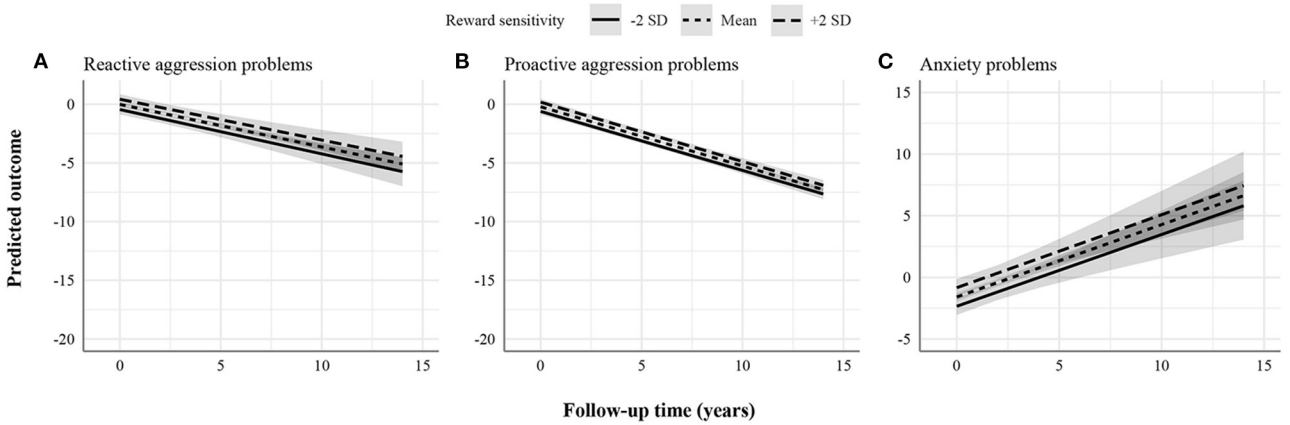

FIGURE 1 | Statistically significant stable associations between reward sensitivity and psychopathology domains. **(A)** Reactive aggression problems. **(B)** Proactive aggression problems. **(C)** Anxiety problems. The figures display the effect of reward sensitivity on psychopathology based on its main effect and in interaction with time. Here, the x-axes show follow-up time in years, whereas the different lines show reward sensitivity levels at 2 SD above and below the mean. The y-axes represent the predicted outcome with all covariates at mean levels and sex coded as 0 (males). The y-axes are only partly shown for better visualization of the findings.

spectrum problems, 0.47 for reactive aggression problems, 0.43 for proactive aggression problems, 0.34 for mood problems, 0.39 for anxiety problems, 0.35 for smoking, 0.20 for alcohol use, and 0.27 for cannabis use. Therefore, 20 to 47% of the variance in the psychopathology domains was attributable to clustering. The intraclass correlations thus indicate both stability of psychopathology and change from early adolescence to young adulthood.

Predictive Role of Reward Sensitivity on the Course of Psychopathology

We then tested whether reward sensitivity predicted the course of psychopathology while controlling for the level of baseline psychopathology, age at baseline, sex, SES, and IQ. Model estimates are provided in **Table 3**.

Figures 1–**3** display the predicted response based on the main effect of reward sensitivity and its effect in interaction with time, with all covariates at mean levels and sex coded as 0 (males). Note that different psychopathology domains change differently over time. For instance, proactive aggression problems decreased more strongly over time compared to reactive aggression problems (**Figure 1**). Thus, to be able to compare the effect of reward sensitivity across different psychopathology domains, the total change over time for each domain needs to be considered. To do that, we use percentages to express differences between the predicted change over time in psychopathology of individuals with low (i.e., 2 SD below the mean) and high (i.e., 2 SD above the mean) reward sensitivity. Percentage difference is the difference between the two values divided by the average of the two values shown as a percentage.

We found a positive effect of reward sensitivity on the course of reactive aggression, proactive aggression, and anxiety problems (**Figure 1**). This association was present in two forms depending on whether normative developmental patterns of psychopathology decrease or increase, on average. First, in reactive and proactive aggression problems, individuals with higher reward sensitivity showed less improvement over time than those scoring lower. The total change over the follow-up period predicted for individuals with low and high reward sensitivity in reactive aggression problems was 5.29 and 4.86 points, respectively. The percentage difference in total change over time between individuals with low and high reward sensitivity was 8.47%. For proactive aggression problems, the total change over the follow-up period predicted for individuals with low and high reward sensitivity was 7.04 and 6.73 points, respectively. The percentage difference in total change over time was 4.50%. Second, in anxiety problems, individuals with higher reward sensitivity showed more worsening over time than those scoring lower. The total change over the follow-up period predicted for individuals with low and high reward sensitivity in anxiety problems was 8.16 and 8.29 points, respectively. The percentage difference in total change over time was 1.58%. These effects were stable over time (i.e., interaction effects of reward sensitivity and time were not significant), meaning that the effect of reward sensitivity remained the same over the study period.

Additionally, we found a positive effect of reward sensitivity on the course of alcohol and cannabis use (**Figure 2**). This effect increased over time, as indicated by the significant interaction effect. Individuals with higher reward sensitivity showed more worsening (i.e., increasingly used more alcohol and cannabis) over time than those with lower levels. For alcohol use, the total change over the follow-up period predicted for individuals with low and high reward sensitivity was 6.25 and 9.61 points, respectively. The percentage difference in total change over time was 42%. For cannabis use, the total change over the follow-up period predicted for individuals with low and high reward sensitivity was 5.01 and 10.23 points, respectively. The percentage difference in total change over time was 68%.

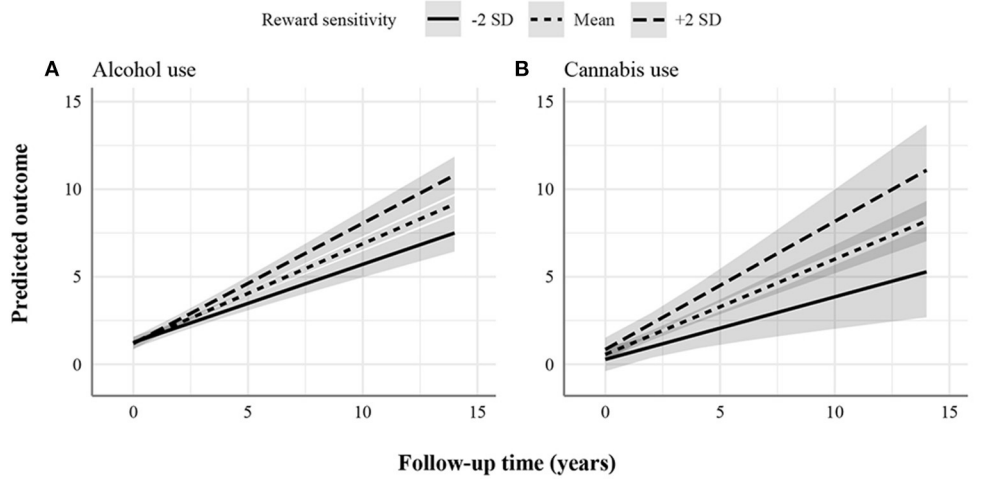

FIGURE 2 | Statistically significant increasing associations between reward sensitivity and psychopathology domains. **(A)** Alcohol use. **(B)** Cannabis use. The figures display the effect of reward sensitivity on psychopathology based on its main effect and in interaction with time. Here, the x-axes show follow-up time in years, whereas the different lines show reward sensitivity levels at 2 SD above and below the mean. The y-axes represent the predicted outcome with all covariates at mean levels and sex coded as 0 (males). The y-axes are only partly shown for better visualization of the findings.

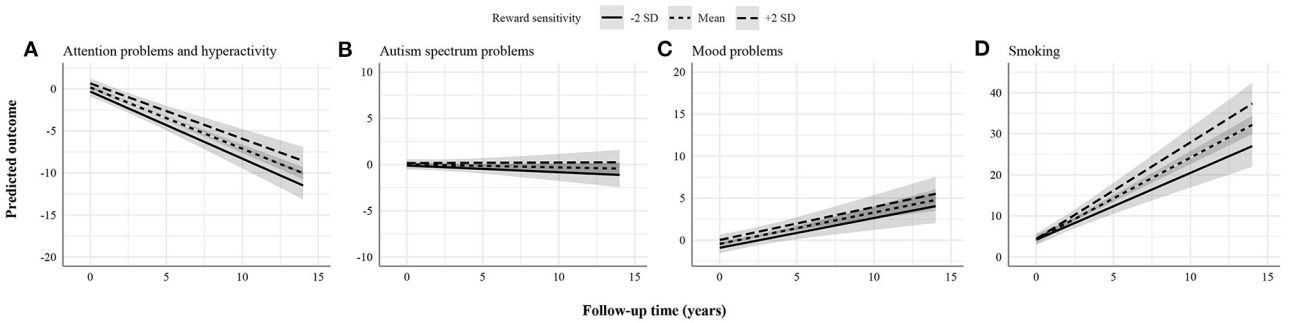

FIGURE 3 | Statistically non-significant associations between reward sensitivity and psychopathology domains. **(A)** Attention problems and hyperactivity. **(B)** Autism spectrum problems. **(C)** Mood problems. **(D)** Smoking. The figures display the effect of reward sensitivity on psychopathology based on its main effect and in interaction with time. Here, the x-axes show follow-up time in years, whereas the different lines show reward sensitivity levels at 2 SD above and below the mean. The y-axes represent the predicted outcome with all covariates at mean levels and sex coded as 0 (males). The y-axes are only partly shown for better visualization of the findings.

Finally, there was no evidence found for the association between reward sensitivity and the course of attention problems and hyperactivity, autism spectrum problems, mood problems, and smoking (**Figure 3**). Particularly, findings for attention problems and hyperactivity were unexpected. These were further explored in *post-hoc* analyses by changing the informant (i.e., self-rated instead of parent-rated attention problems and hyperactivity).

Sensitivity Analyses

Sensitivity analyses (i.e., [a] using the overlapping items across the waves instead of the original scales, [b] removing the overlapping items between reactive and proactive aggression, and [c] adjusting for psychotropic medication use) yielded highly similar results as our main analyses and conclusions remained unaltered. Model estimates are provided in **Supplementary Tables S1, S2**.

Post-hoc Exploratory Analyses

First, based on the findings shown in **Table 1**, we checked if analyses based on the highest correlated BAS subscale would yield similar results to our main findings based on the total BAS score. Model estimates when considering specific subscales are provided in **Supplementary Table S3**. We observed similar or smaller effect sizes for proactive aggression problems, reactive aggression problems, autism spectrum problems, mood problems, anxiety problems, and alcohol use, indicating that the broad BAS mean score measure fits these outcomes (**Supplementary Figure S1**). On the other hand, we observed a positive effect of the fun-seeking subscale on the course of

attention problems and hyperactivity (main effect: 0.36 vs. 0.22) and smoking (main effect: 0.90 vs. 0.06; interaction effect: 0.22 vs. 0.17) (**Supplementary Figure S2**). In addition, we observed a bigger effect size for cannabis use with a statistically significant main effect instead of a significant interaction effect (main effect: 0.47 vs. 0.14).

Second, no evidence was found for the association between reward sensitivity and the course of attention problems and hyperactivity in our main analysis. Since this was unexpected and given that we also had self-reported information on attention problems and hyperactivity, we decided to check whether discrepancies across different informants played a role. When using self-rated attention problems and hyperactivity, we found evidence for the association between reward sensitivity and attention problems and hyperactivity. Individuals with higher reward sensitivity showed persistently less improvement over time than those with lower (**Supplementary Figure S3**). The total change over the follow-up period predicted for individuals with low and high reward sensitivity in attention problems and hyperactivity was 17.65 and 16.17 points, respectively. The percentage difference in total change over time between individuals with low and high reward sensitivity was 8.75%.

DISCUSSION

This study investigated the predictive role of reward sensitivity on the course of psychopathology. We showed that reward sensitivity measured at age 13 was associated with changes over time in reactive and proactive aggression problems, anxiety problems, and alcohol and cannabis use. High reward sensitivity was associated with less decline at each time point in reactive and proactive aggression problems, with a higher increase in anxiety problems at each time point, and with a higher increase in alcohol and cannabis use over time. While the effects were stable over time for reactive and proactive aggression problems and anxiety problems, the effect of reward sensitivity increased over time for alcohol and cannabis use. *Post-hoc* analyses additionally revealed a stable effect for attention problems and hyperactivity when using self-rated measures of psychopathology and when considering specific BAS subscales. Likewise, for smoking, both stable and increasing effects were observed when considering specific BAS subscales. These results show that high reward sensitivity is shared across multiple psychopathology domains, although no role in mood and autism spectrum problems was observed.

The findings that high reward sensitivity was associated with reactive and proactive aggression problems, anxiety problems, alcohol use, and cannabis use, and in the *post-hoc* analysis also with attention problems and hyperactivity, as well as smoking are in agreement with previous cross-sectional studies. For instance, previous research has shown evidence for a positive association between reward sensitivity and both types of aggression (3). Similarly, the associations between reward sensitivity and problems related to attention, hyperactivity, and substance use have been widely explored cross-sectionally (2, 4, 9). The findings on the association between reward sensitivity and anxiety are somewhat mixed. On the one hand, a recent meta-analysis has reported no evidence for this association when measuring reward sensitivity with questionnaires (6). On the other hand, Barker and colleagues have reviewed findings in clinical and cognitive neuroscience that support an increased reward sensitivity in anxiety (5). This positive association is expected due to the activation of both reward and punishment systems that typically happens in highly novel, ambiguous, and unpredictable contexts, resulting in an approach-avoidance conflict (31). We extend these previous findings by showing that these associations can also be observed longitudinally and that they are long-lasting. Additionally, for alcohol and cannabis use, and *post-hoc* specifically for fun-seeking predicting smoking, reward sensitivity effects became stronger with time. Our findings suggest, on the one hand, stable effects for childhood-onset psychiatric problems. On the other hand, we observed larger effects as they increase over time for adolescent- and young adult-onset problems, specifically substance use. During this normative increase, high reward sensitivity may accelerate the use of these substances.

Contrary to our hypotheses and prior research, we did not find that reward sensitivity was associated with less decline in attention problems and hyperactivity over the course of adolescence. Discrepancies across different informants seemed to play a role, i.e., we used a self-rated measure for reward sensitivity but a parent-rated measure for attention problems and hyperactivity in our main analyses. However, findings were as expected when using self-ratings of attention problems and hyperactivity in *post-hoc* analyses. Our findings show that when both reward sensitivity and attention problems and hyperactivity were self-reported, findings converged better, even though parent report of ADHD symptoms is generally considered as more valid (28). Note that, like attention problems and hyperactivity, reactive aggression was also rated by parents, suggesting that the effect on self-reported reward sensitivity on reactive regression is stronger than that on ADHD symptoms. Further, we also observed the hypothesized effect when exploring parent-rated fun-seeking rather than the total BAS score. Fun-seeking is potentially the most relevant for ADHD (32) and using the total BAS score might thus have underestimated the association with attention problems and hyperactivity. The literature is not fully consistent on the role of reward sensitivity in ADHD either. Gomez and Corr (32) reported in a cross-sectional study that ADHD symptoms were positively associated with reward sensitivity, and like here, more strongly for fun-seeking. In all, we conclude that although we identified a stable association between broad reward sensitivity and ADHD, the association may be, in fact, stronger for fun-seeking. It should be added here that the latter was also found for smoking, which fits with how fun-seeking has been linked to how smoking starts (33).

No evidence for the associations between reward sensitivity and autism spectrum problems and mood problems were found. As previously mentioned, the association between ASD and reward sensitivity had not been widely studied before. Therefore, our hypothesis that autism spectrum problems would be negatively associated with reward sensitivity was mainly based on prior neuroimaging and reaction time tasks research, which

suggests a reduced or slower response to reward stimuli. It is unclear if these brain and cognitive responses tap into the same as reward sensitivity at the behavioral level. The neuroimaging and reaction time tasks were all cross-sectional, but the present cross-sectional associations (total BAS and subscales) were also fairly weak. Similar to autism spectrum problems, our results for mood problems were also not in line with our hypothesis of a negative association. Again, the negative associations are mostly found in relation to neuroimaging and reaction time task responses (34–36). In contrast, a recent meta-analysis including over 100 (cross-sectional) studies found a very small negative association between reward sensitivity and mood problems (6). However, the association was no longer significant when considering only self-rated mood problems, indicating that the present null finding fits within this pattern of small negative or no relations.

The main strength of our study is its prospective longitudinal design with a 14-year follow-up. TRAILS benefits from multiple measurement waves (here: five waves encompassing ages 13 to 26), and relatively high retention rates (12). Additionally, TRAILS is characterized by broad measurement, with the current study in particular, benefitting from the multiple psychopathology domains repeated over time. Our study bridges the current fragmentary knowledge on the association between reward sensitivity and psychopathology, in which research papers tend to focus on one type of psychopathology at a time, while we provided an overview of these associations across different domains of psychopathology. This work might be seen as a basis to further investigate the potential causal role of reward sensitivity in the onset and course of psychopathology. A potential limitation is that our findings do not directly translate to psychiatric disorders as we studied dimensional measures of psychopathology. Thus, the current study is predominantly useful for extending the available knowledge on the role of reward sensitivity in psychopathology rather than having immediate clinical impact. We nonetheless want to stress that given its long-lasting widespread relations with psychopathology, reward sensitivity could be a cross-diagnostic theme that may be probed during diagnostic assessment and potentially targeted in treatment. A second limitation is that we only used reward sensitivity to predict future change. Thus, there are two things to consider. First, even though reward sensitivity is thought to be stable over the lifespan, this has not been widely studied in longitudinal studies so far. For example, onset of symptoms of depression may, in turn, reduce reward sensitivity. We were unable to study change like these since we had no repeated measures of reward sensitivity. Second, we studied trajectories of homotypic continuity in the current paper, but psychopathology may change from one type of symptoms to another during development. For example, the currently identified stable link of reward sensitivity with ADHD and the increasing link with cannabis use may be partly driven by children with high ADHD symptoms who start using cannabis (37). Heterotypic continuity as a function of reward sensitivity was not addressed here, first, because the paper was already complex by including nine types of outcomes, and second, because larger samples are necessary for establishing such complex relations among these nine problem domains. We want to additionally note that the BAS scale is only one way to measure reward sensitivity. We would like to see confirmation of our longitudinal findings based on different reward sensitivity instruments.

In conclusion, our study showed that reward sensitivity has a long-lasting effect on the future course of psychopathology between adolescence and young adulthood. Thus, our work adds to the understanding of the role of reward sensitivity in psychopathology, providing an overview of the prospective associations across different psychopathology domains.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets analyzed in this study are subject to the European Union's General Data Protection Regulation and are not publicly available. However, data can be requested by means of a publication plan. Requests to access these datasets should be directed to https://easy.dans.knaw.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the University Medical Center Groningen. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RC analyzed the data and drafted the manuscript. RG and CH reviewed and edited the manuscript. All authors designed the study and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.818047/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Trajectories of Adaptive Behaviors During Childhood in Females and Males in the General Population

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Little is known about the trajectory patterns and sex differences in adaptive behaviors in the general population. We examined the trajectory classes of adaptive behaviors using a representative sample and examined whether the class structure and trajectory patterns differed between females and males. We further explored sex differences in neurodevelopmental traits in each latent class. Participants (n = 994) were children in the Hamamatsu Birth Cohort for Mothers and Children (HBC Study)—a prospective birth cohort study. Adaptive behaviors in each domain of communication, daily living skills, and socialization were evaluated at five time points when participants were 2.7, 3.5, 4.5, 6, and 9 years old using the Vineland Adaptive Behavior Scales–Second Edition. Parallel process multigroup latent class growth analysis extracted sex-specific trajectory classes. Neurodevelopmental traits of children at age 9, autistic traits, attention deficit hyperactivity disorder (ADHD) traits, and cognitive ability were examined for females and males in each identified class. A 4-class model demonstrated the best fit. Moreover, a 4-class model that allowed for differences in class probabilities and means of growth parameters between females and males provided a better fit than a model assuming no sex differences. In the communication domain, females scored higher than their male counterparts in all four classes. In the daily living skills and socialization domains, the two higher adaptive classes (Class 1: females, 18.6%; males, 17.8%; Class 2: females, 48.8%; males, 49.8%) had similar trajectories for males and females, whereas in the two lower adaptive behavior classes (Class 3: females, 27.5%; males, 29.4%; Class 4: females, 5.1%; males, 3.0%), females had higher adaptive scores than their male counterparts. In Class 4, females were more likely to have autistic and ADHD traits exceeding the cutoffs, while males were more likely to have below-average IQ. Different trajectories in females and males suggest that adaptive skills may require adjustment

based on the sex of the child, when standardizing scores, in order to achieve better early detection of skill impairment.

Keywords: trajectory, adaptive behavior, sex differences, neurodevelopmental traits, childhood, autism spectrum disorder, attention deficit hyperactivity disorder, cognitive ability

INTRODUCTION

Adaptive behavior is an individual's acquired social and practical skills for application in typical everyday situations (1). These involve functional use of verbal and non-verbal communication, daily living skills (e.g., being able to take care of one's own health and safety), and socialization skills (e.g., behaving in a socially acceptable manner) (2, 3). Moreover, adaptive skills increase in complexity with age and must be understood within a developmental context (4).

Impairment of adaptive behaviors, especially socialization skills, has often been reported in individuals with autism spectrum disorders (ASD). Since adaptive behaviors predict functional outcomes of children with ASD, independent of symptoms, it is crucial to understand the developmental trajectories of adaptive behaviors. Thus, previous studies have focused on individuals with ASD or with an elevated likelihood of receiving a diagnosis of ASD (5–8). However, first, it is important to understand what trajectory patterns exist in the general population, and then, to determine which trajectory patterns children with ASD most often assigned to. In addition, adaptive behavior is an important developmental indicator for children with broader neurodevelopmental conditions (9). For example, individuals with attention deficit hyperactivity disorder (ADHD) and intellectual disability may experience challenges with adaptive behaviors (10). Therefore, it would be meaningful to explore the class structure in a general population including children with various neurodevelopmental conditions as well as children with typical development (TD). Moreover, it is meaningful to determine to which classes individuals with diverse neurodevelopmental traits would likely be assigned based on given class patterns.

Most crucially, to the best of our knowledge, there are no studies that have longitudinally investigated sex differences in adaptive behaviors, despite the reported sex differences in early milestone acquisition. For example, females are generally reported to achieve developmental milestones, including language acquisition and social–emotional development, earlier than males (11). In addition, the overall prevalence of neurodevelopmental disorders such as ASD and ADHD has been reported to be higher in males than in females (12). However, it is not known whether the class structure reported in previous studies differs between females and males, nor to which classes are females and males with neurodevelopmental traits assigned. Notably, recent studies have highlighted that the male-to-female ratio of prevalence is not as large as previously estimated, possibly because some ASD and ADHD cases in females may be overlooked (13, 14). Females are less likely to manifest distinct early signs of such disorders and are diagnosed at a later age than males (15). The bias toward greater risks for males than females may be attributed to previous studies conducted with predominantly male participants (16). A recent study also reported that females display specific neurodevelopmental phenotypes that are qualitatively different from those of males (17), thereby requiring same-sex comparison when assessing their early signs. It is crucial to examine whether there are sex-specific trajectories of adaptive behaviors in early developmental stages.

This study has two main objectives. First, we explored the trajectory classes of adaptive behaviors in a representative sample of children enrolled in and followed through our birth cohort study, using a latent class growth analysis. Second, this study aimed to evaluate sex differences in these trajectories and neurodevelopmental traits of children assigned to each trajectory class. We evaluated these trajectories while considering the effect of sex, assuming that heterogeneity by sex exists. Using a multigroup approach, a model including all children was compared to a model that allows for different class probabilities for females and males, and to another model that allows for different means of growth parameters (i.e., different trajectories) for females and males in addition to different class probabilities. We hypothesized that there would be greater variation in the classes identified in this study compared to studies using a sample of children with ASD or with an elevated likelihood for the condition. We also hypothesized that class membership and growth trajectories would differ between females and males, and that females would generally have higher adaptive behaviors than males from early childhood to school age, especially in communication and socialization domains. Children (both females and males) with higher neurodevelopmental traits than their same-sex peers would likely be assigned to the lower adaptive behavior classes.

METHODS

Study Design and Participants

This study was conducted as part of an ongoing prospective cohort study, the Hamamatsu Birth Cohort Study for Mothers and Children (HBC Study), comprising mothers (n = 1,138) and their children (n = 1,258) (18, 19). The HBC Study invited all women who were in the first or second trimester of pregnancy who visited the Hospital of Hamamatsu University School of Medicine or the Kato Maternity Clinic between November 2007 and March 2011. Most (99%) of the enrolled mothers were Japanese. Adaptive behaviors were assessed when the children were 2.7, 3.5, 4.5, 6, and 9 years old. The 264 participants without any measures of adaptive behavior in the five measurements at any time point were excluded from the analysis, leaving 994 children and 893 mothers included in the analyses. The participating children are representative of the

Japanese population in terms of demographic characteristics and standardized test scores (**Supplementary Table 1**). Further details of the study have been described previously (19).

All procedures contributing to this work comply 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. All procedures were approved by the Institutional Review Board of the Hamamatsu University School of Medicine (Ref. 18-166, 19-9, 20-82, 22-29, 24-67, 24-237, 25-143, 25-283, E14-062, E14-062-1, E14-062-3, 17-037, 17-037-3, 20-233). Written informed consent was obtained from all caregivers for their own and their children's participation.

Measures

Adaptive Behaviors

Daily functional abilities from early childhood to school ages were quantified using the Japanese version of the Vineland Adaptive Behavior Scales–Second Edition (VABS-II) (20, 21). The VABS-II is based on a semi-structured parental interview comprising four domains: communication, daily living skills, socialization, and motor skills. We used age-adjusted standard scores (mean = 100, SD = 15) for the three domains of communication, daily living, and socialization. Higher scores indicate better adaptive behaviors.

Neurodevelopmental Traits at 9 Years of Age

Autistic traits were evaluated using the Social Responsiveness Scale, Second Edition (SRS-2) school age form (22) comprising 65 items. The SRS-2 raw scores were converted to total T-scores (mean = 50, SD = 10), which were normalized based on a nationally representative standardization sample stratified by sex (22, 23). The translated version of the SRS-2 has been explored for validity in the general population, and high correlation (ICC = 0.66) with the Autism Diagnostic Interview-Revised (ADI-R), which is a research standard for establishing a diagnosis of autism, was confirmed. When used for primary screening of the general population, the optimal cutoff point was 53.5 for males (equivalent to T-score 60; sensitivity 0.91, specificity 0.48) and 52.5 for females (equivalent to T-score 62; sensitivity 0.89, specificity 0.41) (23). Accordingly, children with scores exceeding these cutoffs were considered to have autistic traits.

ADHD traits were evaluated using the Japanese version of the ADHD-Rating Scale (ADHD-RS) consisting of 18 items (24). The ADHD-RS has been shown to have appropriate psychometric properties for use as a screening, diagnostic, and treatment outcome measure (25). The subscales have also been found to have high internal consistency reliability, interrater reliability, discriminant validity, and significant correlations with other scales widely used in the assessment of ADHD in a representative sample of Japanese children. The percentile scores stratified by sex were obtained (25), and children with scores above the 85th percentile were classified as having ADHD traits.

Cognitive ability was assessed using the Japanese version of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (26), and full-scale IQ (mean = 100, SD = 15) was evaluated. Full-scale IQs below 85 was classified as below-average.

STATISTICAL ANALYSIS

Using multigroup parallel process latent class growth analysis (27, 28), trajectories of adaptive behaviors were estimated in females and males. Three domains of adaptive behaviors, including communication, daily living skills, and socialization, were processed in parallel. In the first step, a single group latent class growth model was estimated using the entire sample. Growth parameters included the intercept (I), slope (S), and quadratic term (Q) for each of the three adaptive behaviors. Participants were assigned to the latent classes based on the most likely posterior probabilities (maximum-probability assignment rule). To achieve an appropriate number of classes, a sequence of models was fitted, and the optimum model was determined based on the following model fit indices: smallest Bayesian information criterion (BIC), sample size adjusted BIC, and Akaike's information criterion (AIC); $p < 0.05$ on the Lo–Mendell–Rubin likelihood ratio test (LMR-LRT) and the bootstrap likelihood ratio test (BLRT), and entropy (29–31). Theoretical justification and interpretability were also considered. In the next step, the following three types of multigroup latent class growth models were estimated: total invariance, partial invariance, and non-invariance models. In the total invariance model, both class probabilities and means of growth parameters (I, S, and Q) were constrained to be equal between females and males. The partial invariance model allows differences in class probabilities between females and males, but the means were constrained to be equal. The non-invariance model allows for differences in class probabilities and means between females and males. These models were compared by difference testing using log-likelihoods. Missing values were observed in 2.4% of the total data on adaptive behavior. The number of missing values was not associated with the scores of adaptive behaviors at each time point and with sex. Therefore, we employed the full information maximum likelihood algorithm under the assumption of missing at random (32). These analyses were conducted using Mplus 8.5 (33).

To examine the sex differences in neurodevelopmental traits at age 9 in each latent class, simple linear regression analysis was conducted. Since the test was repeated 12 times, q-values, which are the adjusted p-values using a false discovery rate (FDR) approach (34), were obtained. In addition, in order to compare the test results using different sample sizes, the effect sizes of the differences (η^2) were calculated. The following benchmarks of the effect size provided by Cohen (35) were used: medium ($\eta^2 \geq 0.06$) and large ($\eta^2 \geq 0.14$). Raw ADHD-RS scores were logarithmically transformed because of non-normality. Sex differences in the number of children who exceeded the cutoff values were also evaluated using the chi-square test for each latent class, and the effect sizes of Cramér's V were calculated (36). These analyses were conducted using Stata 15.0 (37).

RESULTS

To detect the appropriate number of classes in a single group latent class growth model, we ran the model from one- to five-class solutions. The values of AIC, BIC, and adjusted BIC

continued to decrease, but the rate of decrease from the 4-class to the 5-class solution was very small (**Table 1**). The *p*-values of BLRT were <0.001 up to the five-class solution. The *p*-values of the LMR-LRT were <0.05, up to the 4-class solution. The entropy values were sufficiently high for all class solutions. Based on the results of the LMR-LRT and theoretical justification, we determined that the 4-class solution was optimal.

The comparison of the multigroup latent class growth models revealed that the partial invariance model was better than the total invariance model [$\chi^2(3) = 1{,}115.2, p < 0.001$], and the non-invariance model was better than the partial invariance model [$\chi^2(18) = 76.1, p < 0.001$]. We therefore adopted the non-invariance model, in which the class probabilities and means were assumed to differ between females and males.

Table 2 shows estimated growth parameters in each sex and domain. **Figure 1** shows estimated trajectories (bold lines) and observed values at each time-point (dashed lines with standard errors) in each latent class. Class 1 (females, 18.6%; males, 17.8%) was characterized with higher scores than the average (standard score of 100) in both sexes in all three domains during the follow-up period. Class 1 displayed a positive slope and negative quadratic term values in all domains (**Table 2**), with gentle inverse U-shape trajectories (**Figure 1**). The largest percentages of children were assigned to Class 2 (females, 48.8%; males, 49.8%). In the communication domain, females in Class 2 had moderately high scores and males had average scores, while in daily living skills and socialization domains, females and males exhibited similar trajectories (**Figure 1**). Class 3 (females, 27.5%; males, 29.4%) was characterized by below-average trajectories. Females assigned to Class 3 achieved scores close to average, whereas males had moderately low scores. Both females and males in this class obtained lower initial scores at 2.7 years of age than their peers in Class 2 in all three domains (**Figure 1**). Class 4 (females, 5.1%; males, 3.0%) had low scores in females and particularly in males. Females in this class had lower initial scores than those in Class 2 and displayed gentle *U*-shape trajectories (**Figure 1**). Males had low initial scores and relatively stable trajectories because slope parameters were not significant in all domains (**Table 2**).

Table 3 summarizes sex differences in neurodevelopmental traits at age 9 in each latent class. The distribution of these neurodevelopmental traits are shown in **Supplementary Figures S1–S4**. Males in Class 2 had higher ADHD-RS total raw scores than females, with medium effect size. **Table 4** shows the number of children who exceeded the cutoff values in each latent class. Sex differences in autistic traits were identified in Class 3 and Class 4. The number of children with autistic traits (SRS-2 T-score ≥60 for male and ≥62 for female) was higher for males than females in Class 3, whereas it was higher for females than males in Class 4 (**Table 4**). Sex differences in ADHD traits were identified in Class 2, Class 3, and Class 4. The number of children who exceeded the cutoff value for ADHD-RS (>85th percentile) was higher in males than females in Class 2 and 3, whereas it was the opposite in Class 4. Sex differences in cognitive ability were identified in Class 4, in which the number of children with below-average IQ was higher for males than females.

DISCUSSION

The present study identified four distinct trajectories of adaptive behaviors from early childhood to school age in a general population. Although the number of identified classes was greater than in previous studies (5–8), trajectories were relatively stable, which is similar to the existing literature. However, we identified, for the first time, that class assignment and estimated trajectories differed between females and males. In the communication domain, females scored higher than their male counterparts in all four classes throughout the observation period. This was not the case in the daily living skills and socialization domains; the two higher adaptive classes had similar trajectories for males and females, but females assigned to the lower two classes had higher adaptive scores than their male counterparts. The results also showed that females assigned to the class with the lowest adaptive skills (Class 4) already had lower scores than their same-sex peers at around the age of 3 years, and then, they exhibited declining trajectories compared with females assigned to the other three classes. These results suggest that comparison with same-sex peers is required for early detection of impairment in adaptive skills, especially in females, and that sex-specific standard scores for adaptive behaviors are necessary.

For each domain of adaptive behaviors, females scored higher than males in communication in all four classes during the follow-up period. In children with TD, it has been reported that females acquire language earlier than males (11), but evidence is limited (38), and little is known about sex differences in communicative adaptive behaviors. In the communication domain, females with TD exhibited significantly better adaptive skills compared to males with TD (39, 40), which is consistent

TABLE 1 | Fit indices of each class solution in the multigroup latent class growth model.

Number of classes	1	2	3	4	5
AIC	105,232.76	101,843.19	100,790.09	100,220.01	100,047.17
BIC	105,360.21	102,024.56	101,025.37	100,509.21	100,390.3
Adjusted BIC	105,277.63	101,907.05	100,872.92	100,321.82	100,167.97
Adjusted LMR-LRT *p*-value	–	<0.001	0.036	0.017	0.929
BLRT *p*-value	–	<0.001	<0.001	<0.001	<0.001
Entropy	–	0.886	0.848	0.865	0.823

TABLE 2 | Estimated growth parameters in the multigroup latent class growth model.

Latent classes	Class 1		Class 2		Class 3		Class 4	
Growth parameters	Females (n = 91, 18.6%)	Males (n = 90, 17.8%)	Females (n = 238, 48.8%)	Males (n = 252, 49.8%)	Females (n = 134, 27.5%)	Males (n = 149, 29.4%)	Females (n = 25, 5.1%)	Males (n = 15, 3.0%)
Communication								
I	105.4*	102.8*	102.3*	99.6*	95.5*	90.7*	89.4*	72.0*
S	6.7*	4.8*	2.3*	−1.1	−1.0	−2.7*	−6.2*	1.3
Q	−0.8*	−0.6*	−0.3*	0.2	0.3*	0.6*	0.99*	0.12
Daily living skills								
I	102.4*	101.2*	99.8*	97.6*	94.3*	90.3*	90.2*	79.5*
S	5.6*	5.3*	2.6*	2.3*	1.1*	0.02	−5.3*	−2.3
Q	−0.8*	−0.7*	−0.5*	−0.4*	−0.2*	0.004	0.7*	0.2
Socialization								
I	104.6*	103.5*	102.2*	100.9*	97.7*	93.7*	95.3*	79.3*
S	5.4*	5.8*	2.4*	0.7	−0.08	−0.8	−6.3*	−5.4
Q	−0.7*	−0.8*	−0.5*	−0.3*	−0.02	0.03	0.7*	0.9*

*$p < 0.05$. I, intercept; S, slope; Q, quadratic term.

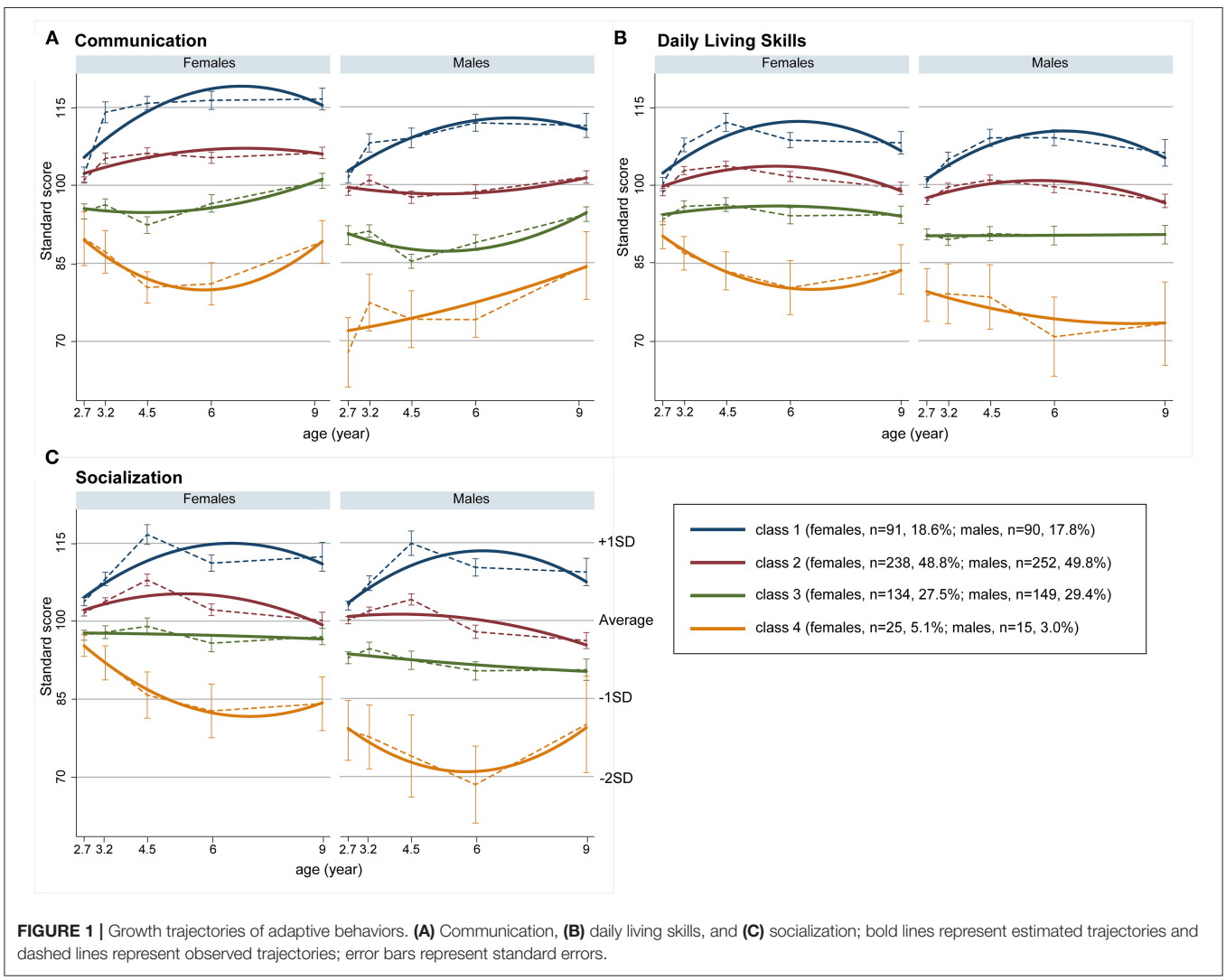

FIGURE 1 | Growth trajectories of adaptive behaviors. **(A)** Communication, **(B)** daily living skills, and **(C)** socialization; bold lines represent estimated trajectories and dashed lines represent observed trajectories; error bars represent standard errors.

TABLE 3 | Sex differences in neurodevelopmental traits at age 9 in each latent class.

		Class 1 (female: *n* = 79; male: *n* = 72)	**Class 2 (female: *n* = 198; male: *n* = 217)**	**Class 3 (female: *n* = 112; male: n=131)**	**Class 4 (female: *n* = 21; male: *n* = 10)**
SRS-2 total raw score; mean (SD)	Female	20.9 (11.1)	30.1 (14.5)	36.1 (17.1)	54.8 (27.0)
	Male	24.5 (12.5)	36.4 (16.0)	45.2 (20.5)	51.2 (21.1)
	Difference testing	$\beta = 0.15$, q = 0.12, $\eta^2 = 0.03$	$\beta = 0.20$, q < 0.001, $\eta^2 = 0.04$	$\beta = 0.23$, q < 0.001, $\eta^2 = 0.05$	$\beta = -0.07$, q = 0.77, $\eta^2 = 0.005$
ADHD-RS total score; mean (SD)	Female	3.2 (3.5)	4.4 (4.7)	5.5 (5.7)	11.5 (7.5)
	Male	4.4 (4.9)	8.4 (7.8)	10.8 (9.1)	12.0 (7.9)
	Difference testing	$\beta = 0.15$, q = 0.12, $\eta^2 = 0.008$	$\beta = 0.30$, q < 0.001, $\eta^2 = 0.08$*	$\beta = 0.32$, q < 0.001, $\eta^2 = 0.05$	$\beta = 0.03$, q = 0.86, $\eta^2 = 0.01$
WISC-IV full scale IQ; mean (SD)	Female	108.4 (11.1)	105.2 (12.7)	98.4 (11.6)	83.6 (16.4)
	Male	109.7 (14.5)	100.8 (12.8)	96.0 (13.5)	78.4 (15.0)
	Difference testing	$\beta = 0.05$, q = 0.66, $\eta^2 = 0.002$	$\beta = -0.17$, q = 0.002, $\eta^2 = 0.03$	$\beta = -0.10$, q = 0.21, $\eta^2 = 0.01$	$\beta = -0.15$, q = 0.59, $\eta^2 = 0.02$

$\eta^2 \geq 0.06$ (medium effect size). SRS-2, the Social Responsiveness Scale, Second Edition; ADHD-RS, ADHD-Rating Scale; WISC-IV, the Wechsler Intelligence Scale for Children-Fourth Edition Compared to the number of children assigned in the latent class growth analysis, there were attrition of 13% for females and 20% for males in Class 1, 17% for females and 14% for males in Class 2, 16% for females and 12% for males in Class 3, and 16% for females and 33% for males in Class 4.

TABLE 4 | Sex differences in the number of children who exceeded the cut-off values of neurodevelopmental traits at age 9 in each latent class.

		Class 1 (female: *n* = 79; male: *n* = 72)	**Class 2 (female: *n* = 198; male: *n* = 217)**	**Class 3 (female: *n* = 112; male: n=131)**	**Class 4 (female: *n* = 21; male: *n* = 10)**
Autistic traits (SRS-2 total T-score ≥60 for male and ≥62 for female); *n* (%)	Female	1 (1.3)	19 (9.6)	22 (19.6)	11 (52.4)
	Male	2 (2.8)	31 (14.3)	41 (31.3)	2 (20.0)
	Difference testing	$\chi^2(1) = 0.44$, q = 0.57, V = 0.05	$\chi^2(1) = 2.1$, q = 0.28, V = 0.07	$\chi^2(1) = 4.3$, q = 0.20, V = 0.13†	$\chi^2(1) = 2.9$, q = 0.21, V = −0.31‡
ADHD traits (ADHD-RS score >85th percentile); *n* (%)	Female	3 (3.8)	22 (11.1)	20 (17.9)	11 (52.4)
	Male	4 (5.6)	39 (18.0)	46 (35.1)	8 (40.0)
	Difference testing	$\chi^2(1) = 0.26$, q = 0.66, V = 0.04	$\chi^2(1) = 3.9$, q = 0.21, V = 0.10†	$\chi^2(1) = 9.1$, q = 0.04, V = 0.19†	$\chi^2(1) = 0.42$ q = 0.62, V = −0.12†
Below-average IQ (WISC-IV full scale IQ < 85); *n* (%)	Female	1 (1.3)	8 (4.1)	11 (9.9)	9 (42.9)
	Male	0 (0)	18 (8.3)	21 (16.0)	5 (62.5)
	Difference testing	$\chi^2(1) = 0.92$, q = 0.46, V = −0.08	$\chi^2(1) = 3.15$, q = 0.23, V = 0.09	$\chi^2(1) = 1.96$, q = 0.32, V = 0.09	$\chi^2(1) = 0.90$, q = 0.46, V = 0.18†

† *Cramér's V ≥ 0.10 (weak association).*

‡ *Cramér's V ≥ 0.20 (moderate association).*

SRS-2, the Social Responsiveness Scale, Second Edition; ADHD-RS, ADHD-Rating Scale; WISC-IV, the Wechsler Intelligence Scale for Children-Fourth Edition Compared to the number of children assigned in the latent class growth analysis, there were attrition of 13% for females and 20% for males in Class 1, 17% for females and 14% for males in Class 2, 16% for females and 12% for males in Class 3, and 16% for females and 33% for males in Class 4.

with our findings. Females with TD were also reported to possess higher scores than males with TD in daily living skills, but scores did not differ between females and males in socialization (40). In contrast, in daily living skills and socialization domains, trajectories in two higher adaptive behavior classes were similar for females and males in the present study. The previous studies reported that males and females with ASD exhibited no significant differences in adaptive behaviors (39, 40). Conversely, in the two lower classes in this study, males generally scored lower than females. The results are not comparable because previous studies included children who had already been diagnosed with ASD, whereas the present study included children with various developmental conditions. Further study is needed on sex differences in adaptive behavior trajectories for children with a variety of conditions as well as children with TD.

The relationship between class assignment and neurodevelopmental traits at age 9 differed between females and males. Males assigned to Class 3 were more likely to have autistic and ADHD traits exceeding the cutoff values, whereas females assigned to Class 4 were more likely to have autistic and ADHD traits. These neurodevelopmental traits were reported to cause a decline in adaptive behaviors (41–43). Females in Class 4 (52.4% having autistic and 52.4% having ADHD traits above sex-stratified cutoffs) already had lower adaptive scores before age 3 compared to their same-sex peers, and this gap widened as time progressed. In addition, their adaptive scores were lower than males in Class 3. A cross-sectional study examining sex differences in adaptive behaviors also found that females with ASD showed lower adaptive functions than males with ASD at older ages, despite females performing better at younger ages (44), which is consistent with our results. These results imply that some females may not be diagnosed with ASD in early childhood and miss opportunities to receive early interventions, leading to the failure to acquire age-appropriate adaptive behaviors over time. Therefore, our results highlight the importance of early interventions to prevent further declines in adaptive behaviors in females with these challenges and those with elevated neurodevelopmental traits. Males assigned to Class 4 displayed lower cognitive scores. Although the percentages exceeding the cutoff for autistic and ADHD traits were not large, the raw scores for those traits were high, suggesting that some males with severe traits were included in Class 4. Males assigned to Class 4 also had demographic characteristics such as lower birth weight, higher birth order, and higher parental age at birth (**Supplementary Table 2**). In addition to the neurodevelopmental traits of children, these characteristics may have influenced their adaptive behaviors. Males with ADHD traits exceeding the cutoffs were assigned to Class 3 as well as Class 4 (**Table 4**). Males assigned to Class 3 also already had lower adaptive scores before age 3 compared to their same-sex peers, but their adaptive behaviors did not decline with age. In addition, females and males assigned to Class 4 showed slight improvements in some adaptive domains at age 9. The reason for these findings is unclear, but one possibility is that adaptive functions were retained or improved in some children by therapeutic interventions such as speech and behavioral therapy, and/or specific educational strategies. To make early interventions possible, it is necessary to identify early signs and patterns of declining adaptive behaviors. Such early signs could be less likely to be identified in females than in males when children of the same age group are taken as a whole, suggesting that it is important to compare the data of individuals against same-sex peers. As suggested in the field of ASD in assessing social functioning (45), establishing sex-specific standard scores would be a useful index for comparison with same-sex peers in the assessment of adaptive behaviors. Because adaptive behaviors are acquired, thus, modifiable, the expansion of the evaluation system and the early support and intervention systems for promoting adaptive behaviors are increasingly critical for effective home, family, school, community, and vocational planning throughout life (46).

STRENGTH AND LIMITATIONS

In the present study, we longitudinally examined sex differences in the trajectories of adaptive behaviors from early childhood to school age using a representative sample and advanced statistical methodologies. However, there are some limitations that must be considered when interpreting the findings. We excluded 264 children from the analysis because they had no measurements on adaptive behaviors. A comparison of the demographic characteristics of the groups included and excluded from the analysis revealed no differences regarding birth weight or gestational age of the children; however, parental age at birth differed between groups. Parental age has been associated with neurodevelopmental disorders (47) and could have influenced the results of the present study. Another limitation is the relatively low prevalence, because our cohort was a representative sample from the general population. Therefore, the lowest adaptive behavior class did not possess sufficient statistical power for subsequent analysis. Future studies involving larger cohorts are required to confirm these results. Finally, neurodevelopmental traits examined in the present study were based on the cutoff point of the scales, but not diagnosis. Neurodevelopmental traits above a cutoff value do not necessarily correspond to a clinical diagnosis. Further research is needed to determine the trajectory of adaptive behavior of children with the actual diagnosis in the general population.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available because they contain information that could compromise the privacy of research participants. Requests to access these datasets should be directed to KT, tsuchiya@hama-med.ac.jp.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Hamamatsu

University School of Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TN conceptualized the study, conducted the statistical analysis, and drafted the original manuscript. TK, THi, MT, and MA provided major revisions to the drafts. AS and KT supervised and critically revised the manuscript. AO, THa, TI, MR, HK, ST, YN, and NT provided feedback and edited the final manuscript. TN, AO, THa, TI, and KT conducted the data acquisition. All authors contributed to the manuscript and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.817383/full#supplementary-material

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Self-Reported Maternal Parenting Stress From 9 m Is Longitudinally Associated With Child ADHD Symptoms at Age 12: Findings From a Population-Based Birth Cohort Study

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Background: Attention-deficit/hyperactivity disorder (ADHD) develops in early childhood and carries lifelong impact, but early identification and intervention ensure optimal clinical outcomes. Prolonged or excessive parenting stress may be a response to infant behavioral differences antecedent to developmental disorders such as ADHD, and therefore represents a potentially valuable inclusion in routine early-life assessment. To investigate the feasibility of using routinely-collected self-reported maternal parenting stress as a risk marker for child ADHD, this study investigated the longitudinal association between maternal parenting stress from 1 to 36 months after childbirth and child ADHD in early adolescence.

Methods: The sample comprised 2,638 children (1,253 girls) from the Tokyo Teen Cohort population-based birth cohort study. Mothers recorded parenting stress five times from 1 to 36 months following childbirth in the Maternal and Child Health Handbook, a tool used for routine early-life assessment in Japan. Nine years later, mothers evaluated their child's ADHD symptoms at 12 y using the hyperactivity/inattention subscale from the Strength and Difficulties Questionnaire.

Results: Approximately 7.5% of parents reported that they had parenting stress at 36 m after childbirth. 6.2% of children were evaluated as above the cut-off for ADHD symptoms at 12 y. Parenting stress at 1 and 3–4 m was not associated with child ADHD

symptoms at 12 y. However, child ADHD symptoms at 12 y was significantly associated with parenting stress at 9–10 m (unadjusted OR = 1.42, p =.047, 95% CI [1.00, 2/00]), 18 m (unadjusted OR = 1.57, p =.007, 95% CI [1.13, 2.19]) and 36 m (unadjusted OR = 1.67, p =.002, 95% CI [1.20, 2.31]). These associations remained after adjustment for child's sex, age in months and family income.

Conclusions: We identified associations between parenting stress at 9–10, 18 and 36 m after childbirth and child ADHD symptoms at 12 years old. Self-reported parenting stress data may have utility as an early indicator for ADHD risk. Participation in early-life health checks, assessment of parenting stress, and tailoring support to family needs should be promoted for early identification and intervention for ADHD.

Keywords: maternal parenting stress, ADHD, birth cohort, Maternal and Child Health handbook, adolescent

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a psychological disorder impacting individuals across the lifespan, and may lead to poorer health outcomes such as depression, psychotic disorder, attempted suicide, and completed suicide (1–3). Approximately 30% of people with ADHD in childhood experience persisting symptoms in adulthood (1). While ADHD is a chronic condition, early identification and intervention have been shown to greatly improve outcomes. For example, interventions for preschool and school-aged children may facilitate social skills and reduce behavioral problems (4, 5). Additionally, parent training has demonstrated benefits for both child, via reduced internalizing and externalizing behaviors, and parent, via increased confidence and decreased parenting stress (6, 7).

Parenting a child is often stressful for parents in general, but parenting children with developmental difficulties may be especially challenging (8). A previous meta-analysis suggested that parents of children with ADHD symptoms experience significantly more parenting stress compared to parents of children without ADHD symptoms (9). Although early precursors of ADHD may be expressed as early as 3–18 months (10–14), ADHD is usually only considered for diagnosis once a child begins pre-school (15). As a result, parents caring for very young children with early ADHD symptoms may endure increased stress for prolonged periods before detection by support services. Prolonged parenting stress may lead to poorer parent mental health outcomes and harsh parenting strategies, both of which are reciprocally related to child ADHD symptom severity (16–18). Therefore, measuring parenting stress could have utility as both an early-life ADHD risk indicator and a signal to health professionals to provide relevant support for caregivers and their child before this cycle begins.

In the present study, we wished to investigate whether parenting stress could be clinically useful as a broad screening method for childhood ADHD risk. Using data from the Tokyo Teen Cohort (TTC), a prospective population-based birth cohort study in Japan (N = 3171), we investigated longitudinal associations between maternal parenting stress during the first 3 years following childbirth and child ADHD at age 12 within a community sample. To ensure clinical feasibility of potential screening, we used the Maternal and Child Health handbook (MCH), which is an already widely-adopted and routinely-used tool for infant health assessment in Japan. The MCH collects parenting stress data via a single self-report item and thus presents minimal time or response burden.

MATERIALS AND METHODS

Participants

We used data from the TTC study (19), which is a population-based birth cohort study of child health and development using data from children and their caregivers. For the first wave of this cohort study, 3171 households with a child aged 10 were randomly sampled using the resident register from three municipalities (Setagaya, Chofu, and Mitaka) in Tokyo, Japan. For the second wave (age 12), 3,007 households participated (follow-up rate: 94.8%). At both waves, trained interviewers obtained written informed consent from the child's primary caregivers. As part of TTC's wider data collection procedure, participants were asked to complete a set of questionnaires. The study protocol of TTC was approved by the institutional review boards from the Tokyo Metropolitan Institute of Medical Science (Approval number [12–35]), SOKENDAI (Graduate University for Advanced Studies [2012002]), and the University of Tokyo [10057].

Measurements

Participants were asked to fill in anonymous self-report questionnaires including questions about ADHD symptoms and sociodemographic characteristics (child's sex, age in months, and family income). Participants were also requested to report the responses recorded in their Maternal and Child Health handbook (MCH) on maternal parenting stress.

Parenting Stress

The MCH handbook is a booklet distributed to newly pregnant women in Japan to facilitate routine assessment of child development and health by mothers as well as healthcare professionals (20). In 2018, 98% of all pregnant women reported receiving the MCH handbook within the first 20 weeks of pregnancy (21). The MCH handbook is used when mothers and their children attend health check-ups offered by the local

health center or pediatric clinics, scheduled at regular intervals coinciding with developmental milestones (1, 3–4, 9–10, 18, and 36 months). In advance of each check-up, mothers answer the following question: "As a result of parenting, are there times when you feel distressed or find it difficult to cope?" Mothers can choose one of the following three responses: "yes," "no," or "difficult to say". In the analysis, these responses were reclassified into dichotomous categories: "no" or "yes/difficult to say," since we assumed that "difficult to say" may reflect that respondents were experiencing parenting stress but were reluctant to indicate so. The primary caregiver copied the parenting stress information from MCH handbook on the self-report questionnaire at the first wave of TTC (age 10).

ADHD

Child ADHD symptoms were assessed using the hyperactivity/inattention subscale from the parent-report Strength and Difficulties Questionnaire (SDQ) (22, 23) at the second wave of the TTC study (age 12). The subscale consists of two items for inattention, two items for hyperactivity, and one item for impulsiveness (24). The three possible responses were "not true" [0], "somewhat true" (1), and "certainly true" (2). The responses from these five items were summed to produce a score from 0 to 10, with higher scores reflecting greater ADHD symptom burden. This subscale offers good predictive and discriminant validity across gender and age groups in adolescence (24). A cut-off value of 7 points or more was used for indicating high risk of ADHD, in line with previous studies (25–27).

Sociodemographic Characteristics

Child age in months (calculated from birth date and survey response date), sex and socio-economic status (measured via family income) were adjusted for in analyses as potential confounders. Family income was categorized into 0–5, 5–10, and 10+ million yen per year, representing the lower, middle and upper thirds of household income distribution in Tokyo.

Analysis

Bivariate binomial logistic regression analysis was used to examine the association between the presence of parenting stress at 1, 3–4, 9–10, 18, and 36 m, and child ADHD symptoms at age 12. Multiple binomial logistic regression analysis adjusting for sex, age in months, and annual household income followed for the above analysis. A full information maximum likelihood (FIML) estimation procedure was adopted to handle missing data (28) under the assumption of missing at random (MAR). All analyses were performed in Mplus 8.4.

RESULTS

Of the 3,007 households that participated the second wave (age 12) survey of the TTC study, 353 were excluded for the following reasons: did not own an MCH handbook, could not confirm whether they possessed an MCH handbook, had not responded to any items in the MCH handbook regarding parenting stress, had not reported child ADHD symptoms at age 12. Thus, the final analysis included 2,654 households (88.2%). Among the 2,654 cases, about half (52.5%) of children were boys. The mean age in months at the second survey wave was 145.9 months. 64.5% of participating households had annual household incomes below 10 million yen. Among 3,007 participants, more than 70% recorded parenting stress at all timepoints (73.4% at 1, 86.4% at 3–4, 85.3% at 9–10, 85.5% at 18, and 85.4% at 36 months).

TABLE 1 | Prevalence of maternal parenting stress during the first 3 years following childbirth, child ADHD at age 12, and demographic characteristics at age 12.

		n	(%)	*N*
Presence of maternal parenting stress[a]				
At 1 month of child's age		913	41.4%	2,206
At 3–4 months of child's age		822	31.7%	2,597
At 9–10 months of child's age		680	26.5%	2,565
At 18 months of child's age		779	30.3%	2,570
At 36 months of child's age		800	31.1%	2,569
Child's ADHD symptoms[b] at age 12		163	6.1%	2,654
Demographic characteristics				
Boys		1,393	52.5%	2,654
Child age in months at 12 y [mean/SD]		145.90	3.62	2,654
Family income at 12 y, million yen per year				
	0–5	392	16.3%	2,399
	5–10	1,155	48.1%	
	10+	852	35.5%	

N, Number of valid responses.

[a] Maternal parenting stress assessed using single self-report item from the Maternal and Child Health handbook (MCH).

[b] Child ADHD assessed using the hyperactivity/inattention subscale from caregiver-report Strength and Difficulties Questionnaire (SDQ).

As shown in **Table 1**, the prevalence of mothers reporting parenting stress was highest at 1 m (41.4%) and lowest at 9–10 m (26.5%). 6.1% of children had SDQ attention/hyperactivity scores indicating high risk of ADHD symptoms at age 12.

Table 2 shows the result of binomial logistic regression analysis of ADHD symptoms at age 12 from maternal parenting stress during the first 3 years after childbirth. At 1 m and 3–4 m, associations between parenting stress and ADHD symptoms at age 12 were not significant. However, ADHD symptoms at age 12 was significantly associated by parenting stress at 9–10 m (OR = 1.42, $p = 0.047$, 95% CI [1.00, 2.00]), 18 m (OR = 1.57, $p = 0.007$, 95% CI [1.13, 2.19]) and 36 m (OR = 1.67, $p = 0.002$, 95% CI [1.20, 2.31]) with increasing strength at each time point. After adjustment for child's sex, age in months, and annual household income, ADHD symptoms at age 12 remained significantly associated by parenting stress at 9–10 m (OR = 1.43, $p = 0.048$, 95% CI [1.00, 2.05]), 18 m (OR = 1.57, $p = 0.010$, 95% CI [1.11, 2.21]) and 36 m (OR = 1.64, $p = 0.005$, 95% CI [1.16, 2.30]) while associations between parenting stress at 1 and 3–4 m and ADHD symptoms at age 12 remained insignificant.

DISCUSSION

To our knowledge, this is the first study to investigate the longitudinal association between maternal parenting stress at multiple intervals from 1 to 36 months post-childbirth and child

TABLE 2 | Logistic regressions ofchild ADHD at age 12[a] from maternal parenting stress during first 3 years following childbirth.

	Unadjusted					Adjusted[c]				
	OR	95%CI			p	OR	95%CI			p
Presence of maternal parenting stress[b]										
At 1 month of child's age	1.13	0.78	-	1.61	0.524	1.11	0.76	-	1.62	0.601
At 3–4 months of child's age	1.02	0.73	-	1.44	0.900	1.04	0.73	-	1.48	0.833
At 9–10 months of child's age	**1.42**	**1.00**	**-**	**2.00**	**0.047**	**1.43**	**1.00**	**-**	**2.05**	**0.048**
At 18 months of child's age	**1.57**	**1.13**	**-**	**2.19**	**0.007**	**1.57**	**1.11**	**-**	**2.21**	**0.010**
At 36 months of child's age	**1.67**	**1.20**	**-**	**2.31**	**0.002**	**1.64**	**1.16**	**-**	**2.30**	**0.005**

OR, odds ratio; CI, confidence interval. Bold text indicates p < 0.05.

[a] *Child ADHD assessed using the hyperactivity/inattention subscale from caregiver-report Strength and Difficulties Questionnaire (SDQ).*

[b] *Maternal parenting stress assessed using single self-report item from the Maternal and Child Health handbook (MCH).*

[c] *Adjusted for sex, age in months, and family income at age 12.*

ADHD symptoms at 12 years old in a population-based birth cohort sample. Our analyses found that parenting stress at 9–10, 18 and 36 months was associated (with subsequent increasing strength) with child ADHD symptoms at 12 years old, though parenting stress at earlier time points showed no such association. This finding suggests that self-reported parenting stress from 9 months may be a useful measure for early identification of children at risk of ADHD.

Our finding that parenting stress at 9–10 months associated ADHD symptoms in adolescence, with increasing strength at 18 and 36 months, raises the question of what differences emerge from 9 to 36 months in children who later develop ADHD that underlie this increase in parenting stress. Sleep disturbances between 0 and 5 years are associated with ADHD in adolescence (29, 30), and are associated with poorer parent mental health (31). Recent studies have also found heightened emotional reactivity at 6 and 9 months to be associated with ADHD, suggesting temperamental differences may emerge around this period (11, 12). The increasing strength of the relationship at 18 and 36 months may reflect that as motor development progresses and the child becomes more mobile, behavior manifesting core ADHD symptoms (e.g., hyperactivity and attentional difficulties) begins to emerge and impact more strongly on parents' wellbeing. Further research with young children with ADHD is necessary to determine how and what developmental differences emerge at this early age.

Parenting stress is a contributor to the increased likelihood of parents of children with ADHD using harsh or negative parenting strategies (16, 32), which may in turn exacerbate externalizing behaviors and other deleterious outcomes associated with ADHD (16, 33), highlighting the pressing need for early intervention. Several meta-analyses have demonstrated that behavioral parent training (PT) may reduce parenting stress, lead to positive parenting, and improve long-term outcomes for both the child and the parent (34–37). PT may confer reduced benefits when the parent themselves has ADHD (38, 39), though a more recent study found limited impact of parental ADHD symptoms on treatment outcomes (40). In either case, since ADHD is a highly heritable condition (41), health practitioners should ensure parental treatment needs (if any) are addressed alongside those of the child to ensure optimal outcomes for both.

This study shows the utility of the MCH handbook (and by extension, single-item self-report measures of parenting stress) for early identification of ADHD risk. This builds on a recent study examining the possibility of early identification of autism via developmental delay recorded in the MCH handbook (42) to encourage utilization of MCH data for early screening of mental health problems. We recommend that health professionals working with families aim to routinely capture parenting stress information, and specifically target parenting stress reduction when building family-specific support programmes.

Our study has a number of strengths. First, we used a large, representative population-based birth cohort, giving substantial ecological validity to our findings and allowing us to control for common sociodemographic confounders. Using the MCH handbook gave access to parenting stress data at frequent intervals over the first 36 months. In addition, since MCH handbook data was collected concurrently with infant health check-ups, our retrospective study design avoids the problem of recall bias. However, this study also had some limitations. First, we did not have parenting stress data beyond 36 months, as the MCH handbook does not record parenting stress after this time point. As such, we were unable to determine if this trend of increasing strength of parenting stress on adolescent ADHD symptoms persists as the child ages; this would be a potentially beneficial target for future research. Second, we used parent-reported child ADHD symptoms, rather than researcher-conducted interviews, teacher ratings, or clinical diagnosis. However, the SDQ attention/hyperactivity subscale has robust psychometrics for detecting ADHD (24, 43, 44), which may substantially offset this limitation. Lastly, the presence of parenting stress was captured by a binary-response question used in the MCH handbook, and since there is high social pressure on parenting success there may be a social desirability bias in response patterns. To get a more detailed picture of how parenting stress relates to child ADHD symptoms, future studies may consider using scales such as the Parenting Stress Index (45). This is particularly prescient as many developmental differences in temperament and behavior associated with ADHD may not be disorder-specific; for example, many are also associated with autism (13, 46). Future studies seeking to

understand mechanisms or specificity of associations with early parenting stress may therefore benefit from including measures of autistic traits or other developmental differences in their analyses, either as control variables or additional outcomes of interest.

In conclusion, our study found that maternal parenting stress from 9 months post-childbirth was associated with child ADHD symptoms at age 12, with increasing strength at 18 months and 36 months. Maternal parenting stress from 9 months may be an indicator of later child ADHD. This time period may be extremely valuable for early intervention to ensure optimal outcomes in families caring for a child with ADHD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tokyo Metropolitan Institute of Medical Science. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AN, KE, and DS conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript, being supervised by KK, MH-H, SA, and MN. JN, SK, SF, YM, MH, KB, NO, NN, KS, and MM critically reviewed the manuscript for important intellectual content and contributed to the discussion. SY supervised the statistical analysis. All authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Being Praised for Prosocial Behaviors Longitudinally Reduces Depressive Symptoms in Early Adolescents: A Population-Based Cohort Study

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Background: Depression is highly prevalent and causes a heavy burden in adolescent life. Being praised for prosocial behavior might be a preventive factor because both being praised and prosocial behavior are protective against depression. Here, we investigated the longitudinal relationship between being praised for prosocial behavior and depressive symptoms in adolescents.

Methods: In Tokyo Teen Cohort study (TTC), an ongoing prospective population-based cohort study, we collected 3,171 adolescents' data on self-reported experiences of being praised for prosocial behavior, depressive symptoms, and caregiver-evaluated prosocial behavior. Ten-year-old children were asked to freely describe answers to the question "What are you praised for?". Only children who clearly answered that they were praised for their prosocial behavior were designated the "prosocial praise group." The degree of depression at ages 10 and 12 was measured with the Short Mood and Feelings Questionnaire (SMFQ), a self-report questionnaire about depression. Objective prosocial behavior of the 10 year-old children was assessed by the Strength and Difficulty Questionnaire (SDQ). Multiple linear regression analysis was performed using the SMFQ score at age 12 as the objective variable and being praised for prosocial behavior as the main explanatory variable, and the SMFQ score at age 10 and the objective prosocial behavior at age 10 were included as confounders.

Results: Depressive symptoms (SMFQ scores) in the "prosocial praise group" were significantly lower than those in the other group both at age 10 (4.3 ± 4.4 vs. 4.9 ± 4.6, $p < 0.001$) and at age (3.4 ± 4.2 vs. 4.0 ± 4.6, $p < 0.01$). In the single regression analysis, the children who reported being praised for prosocial behavior at age 10 had significantly lower depressive symptoms at age 12 (partial regression variable: −0.57,

95% confidence interval (CI) [−0.96, −0.17]). This association remained significant after adjusting for confounders, including baseline depressive symptoms (partial regression variable: −0.44, 95% CI [−0.80, −0.08]). Prosocial behavior alone was not associated with depressive symptoms.

Conclusions: Being praised for prosocial behavior rather than objective prosocial behavior at 10 years of age predicted lower depressive symptoms 2 years later. Praise for adolescents' prosocial behavior can be encouraged to prevent depression.

Keywords: adolescents, depressive symptoms, prosocial behavior, cohort study, longitudinal study, praise

INTRODUCTION

Depression is highly prevalent and causes a heavy burden in adolescent life (1); depression is the 8th cause of global years lived with disability (YLDs) in 10–14 years of age, 2nd in 15–19 years of age and 1st in 20–24 years of age. Thus, prevention strategies are required at all levels, including the individual, family, school, and society levels. Since praise influences self-esteem (2, 3), which is associated with depression (4), praising could prevent depressive symptoms in adolescents. An empirical research showed that parental verbal affection associated with well-being in late adolescence (5). Further, perceived praise from parents was associated with lower levels of depression in adolescents (6).

The manner and content of praise influences the self-esteem and positive attitude of adolescents. Overly positive and inflated praise has been suggested to lower self-esteem in children (3). It was also suggested that person-focused but not process-focused praise leads children to avoid challenges in school (7). Furthermore, praise for behavior (process) was better than praise for personal qualities in terms of the effect on the self-esteem of children (2). Taken together, praise for behavior may be important in preventing depressive symptoms in adolescents, but it is still unknown which behaviors of children should be praised.

A negative correlation between prosocial behavior and depressive symptoms has been noted (8). Further, since prosocial behavior predicted future decreased depressive symptoms in adolescents (9), praise for prosocial behavior is a candidate preventive strategy against depressive symptoms in adolescents. However, no study has investigated the association between recognition of being praised for prosocial behavior and depressive symptoms in adolescents. Furthermore, no study has examined whether being praised for prosocial behavior has a preventive effect on depressive symptoms in adolescents. We hypothesized that being praised for prosocial behavior would be longitudinally associated with decreased depressive symptoms in adolescents. This study aimed to examine the longitudinal relationship between being praised for prosocial behaviors and depressive symptoms using a large-scale cohort of adolescents sampled from the general population.

Abbreviations: YLDs, years lived with disability; TTC, Tokyo Teen Cohort study; SDQ, the Strength and Difficulty Questionnaire; SMFQ, the Short Mood and Feelings Questionnaire; IQ, intelligence quotient; WISC, the Wechsler Intelligence Scale for Children; K6, Kessler Psychological Distress Scale; SD, standard deviation; CI, confidence interval.

METHODS

Study Design and Survey Participants

The purpose of this study was to test the hypothesis that being praised for prosocial behavior would be longitudinally associated with decreased depressive symptoms in adolescents. We adopted 10–24 years as the definition of the age of adolescence according to the recent review (10), thus called the study participants as early adolescents. This study used data from the Tokyo Teen Cohort study (TTC), a prospective population-based cohort study that is currently underway and aims to investigate the developmental trajectory of adolescents (11). Children born between September 2002 and August 2004 in three local governments in Tokyo (Setagaya, Mitaka, and Chofu) were randomly extracted using the Basic Resident Register. Of the 10,234 pairs of children and their primary caregivers who were asked to participate, 4,478 pairs agreed to cooperate in the baseline survey (the 1st wave of data collection) at the age of 10 years. An oversampling method was used with the goal of having 3,000 pairs remain in the 2nd wave survey (11). Given the low follow-up rate of low-income families, all 620 pairs whose annual household incomes was lower than five million yen were asked to participate in the 2nd wave survey. Of the remaining 3,858 pairs, 2,551 were randomly asked to participate in the 2nd wave. A total of 3,172 pairs were asked to participate in the longitudinal cohort study, resulting in 3,007 pairs participating in the second wave of data collection at the age of 12 years (follow-up rate was 94.8%).

In each of the 1st and 2nd waves of data collection, trained investigators visited the participants' home twice and interviewed children and their primary caregivers. At the first visit, the investigators explained the research to both the child and the primary caregiver, obtained written consent, and asked them to complete the self-report questionnaire by the second visit. At the second visit, the child and the primary caregiver separately answered a self-report questionnaire containing sensitive content and sealed it immediately after completion. All questionnaires and data were collected anonymously. At this visit, the investigators also administered face-to-face psychological tests to the child.

TTC is a joint study of three institutions (Tokyo Metropolitan Institute of Medical Science, the University of Tokyo, and

the Graduate University for Advanced Studies) and has been approved by the ethics committees of the three institutions.

Measures

The children answered self-report questionnaires including items on experiences of being praised, depressive symptoms and other variables, such as the number of siblings. Caregivers answered self-report questionnaires that included questions about the caregiver's age, psychological distress, educational background and annual household income.

Experience of Being Praised for Prosocial Behavior

In the self-report questionnaire at the 1st wave, 10 year-old children were asked to freely describe answers to the question "What are you praised for?". We dichotomized the answers to "prosocial praise group" and "other praise group." We did not score the degree of prosociality but just divided the answers to the two groups. A qualitative classification was made by several researchers (DN, NT, HN, MT) as to whether prosocial behavior was included in the answers, double-checked by other researcher (DN, NT), and was finally confirmed by several experienced researchers (MM, TK). Based on a previous study (12), we defined prosocial behavior as voluntary, intentional behavior that results in benefits for another; the motive is unspecified and may be positive, negative, or both. Only children who clearly answered that they were praised for their prosocial behavior such as "helping with housework" were designated the "prosocial praise group," and other children who did answer but did not include prosocial behavior in their responses such as "getting a good score on the exam" were designated the "other praise group." Children who made multiple responses were also classified as the "prosocial praise group" if more than one of their answers included prosocial behaviors. Blank fields were treated as missing values.

Objective Prosocial Behavior

There may be children who behave prosocially but not be praised for their prosocial behaviors. There may also be children who are praised for their prosocial behaviors but do not recognize they are praised for their prosocial behaviors. The children's recognition of being praised for prosocial behavior does not necessarily correspond to the children's objective prosocial behavior. Objective prosocial behavior of the 10 year-old children was assessed by the Strength and Difficulty Questionnaire (SDQ), for which the primary caregivers answered in the self-report questionnaire in the 1st wave of data collection. The subscale score for prosocial behavior in the SDQ was calculated (13).

Depressive Symptoms

The Short Mood and Feelings Questionnaire (SMFQ), a self-report questionnaire about depression (14, 15), was used to investigate the degree of depression in children in the 1st (10 years old) and 2nd (12 years old) waves of data collection. Each of the 13 items had three response choices: "True" (2 points), "Sometimes true" (1 point), and "Not true" (0 points). The scores for each item were summed into the total score (0–26 points), and higher total scores meant stronger depression.

Confounding Variables

Previous studies on the relationship between praise for children and prosocial behavior adjusted for the children's sex, age, number of siblings, caregivers' age and educational history (16–18), and one study suggested socioeconomic status as a potential confounder in future studies (18). Therefore, we included children's sex, age, number of siblings, caregivers' age and education, and annual household income as potential candidates for confounders. In addition, using external knowledge, we added children's estimated intelligence quotient (IQ) and psychological distress of primary caregivers (mainly mothers) in the 1st wave as potential candidates for confounders. Children's IQ was estimated from two subsets (Information and Picture Completion) of the Wechsler Intelligence Scale for Children (WISC-III) (19). Psychological distress of primary caregivers was assessed by the Kessler Psychological Distress Scale (K6) (20). Among these potential confounders, we regarded the variables that showed a significant association with the prosocial self-report as confounders.

Statistical Analysis

For comparison of the demographic characteristics between the "prosocial praise group" and the "other praise group," *t*-tests, tests of differences in population ratios, or χ^2 tests were used. To investigate the relationship between being praised for prosocial behavior and depressive symptoms, linear regression analysis was performed using the SMFQ at the 2nd wave (12 years old) as the objective variable and being praised for prosocial behavior as the main explanatory variable. The variables which showed significant difference between the "prosocial praise group" and "other praise group" were treated as confounders. In addition, the SMFQ score at the 1st wave (10 years old) and other confounders were treated as covariates, and multiple regression analysis was performed after supplementing missing values using the multiple substitution method (number of multiple imputations: $m = 200$). Furthermore, since there is a gender difference in the development of prosocial behaviors in adolescence (18), we examined the interaction effect of sex and prosocial self-reports on depressive symptoms. An interaction term of sex X prosocial self-report was added in the multiple regression analysis. For statistical analyses, open-source statistical software R (version 3.6.1) and the multiple substitution method calculation package mice (version 3.6.0) were used.

RESULTS

Demographic Characteristics

Table 1 shows the demographic characteristics of 3,007 pairs of children and primary caregivers who participated in both the 1st (10 years old) and 2nd (12 years old) waves. Regarding the question "What are you praised for?", 845 (28.1%) children answered that they were praised for prosocial behavior (prosocial praise group), while 2,118 (70.4%) did not report any prosocial behaviors (other praise group). The prosocial praise group had a

TABLE 1 | Descriptive statistics of the study participants ($n = 3007$).

	Source	All participants	Missing	Being praised for prosocial behaviors ($n = 845$, 28.1%)	Being praised for other behaviors ($n = 2,118$, 70.4%)	*p*-value
		Mean ± SD/*n* (%)	(*n*)	Mean ± SD/*n* (%)	Mean ± SD/*n* (%)	
Characteristics of child						
Age		10.2±0.3	4	10.2±0.3	10.2±0.3	0.279
Female sex		1,418 (47.2)	0	477 (56.4)	925 (43.7)	<0.001***
Estimated IQ[a]	Child	107.7±14.1	3	107.2 ±13.9	108.0±14.1	0.157
Depressive symptoms[b] at age 10	Child	4.7 ±4.6	45	4.3± 4.4	4.9±4.6	<0.001***
Depressive symptoms[b] at age 12	Child	3.8 ±4.5	490	3.4 ± 4.2	4.0±4.6	0.001**
Prosocial behavior[c] observed	Caregiver	6.7 ±2.0	10	7.1 ±2.0	6.5 ±2.0	<0.001***
Family characteristics						
Age of primary caregiver	Caregiver	42.1 ±4.2	4	42.0±4.2	42.1 ±4.2	0.512
Age of primary caregiver's partner	Caregiver	44.1 ±5.1	144	43.9±5.1	44.2 ±5.1	0.184
Number of siblings	Child	1.1 ±0.8	0	1.2 ±0.8	1.1±0.8	0.019**
Psychological distress[d] of primary caregiver	Caregiver	8.9 ±3.3	16	9.0 ±3.3	8.9 ±3.3	0.561
Educational background of primary caregiver	Caregiver					
High school or less		503 (16.7)		147 (17.4)	346 (16.3)	0.870
Vocational school or two-year college		1,314 (43.7)		362 (42.8)	936 (44.2)	
Four-year university		1,075 (35.7)		305 (36.1)	754 (35.6)	
Six-year university or graduate school		105 (3.5)		30 (3.6)	73 (3.4)	
Missing		10 (0.3)		1 (0.1)	9 (0.4)	
Educational background of primary caregiver's partner	Caregiver					
High school or less		497 (16.5)		151 (17.9)	334 (15.8)	0.624
Vocational school or two-year college		384 (12.8)		104 (12.3)	278 (13.1)	
Four-year university		1,588 (52.8)		450 (53.3)	1,117 (52.7)	
Six-year university or graduate school		346 (11.5)		97 (11.5)	244 (11.5)	
Missing		192 (6.4)		43 (5.1)	145 (6.8)	
Annual household income	Caregiver					
0 to 2.99 million yen		130 (4.3)		33 (3.9)	96 (4.5)	0.546
3 to 4.99 million yen		452 (15.0)		134 (15.9)	304 (14.4)	
5 to 9.99 million yen		1,446 (48.1)		411 (48.6)	1,018 (48.1)	
≥10 million yen		866 (28.8)		234 (27.7)	623 (29.4)	
Missing		113 (3.8)		33 (3.9)	77 (3.6)	

SD, standard deviation; IQ, intelligence quotient.

*** $p < 0.001$, ** $p < 0.01$ *(p-value for t-test or χ^2 test).*

[a] *IQ was estimated from the two kinds of scores in the Wechsler Intelligence Scale for Children (WISC-III).*

[b] *Depressive symptoms were self-reported with the Short Mood and Feelings Questionnaire (SMFQ).*

[c] *Prosocial behaviors were parent-evaluated with a subscale from the Strength and Difficulties Questionnaire (SDQ).*

[d] *Psychological distress was self-reported with the Kessler Psychological Distress Scale (K6).*

significantly higher percentage of girls (female: 56.4% vs. 43.7%, $p < 0.001$) and had more siblings (1.2 ± 0.8 vs. 1.1 ± 0.8, $p < 0.05$) than the other praise group. Depressive symptoms (SMFQ scores) in the prosocial praise group were significantly lower than those in the other praise group both at the 1st wave (4.3 ± 4.4 vs. 4.9 ± 4.6, $p < 0.001$) and at the 2nd wave (3.4 ± 4.2 vs. 4.0 ± 4.6, $p < 0.01$). The rate of children with objective prosocial behavior (subscale score for SDQ) at 10 years old was significantly higher in the prosocial praise group than in the other praise group (7.1 ± 2.0 vs. 6.5 ± 2.0, $p < 0.001$). The estimated IQ at age 10 tended to be lower in the prosocial praise group (107.2 ± 13.9 vs. 108.0 ± 14.1, $p = 0.16$). There were no significant differences in the age of children, age of caregivers, psychological distress of primary caregivers (K6 scores), educational background of caregivers, or household income between the two groups.

The Association Between Prosocial Self-Reports at 10 Years of Age and Depressive Symptoms at 12 Years of Age

Table 2 shows the results of simple linear regression analysis and multiple linear regression analyses to investigate the longitudinal relationship between prosocial self-reports and depressive symptoms in children. In the single regression analysis, the children who reported being praised for prosocial behavior at age 10 had significantly lower depressive symptoms at age 12 [partial regression variable: −0.57, 95% confidence interval (CI): −0.96 to −0.17, $p < 0.01$]. In the multiple regression analysis, in addition to the child's age and sex, objective prosocial behavior, the estimated IQ and the number of siblings were added as confounders because they were significantly different between the prosocial praise group and the other praise group (**Table 1**). Caregivers' age and education, annual household income, and psychological distress of primary caregiver (K6 scores) were excluded from confounders because there were no significant differences between the prosocial praise and other praise groups. Statistical analysis was performed after missing values were complemented by multiple substitution. Even after adjusting for confounders, being praised for prosocial behaviors at 10 years of age was significantly associated with lower depressive symptoms at 12 years of age (partial regression variable: −0.44, 95% CI: −0.80 to −0.08, $p < 0.05$). There was no evidence for the interaction effect of sex and prosocial self-report on depressive symptoms ($p = 0.22$).

DISCUSSION

This is the first study that investigated the longitudinal relationship between the perceived experience of being praised for prosocial behaviors and depressive symptoms using a large-scale cohort of early adolescents from the general population. Based on the multiple linear regression analyses, the self-report of being praised for prosocial behaviors at 10 years old, but not objective prosocial behavior, predicted lower depressive symptoms 2 years later even after adjusting for baseline depressive symptoms.

Self-report of being praised for prosocial behavior predicted lower depressive symptoms 2 years later in adolescents. Being praised for prosocial behavior means being praised for behavior (process) and being praised for altruism, both of which can be preventive against depression. According to the theory about praise, process praise maintains self-esteem (2). Additionally, prosociality can be preventive against depression. A previous study suggested that helping others may increase self-acceptance and self-confidence and consequently improve depression (21).

Furthermore, rather than objective prosocial behavior alone, being praised for prosocial behavior decreased future depressive symptoms in adolescents. There may be several explanations for the findings of the present study. First, being praised might be an important process of fostering self-acceptance and self-confidence as a result of prosocial behaviors. Being praised might

TABLE 2 | The association between being praised for prosocial behaviors at age 10 and depressive symptoms at age 12.

	Unadjusted			Adjusted		
	B	**95% CI**	***p*-value**	**B**	**95% CI**	***p*-value**
Being praised for prosocial behavior	−0.57	(−0.96 to −0.17)	0.005**	−0.44	(−0.80 to −0.08)	0.017*
Depressive symptoms at baseline[a]				0.43	(0.39 to 0.47)	<0.001***
Prosocial behavior at baseline[b]				−0.05	(−0.13 to 0.03)	0.221
Female sex				0.47	(0.11 to 0.77)	0.004**
Age in month				0.03	(−0.02 to 0.07)	0.321
Estimated IQ[c]				0.00	(−0.01 to 0.02)	0.497
Number of siblings				0.17	(−0.02 to 0.39)	0.082

B, regression coefficient; CI, confidence interval; IQ, intelligence quotient.

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Unadjusted: simple regression analysis.

Adjusted: multiple regression analysis (multiple assignment methods, number of multiple imputations = 200) adjusted for depressive symptoms at age 10, parent-evaluated prosocial behavior at age 10, sex, age in months at age 10, estimated IQ at age 10, and number of siblings at age 10.

[a] *Depressive symptoms were self-reported with the Short Mood and Feelings Questionnaire (SMFQ).*

[b] *Prosocial behaviors were parent-evaluated with a subscale from the Strength and Difficulties Questionnaire (SDQ).*

[c] *IQ was estimated from the two kinds of scores in the Wechsler Intelligence Scale for Children (WISC-III).*

strengthen the recognition of adolescents' prosocial behaviors, which then leads to self-acceptance. Second, being praised might prompt further prosocial behavior and attitudes, which then leads to self-acceptance. Third, this study results may reflect the relatively strong relationship between interdependent self-construal and depressive symptoms in the Japanese culture (22). Being praised for prosocial behavior might affect self-construal stronger than the prosocial behavior itself, then lead to decrease of depressive symptoms. In any case, the present study further added that the recognition of being praised for prosocial behavior might decrease depressive symptoms more than the prosocial behavior itself.

This result would not necessarily be contrary to a previous study which showed that prosocial behavior served as a protective factor against depressive symptoms in adolescents (9) because the previous study did not assess being praised for prosocial behavior. It should also be noted that the previous study targeted a social minority (Latino immigrants to the United States) with a mean age of 14.5 years, so it was not entirely consistent with the population of interest in this study.

There are several strengths of this study. First, this study revealed a longitudinal relationship between recognition of being praised for prosocial behavior and depressive symptoms with the 2 year follow-up period. Second, since this study used a large-scale (n = 3,007) general population sample of adolescents, a certain generalizability of the results would be assured. This is significant because it provides suggestions for intervention methods for adolescents, who are at high risk of developing depression. Third, the follow-up rate was very high (94.8%). Fourth, we conducted the analyses while including several confounders, such as depressive symptoms at baseline, estimated IQ, and number of siblings.

There are several limitations to this study related to the fact that we assessed praise for prosocial behavior by asking the children. First, we cannot determine whether the children were actually praised. There may be children who did not describe the experience of being praised for prosocial behaviors in the questionnaire but actually had an experience of being praised for such behaviors. However, on the other hand, we could assess the importance of children's recognition of being praised for their prosocial behavior in preventing depression, which would conversely be a strength of this study. Second, since the participants were 10 year-old children, a recall bias should be noted for their responses. Third, we could not investigate parenting styles or parental habit to praise which could be important factors in how children experience praise. Fourth, since the study participants were sampled only in Japan, the generalizability to other countries is questionable. Similar investigation in other countries is needed in the further research.

Clinical implications can be derived from the results of this study. With regard to preventing depressive symptoms, caregivers and professionals in relation with adolescents should consider praising prosocial behaviors when they see them. In addition, we should devise ways to praise so that children receive the message that they have been praised for their prosocial behavior. In future research, the objective assessment of praise for prosocial behavior should be considered as well as subjective assessment. Additionally, an intervention study is required to examine the effect of praising children for prosocial behaviors on preventing depressive symptoms.

CONCLUSIONS

Being praised for prosocial behavior rather than objective prosocial behavior at 10 years of age predicted lower depressive symptoms 2 years later. Further study is required to examine the effect of praising children for prosocial behaviors on preventing their depressive symptoms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tokyo Metropolitan Institute of Medical Science (12–35), the University of Tokyo (10057), and SOKENDAI (Graduate University for Advanced Studies) (2012002). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DN, NT, SA, MM, and TK designed the work. DN and NT conducted statistical analyses and wrote the draft of the manuscript. SA, KE, SY, AN, MH-H, and KK contributed to data acquisition. All authors reviewed the draft manuscript critically and approved the final version of the manuscript.

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