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NEUROPSYCHOPHARMACOLOGY REVIEWS

The ABCD study: understanding the development of risk for mental and physical health outcomes

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Following in the footsteps of other large "population neuroscience" studies, the Adolescent Brain Cognitive Development℠ (ABCD) study is the largest in the U.S. assessing brain development. The study is examining approximately 11,875 youth from 21 sites from age 9 to 10 for approximately ten years into young adulthood. The ABCD Study® has completed recruitment for the baseline sample generally using a multi-stage probability sample including a stratified random sample of schools. The dataset has a wealth of measured attributes of youths and their environment, including neuroimaging, cognitive, biospecimen, behavioral, youth self-report and parent self-report metrics, and environmental measures. The initial goal of the ABCD Study was to examine risk and resiliency factors associated with the development of substance use, but the project has expanded far beyond this initial set of questions and will also greatly inform our understanding of the contributions of biospecimens (e.g., pubertal hormones), neural alterations, and environmental factors to the development of both healthy behavior and brain function as well as risk for poor mental and physical outcomes. This review outlines how the ABCD Study was designed to elucidate factors associated with the development of negative mental and physical health outcomes and will provide a selective overview of results emerging from the ABCD Study. Such emerging data includes initial validation of new instruments, important new information about the prevalence and correlates of mental health challenges in middle childhood, and promising data regarding neural correlates of both healthy and disordered behavior. In addition, we will discuss the challenges and opportunities to understanding both healthy development and the emergence of risk from ABCD Study data. Finally, we will overview the future directions of this large undertaking and the ways in which it will shape our understanding of the development of risk for poor mental and physical health outcomes.

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INTRODUCTION

A number of large "population neuroscience" studies have been undertaken over the past two decades, both in the U.S. and internationally, ushering in an exciting new era in understanding the development of risk for negative physical and mental health outcomes. For example, the Adolescent Brain Cognitive Development℠ (ABCD) study is currently underway and was devised to better understand the development of both healthy and disrupted brain and behavioral development [1–3]. The ABCD Study® was begun in the footsteps of several other studies pioneering open access techniques, non-convenience study samples, and including longitudinal and neuroimaging components (for e.g., see ref. [4–6]). The ABCD Study is the largest study in the U.S. to date assessing brain development, examining youth from age 9 to 10 for approximately ten years into young adulthood. The ABCD Study dataset has a wealth of measured attributes of youths and their environment, which will be described below, including neuroimaging, cognitive, biospecimen, behavioral, youth self report and parent self-report metrics, and environmental measures. Initial driving questions of the ABCD Study included examining risk and resiliency factors associated with the development of substance use [3, 7, 8]. However, the ABCD Study has expanded beyond this initial set of questions and will also greatly inform our understanding of the contributions of biospecimen-derived (e.g., pubertal hormones, genomic, and epigenetic factors), neural, and environmental factors to the etiology of mental and physical outcomes from middle childhood through early adulthood [9].

The ABCD Study provides many unique opportunities for understanding the development of both healthy behaviors and risk for mental health challenges. First, the ABCD Study utilized a school-based national recruitment strategy with limited exclusion criteria, helping to overcome challenges to previous general population studies that generally did not include neuroimaging [10] as well as attempts to understand the risk factors associated with negative outcomes that relied on convenience samples [11]. Second, the ABCD Study also includes an embedded twin sample. This will allow researchers to better disentangle the influences of genetic versus environmental factors on development [12]. Third, the ABCD Study has an unprecedented sample size (i.e., 11,875 youth at baseline). This enables the development of reliable standards of development across a number of metrics, including the brain, biospecimens (e.g., pubertal hormones), and cognition. Fourth, the ABCD Study focuses on adolescence. Adolescence is arguably a critical and unique period for understanding the evolution of risk and resiliency [13]. Fifth, the ABCD Study will follow youth longitudinally throughout adolescence. This will enable examining which factors most strongly predict the emergence and

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progression of both positive and negative physical and mental health outcomes.

The current review will describe how the ABCD Study was designed to elucidate factors associated with the development of negative mental and physical health outcomes. This review will also provide a selective overview of results already emerging from the ABCD Study. This review will discuss the challenges and opportunities to understanding the development of risk using the ABCD Study. Lastly, we will discuss the future directions of this massive undertaking that will shape our understanding of the development of risk in adolescence.

OVERVIEW OF THE ABCD STUDY

Sampling strategy

The ABCD Study has completed recruitment for the baseline study sample ($N = 11{,}875$; youth = 9–10-years-old; 47.8% female; 52.1% White, 15.0% Black, 20.3% Hispanic, 2.1% Asian, and 10.5% other [e.g., biracial]) and will be continuing to follow these youth for at least ten years. An important motivation for ABCD Study sampling techniques was to reflect the sociodemographic variation of the US population. The recruitment approach of the ABCD Study was generally through public schools, including charter and private elementary schools, though the embedded twin sample (described below) used a birth record approach. Overall, the ABCD Study aimed to utilize a multi-stage probability sample of eligible youth, selecting a stratified, probability sample of schools across the U.S. in order to capture demographic diversity [14]. However, some participants (<10%) were recruited via other means, including through community events, non-targeted schools, and referral systems. Further, the selection of collaborating sites was constrained by the requirement that engaged locations had to have both the research expertize and the neuroimaging equipment required by ABCD Study protocol [14].

The ABCD Study has 21 sites that are distributed nationally. For each site, the ABCD Study created a catchment area, defined as all schools within 50 miles of the research institution [14]. Each school within the catchment area was coded according to several factors, including geographical location, racial, ethnic and sex composition, and percentage of students receiving free or subsidized lunches as an index of socioeconomic status (SES). Based on this information, the ABCD Study used stratified sampling of schools within each site's catchment area, and a subset of schools was randomly selected from this list of potential schools within each catchment area. Procedures were used to ensure that systematic sampling biases in recruitment at the school level were minimized [14].

The ABCD Study then recruited eligible children from each of the randomly selected schools within the catchment area. Initial recruitment often involved the delivery of hard and electronic copies of recruitment materials to caregivers. In total, 11,875 children completed the baseline assessment. In the end, the ABCD Study sample is epidemiologically informed and designed to reduce selection bias that plagues convenience samples. However, the degree to which this sample is fully representative of the U.S. population will vary across outcome measure examined. The use of weighting methods that evaluate the distributions in relationship to U.S. demographic characteristics will be a helpful additional tool when attempting to make claims about representativeness [15].

In addition to this school-based approach, there are four ABCD Study sites that recruited samples of monozygotic and dizygotic twins (Washington University in St. Louis, University of Minnesota, University of Colorado at Boulder, and Virginia Commonwealth University), resulting in ~860 twin pairs in the baseline sample. These sites each have over 25 years of experiences in the recruitment of twin populations and therefore used existing recruitment processes [12]. For example, these sites used approved vital records approaches to capture a diverse set of twins generally representative of the demographics of their respective states [12]. Each of these sites also recruited "singletons" using the school-based approach described above. The inclusion of twin samples was designed to enhance the ability to make causal inferences about factors contributing to both healthy and disordered brain and behavioral development. For more details on sampling strategy, recruitment, and retention, including twin sample recruitment, please see refs. [12, 14, 16].

Structure of the ABCD Study

The ABCD Study is a consortium composed of a Coordinating Center, a Data Analysis, and Informatics Center, and members from the 21 research sites (https://abcdstudy.org/study-sites/). Work groups facilitate data collection and quality control for current and future ABCD Study data collection waves. All youth are asked to come for in-person assessment sessions once a year, with brief remote assessments at 6 months between in-person sessions. Self-report, behavioral, and biospecimen collections occur yearly, while brain imaging occurs bi-annually (Table 1). Below, measures collected for each of the assessment domains are briefly reviewed. Many of these assessments are described in more detail in a special issue of Developmental Cognitive Neuroscience published in 2018 [1, 7, 17, 18].

Assessment domains

The ABCD Study assessments can be loosely grouped into seven domains: substance use, mental health, physical health and biospecimens, neurocognition, gender identity and sexual health, culture and environment, and brain imaging. Each domain was designed to use instruments with documented reliability and validity, be developmentally sensitive, engage the most appropriate informant depending on the developmental stage and domain (e.g., parent versus youth), minimize participant burden, and be informed by previous relevant literature on both healthy and disordered brain and behavioral development. Furthermore, the inclusion of multiple informants for certain measures, including obtaining information from youth, caregivers, and teachers regarding youth mental health at baseline (youth = 9–10-years-old), helps to mitigate potential unreliability of youth reports due to variability in language skills and retrospective reporting problems. For each domain, additional assessments have been added in follow-up years, which are described in the Annual Release Notes of the ABCD Study data releases on the NIH National Data Archive. Additionally, ABCD consortium members have added several sub-studies to the ABCD Study protocol for future waves of data collection. These sub-studies include adding measures to address reactions to Hurricane Irma and the COVID-19 pandemic, and a sub-study focused on behavior in youth that might put them at risk for involvement in the justice system.

Substance use. For an overview of measures started at baseline and year 1 (youth = 10–11-years-old), please see ref. [7]. The goal of the substance use assessment was to start with the very earliest indicators of exposure to and knowledge about substances, and then to capture the onset, timing, and quantity of any substance use that emerges during the course of the ABCD Study data collection. A variety of measures collected from youth are used to accomplish this goal, with a central one being the Timeline Followback interview [19, 20] designed to establish the specifics of substance use onset and timing. Factors impacting substance use are also assessed, including assessments about intentions to use, expectations about substance effects, curiosity, and motivations regarding substances, perceptions about peer beliefs regarding substances, assessment of sibling use, and community risk and protective factors. Further, parents are asked about their youth's substance use, family rules about substance use, availability of substances in the environment, and a range of community risk and protective factors. Lastly, biospecimens (saliva and hair) are assessed for exposure to alcohol and substances.

Table 1. Adolescent Brain and Cognitive Development Study.

	Baseline (in person)	6 months (phone / on-line)	**Year 1 (in person)**	18 months (phone / on-line)	**Year 2 (in person)**	30 months (phone / on-line)	**Year 3 (in person)**	42 months (phone / on-line)	**Year 4 (in person)**	Ongoing ….
Participant Age	9-10 yrs		10-11 yrs		11-12 yrs		12-13 yrs		13-14 yrs	
Substance Use & Related Factors										
Youth Self-Report on Substance Exposure/Use	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Related Risk and Protective Factors	✓		✓		✓		✓		✓	
Saliva & Hair Samples	✓		✓		✓		✓		✓	
Mental Health & Related Factors										
Parent-Report on Youth	✓		✓		✓		✓		✓	
Youth Self-Report	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Parent Self-Report	✓									
Parent Report on Family	✓									
Physical Health & Related Factors										
Parent-Report on Youth	✓		✓		✓		✓		✓	
Youth Self-Report	✓		✓		✓		✓		✓	
FitBit					✓				✓	
Saliva for Hormone Assessment	✓		✓		✓		✓		✓	
Saliva/Blood for DNA & Health Factors	✓				✓				✓	
Neurocognition										
NIH Toolbox	✓				✓				✓	
Other "cold" cognitive measures	✓				✓		✓		✓	
Other "hot" cognitive measures			✓				✓			
Gender Identity and Sexual Health	✓		✓		✓		✓		✓	
Culture and Environment										
Parent-Report on Youth/Family	✓		✓		✓		✓		✓	
Youth Self-Report	✓		✓		✓		✓		✓	
Geocoding / Neighborhood Factors	✓		✓		✓		✓		✓	
Brain Imaging	✓				✓				✓	

Note. = Questionnaires and interviews; = biospecimen samples (e.g., saliva, hair, blood); = Fitbit; = saliva sample for hormone assessment; = NIH Toobox; = "cold" cognitive measures; = "hot" cognitive measures; = geocoded factors; = brain imaging measures.

Mental health. For an overview of all measures that started at baseline and year 1, please see ref. [1]. The goal of the mental health assessments is capturing categorical and dimensional assessments of current and past mental health from the parent and youth perspective, as well as teacher perspective, and assessing traits and characteristics relevant to understanding risk trajectories for mental health. The core of the categorical assessment of youth mental health is the new computerized Kiddie-Structured Assessment for Affective Disorders and Schizophrenia (KSADS), used to assess parent-report of youth mental health as well as youth's self-report [21–23]. This version of the KSADs is not clinician administered, though youth are aided by research assistants. In early ABCD Study assessment waves, most modules are completed by a parent/caregiver (mood, psychosis, anxiety, externalizing, sleep, and suicidality), with a subset also completed by youth (mood, anxiety, sleep, and suicidality), with the number of modules completed by youth increasing across the course of the study as developmentally appropriate.

A range of dimensional measures of mental health are completed by either or both the parent/caregiver and youth, and the core of these dimensional assessments is the Achenbach system of emprically based assessment (ASEBA) system [24, 25] generously provided at no cost to the ABCD Study. The parent/caregiver annually completes the Child Behavioral Checklist as a broad dimensional assessment of youth mental health. The parent/caregiver also completes additional measures of early signs of mania and autism spectrum symptoms, youth temperament, life events, and emotion regulation abilities, the family's mental health history, and their own mental health and stress. The youth completes additional measures of psychotic-like experiences (PLEs), mania, and conduct disorder, as well as personality traits (e.g., impulsivity, behavioral activation and inhibition, and emotion regulation) and relevant experiences, including friendships, peer relationships, bullying, and life events. The youth completes the ASEBA Brief Problem Monitor (BPM) every 6 months. Lastly, teachers are also asked to report on youth mental health using the BPM for Teachers.

Physical health and biospecimens/genetics. For an overview of all measures that started at baseline and year 1, please see ref. [1]. This assessment includes a lifetime medical, head injury, and developmental history for the youth provided by the parent/

caregiver at baseline, along with annual updates about medical experiences, medications, and head injuries (including sports related). Both the parent/caregiver and youth provide annual descriptions of their pubertal status and saliva assessments of pubertal hormones (including assessing levels of testosterone and DHEA in males and females, as well as estradiol in females). Parent/caregiver and youth also report on experiences with sleep and sleep disorders, including youth reports of sleep chronotypes, respiratory function, and pain experiences. The youth and/or their parent/caregiver provide annual information about diet, frequency of exercise, involvement in sports and other activities, and time spent using various types of electronic media, including TV, videos, social media, etc. Further, in year 2 of data collection (youth = 11–12-years-old), all youth were asked to wear a FitBit for 2 weeks. Fitbits provide data on heart rate, physical activity levels, and sleep. Biospecimens are collected, including baby teeth, saliva, hair, and blood, for purposes of screening for and examining effects of drug use, assessing pubertal hormones, characterizing genetic and epigenetic factors, and assessing the presence and effects of exposure to environmental toxins [9]. Youth who initially provided saliva for DNA assessment are asked to provide blood in later years as they become more comfortable with blood draws.

Neurocognition. For an overview of all measures that started at baseline and year 1, please see ref. [8]. The base of the neurocognitive assessment for ABCD Study is the NIH Toolbox [26, 27], with the complete cognitive Toolbox administered at baseline, and the majority of tasks administered every 2 years. The Toolbox measures were complemented at baseline by additional assessments of verbal learning, matrix reasoning, spatial processing, and delay discounting, with all of these measures other than matrix reasoning repeated approximately for every 2 years [8]. Additional cognitive measures are administered in alternating years, including those that focus on more "hot" aspects of cognition, including an emotional Stroop task, a monetary decision-making task, and a social influence task. Assessments of math ability were introduced in year 3 (youth = 12–13-years-old). These assessments are contextualized by vision assessments for every 2 years, and a measure of hand dominance.

Gender identity and sexual health. The goal of the gender identity and sexual health assessments are to provide developmentally appropriate assessments of gender identity and expression, as well as sexual identity and communication about sexual health. Both youth and parent complete a questionnaire about gender identity, including questions on gender identity and gender expression, with the youth also reporting on dimensional assessments of gender identity.

Culture and environment. For an overview of all measures that started at baseline and year 1, please see ref. [18]. The assessments of culture and environment include both youth and parent/caregiver's perspectives on family relationships, conflict, parent acceptance and rules, familial cultural experiences and values, pet ownership, and other aspects of the home environment such as the nature of home spaces and parent–youth interactions in the home around cognitive and emotional behaviors. This domain also assesses characteristics of the neighborhood from the perspective of the youth and/or parent/caregiver, including perceptions of crime and safety, community cohesion, and school attributes. Data releases also include several variables geocoded based on the participant's address and derived from publicly available data such as the American Community Survey's metrics of socioeconomic characteristics. These variables include population density, neighborhood walkability, county-level crime exposure information, census-tract level estimates of area deprivation indices, air pollution exposure (estimated with a resolution of 100 km^2 of address), and lead exposure risk.

Brain imaging. For an overview of all measures that started at baseline, see ref. [17] and for processing approaches and information about released data, see ref. [28]. Youth participate in a magnetic resonance imaging (MRI) session for every 2 years. This MRI assessment includes measures of brain structure, with both T1 and T2 weighted imaging and diffusion imaging for assessment of white mater integrity. The MRI assessment also includes 20 min of resting state functional connectivity data and functional MRI during three different task domains. These domains were designed to capture brain activity during numerous aspects of cognition and emotion function in as short a time as possible, including working memory, response inhibition, anticipation and receipt of rewards and losses, face processing (both neutral and emotional), and subsequent memory. Processed data from each of these domains is released in tabular format as part of the ABCD Annual Releases using a variety of brain atlases. Raw MRI data is available through the Fast Track release mechanism (https://nda.nih.gov/abcd/query/abcd-fast-track-data.html).

Relationship of the ABCD Study to other studies in youth and adults

The ABCD Study was begun in the footsteps of several other large population neuroscience studies. These studies include the Sanguenay Youth Study (http://saguenay-youth-study.org; N = 1029) [29], the National Institutes of Health Pediatric MRI Database (N = 550) [30], IMAGEN (N = 2000) [6], Pediatric Imaging, Neurocognition, and Genetics study (PING) (N = 1493) [31], National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) (N = 831) [4], Human Connectome Project (HCP) (N = 1200) [32, 33], and HCP-Development (HCP-D; N = 1350 [34]), UK Biobank (N = over 500,000) [35], Generation R (N = 9778) [5], Philadelphia Neurodevelopment Cohort (PNC) (N = ~9498) [36], and the Dunedin Multidisciplinary Health and Development Study (N = 1037) [37], among others. As can be seen in Table 2, in general these previous studies were large (sample sizes > 800), examined a range of ages from beginning prenatally (Generation R) to adulthood populations (e.g., HCP, UK Biobank). Some followed the sample longitudinally (e.g., IMAGEN, UK Biobank, Generation R, Dunedin, NCANDA), or followed a subset longitudinally (e.g., PNC). All included neuroimaging data (e.g., IMAGEN, PING, NCANDA, HCP; note the Dunedin study did not collect neuroimaging data during childhood or adolescence), or included neuroimaging on a subset of participants (e.g., PNC, UK Biobank). Notably, several even included longitudinal imaging (e.g., NCANDA, Generation R, IMAGEN). The ABCD Study complements and extends beyond these other studies by examining measures across development from middle childhood-adulthood at 21 different sites across the U.S. and conducting assessments for every 6 months and imaging for every 2 years. Furthermore, a critical component of the ABCD Study is the open science framework, whereby the ABCD Consortium is releasing data collected from the study in annual data releases to the scientific community. This approach builds upon the open science framework of release while data is still being collected pioneered by a number of previous studies, including the HCP and UK Biobank projects.

Overview of emerging findings from the ABCD Study

The ABCD Study has submitted two data releases, and numerous investigators both within the consortium and from without have been utilizing these data to begin to address questions relevant to both healthy and disordered brain and behavioral relationships. Here, we provide a selective review of some of this emerging research. Notably, the majority of the published emerging work to date is cross-sectional and focused on the initial baseline data set.

Table 2. Examples of previous large population neuroscience studies.

Study Name	Sample Size[a]	Site location	Design	Domains assessed	Ages of sample
Sanguenay Youth	1029	Quebec, Canada	Longitudinal	Imaging, genetic, mental and physical health, and neurocognition	12–18
NIH-PD	550	Six sites across U.S.	Longitudinal	Imaging, mental and physical health, neurocognition, and biospecimen	newborn-adulthood
IMAGEN	2000	Eight sites across four European countries	Longitudinal	Imaging, genetic, mental and physical health, and neurocognition	14, 16, 19, 22
PING	1493	Ten sites across U.S.	Cross-sectional	Imaging, genetic, neurocognition assessments, and mental and physical health	3–20
NCANDA	831	Five sites across U.S.	Longitudinal	Imaging, mental and physical health, and neurocognition	12–21
HCP	1200	Washington University, University of Minnesota	Cross-sectional	Imaging, genetic, mental and physical health, neurocognition	22–35
HCP-D	1350	Washington University, University of Minnesota, Harvard University, University of California at Los Angeles	Cross-sectional[b]	Imaging, genetic, mental and physical health, neurocognition, and biospecimens	5–21
UK Biobank	Over 500,000	UK	Longitudinal (1 follow-up assessment)	Imaging, genetic, mental and physical health, neurocognition, and biospecimen	40–69
Generation R	9778	Rotterdam, Netherlands	Longitudinal	Imaging, mental and physical health, neurocognition, and biospecimen	Prenatal-adulthood
PNC	~9498	Pennsylvania, U.S.	Cross-sectional[b]	Imaging[c], genetic, mental health, and neurocognition	8–21
Dunedin Multidisciplinary Health and Development Study	1037	Dunedin, New Zealand	Longitudinal	Imaging (at age 45), genetic, mental and physical health, biospecimen, and neurocognition	3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, 45

NIH-PD National Institutes of Health Pediatric MRI Database, PING pediatric imaging, neurocognition, and genetics, NCANDA National Consortium on Alcohol and NeuroDevelopment in Adolescence, *HCP* Human Connectome Project, HCP-D HCP-development, PNC Philadelphia neurodevelopment cohort.
[a]Sample size at baseline for longitudinal studies.
[b]Subset followed-up longitudinally (HCP-D $n = \sim 240$; PNC $n = \sim 500$).
[c]Subset ($n = 1445$) obtained imaging.

However, several emerging studies have utilized the partial data available from year 1 [38, 39]. ABCD release 3.0 is slated for release during August 2020, and will include the entire year 1 and part of year 2, which will include repeated neuroimaging assessments. These emerging studies vary in scientific rigor, including using appropriate analytic methods (e.g., nested models), using rigorous multiple comparison control, controlling for potential confounds (e.g., age, sex, race/ethnicity, and SES), and replicating findings. Several of the emerging studies have implemented each of these rigorous inclusions [40–43], and 88% included at least one of these methodologies/techniques.

Measure development and validation. Emerging studies from the ABCD Study have been utilizing a variety of measures to examine an array of both adaptive and maladaptive aspects of cognitive, social, emotional, and neural correlates in middle childhood [1, 7–9, 17, 18]. Many of the measures already have extensive psychometric data. However, in some cases, measures were shortened to reduce participant burden, adapted for use in a younger population, or created from items selected from various other scales. As such, several early emerging studies from the ABCD Study have examined psychometric properties and validity for several measures [44, 45]. Further, emerging studies have begun to utilize the large sample to create short forms [38]. These emerging studies highlight several exciting avenues for examining the properties and novel uses of the ABCD Study measures.

One of the first emerging studies to analyze ABCD Study baseline data examined the properties and conducted some initial validation analyses for a measure of PLEs entitled the Prodromal Questionnaire-Brief Child Version (PQ-BC) [44], including conducting measurement invariance analyses and finding the PQ-BC functioned similarly across sex and race/ethnicity. Another recent emerging study conducted item response theory analyses on the PQ-BC and used information gleaned from these analyses to begin the process of creating a short form that theoretically can be used for future clinical purposes [38]. Similarly, another emerging study examined validity evidence for a novel, abbreviated measure of impulsivity in youth, the UPPS-P Impulsive Behavior Scale [45]. The authors found adequate measurement invariance across gender, race/ethnicity, household income, and parental education, and examined convergent and discriminant validity across a number of relevant characteristics, including youth-reported and parent-reported psychopathology and measures of cognition. Lastly, researchers also used ABCD Study measures to create a 4-item measure of callous-unemotional traits [40], finding evidence for good psychometric properties, including measurement invariance across age, sex, and race, and expected associations with related constructs such as conduct problems, attention deficit and hyperactivity disorder symptoms, and oppositional defiant disorder symptoms. Importantly, these findings replicated in an independent sample. These studies provide important evidence that the ABCD Study sample can be leveraged to conduct rigorous research practices, including examining the psychometric evidence for using existing (or newly created) measures in a middle childhood sample, supporting the use of these measures to better understand the development of risk.

Prevalence and behavioral correlates of psychopathology. There has been great interest in understanding the prevalence and correlates of a range of forms of psychopathology using the ABCD Study's large-scale population-based data. Several emerging studies have utilized the ABCD Study data to examine the prevalence of psychopathology in middle childhood, as well as behavioral and cognitive correlates of psychopathology.

As previously mentioned, one of the first emerging studies published examining ABCD Study baseline data examined associations between PLEs and correlates of psychosis spectrum symptoms [44]. This emerging study found PLEs were associated with several expected associations, such as cognitive impairments (including working memory impairments), motor and speech developmental delays, higher internalizing and externalizing symptoms, greater family history of psychosis, and higher scores on other measures of psychosis spectrum symptoms. Another emerging study found maladaptive guilt was associated with several expected correlates, including family SES, youth-reported family conflict, history of maternal depression, and parental rejection [46]. Emerging research also examined prevalence of eating disorder diagnoses in middle childhood [47], finding the prevalence of overall eating disorder diagnoses was 1.4%, and the prevalence of anorexia nervosa diagnoses was 0.1%. Lastly, an emerging study examined the prevalence and associations with suicidality in middle childhood [48], finding the prevalence of passive suicidal ideation (as reported by youth or parent) was ~6.4%, active suicidal ideation (either non-specific or specific) was ~6.8%, and suicide attempts were ~1.3%. Further, the prevalence of non-suicidal self-injury was ~9.1%. Low parental monitoring was associated with suicidal ideation, suicide attempt, and non-suicidal self-injury, and as with maladaptive guilt, family conflict was associated with suicidal ideation and non-suicidal self-injury. Importantly, the authors replicated these findings in a hold-out ABCD Study baseline sample (i.e., 30% of the baseline sample). Together these emerging studies are beginning to provide an important additional information on the prevalence of various forms of psychopathology in a middle childhood sample, complementing the already existing epidemiological data that is more common in adolescence and adulthood. In particular, this novel data on rates of suicidal ideation and attempts starting in middle childhood is critically informative about the timing of emergence of such thoughts and behavior in relationship to the rates in adolescence already identified by the Centers for Disease Control and Prevention.

Associations between psychopathology and both physical health and the environment. In addition to examining prevalence and behavioral correlates, the ABCD Study baseline sample has also been utilized to assess associations between psychopathology and several environmental and health-related variables. These emerging studies point to several factors, including prenatal drug use, body mass index (BMI), and cognition already showing associations with psychopathology and other health-relevant variables in middle childhood. Emerging work indicates that prenatal cannabis exposure after knowledge of pregnancy is associated with PLEs, but not internalizing, externalizing, or attention symptoms [49]. Another emerging study examined associations between health and environment, including correlates of BMI in middle childhood [50], finding attention problems, social problems, and screen time were all associated with higher BMI, with some evidence that demographic factors (e.g., Hispanic ethnicity, lower income) were most strongly associated with greater BMI. Other emerging research examined associations with sexual orientation and/or gender identity status [51], finding that less than 1% of the sample identifies as a sexual orientation or gender identity minority, and that minority status was not a source of substantial family or school problems. However, further emerging research did show that sexual orientation minority status was associated with greater prevalence of mood disorders and suicidality than in heterosexual-identifying youth [52]. Another emerging study examined the structure of cognition and found evidence for three broad factors representing general cognition, executive function and learning/memory [53], additionally finding that while parent-reported psychopathology (perhaps especially externalizing symptoms and stress reactivity) was associated with cognition, the sizes of the effects were small in magnitude. Furthermore, other emerging work found little evidence that learning a second language was associated with higher executive functioning [54]. Another emerging study examined associations between global cognition and health-related variables, finding higher global cognition scores were associated with meeting recommendations for sleep, screen time, and physical activity [55]. These emerging studies provide important information that will be critical for understanding the development of risk for physical and mental health-related outcomes, as well as several potential avenues for the development of health-related resources and interventions.

Youth behavior and brain structure, function, and connectivity. Research has begun to utilize the wealth of neuroimaging data available from the baseline sample (i.e., Data Releases 1.1 and 2.0.1) in novel and innovative ways to begin to analyze important questions about early neural markers of risk. Emerging research examining resting state functional connectivity (RSFC) to delineate the functional architecture of the brain found RSFC networks were highly reproducible across two samples of ABCD Study data, shared many features of adult-level networks, and showed associations with cognitive functioning [42]. Other emerging research found RSFC associations with general cognitive ability were generalizable across ABCD Study sites and that RSFC within and between task control networks were associated with variability in general cognitive ability [56]. Other emerging work examining brain-cognition associations found that with higher risk of lead exposure, lower family income was associated with lower cognitive functioning, lower cortical volume, and lower surface area [57]. Emerging findings also found higher screen media activity was associated visual brain areas (e.g., occipital cortex) [58], with these associations showing mixed positive and negative relations to cognitive functioning.

Other emerging baseline research has found that higher BMI is associated with lower cortical thickness, especially in prefrontal regions, and lower executive functioning performance [59, 60]. Interestingly, other emerging work found an association between sleep duration and both cognitive function and psychopathology in youth, as well as with variation in brain volume in a variety of regions in the prefrontal, parietal, and temporal cortices [39]. Furthermore, hippocampal volume was associated with depressive symptoms in males and involvement in sports was associated with fewer depressive symptoms, with some evidence that hippocampal volume mediated the association between sports involvement and depressive symptoms [61]. Other emerging research found risk for depression, as assessed by parental history of depression, was associated with lower putamen volume [43]. Further, emerging research examining specifically anhedonia found associations with hypoconnectivity in several RSFC networks, as well as lower activation compared to a group not endorsing anhedonia during reward anticipation, including in cingulo-opercular (CON) network regions and the striatum [62]. Other emerging research found evidence that higher PLEs were associated with lower functional connectivity in several RSFC networks, including lower CON and default mode connectivity [63]. Another interesting emerging study found youth with disruptive behavior problems who also had callous and unemotional traits showed lower gray matter in the amygdala and the insula compared to typically-developing youth. Further, youth with disruptive behavior problems with and without callous/unemotional traits showed alterations in several regions including lower hippocampal volume, though it was limited to the left hippocampus in disruptive youth without callous/unemotional traits [64].

Collectively such data begin to establish the early emergence of alterations in brain structure, function and connectivity associated with a range of forms of psychopathology and individual

differences in cognitive function and behavior, as well as critical environmental influences that shape brain development. Crucially, they also begin to identify both commonalities and dissociations in these relationships. For example, lower hippocampal volume has been associated with both depression and disruptive behavior, while lower amygdala volume has only been associated with disruptive behavior. In terms of connectivity, disruption in the connectivity of the CON network has been associated with higher PLEs, while disrupted connectivity between the CON and the striatum has been associated with anhedonia. It will be critical to determine whether these similarities and dissociations remain over the course of development or whether the patterns of disrupted brain structure, function and connectivity evolve throughout development.

Challenges and opportunities of the ABCD Study

Challenges. One challenge the ABCD Study has encountered is that given data is open access, multiple groups can publish the same or very similar articles. Although members of the ABCD Consortium are encouraged to publish research proposals on the internal ABCD Study site, this information is not available to the public. Other challenges for large-scale studies in general include retaining subjects followed across a decade and potential biases in drop-out rates (e.g., lower SES populations). The ABCD Study has attempted to mitigate these challenges by developing strategies to maintain rapport, keeping detailed current locator information, offering participation-related resources (e.g., travel assistance), and monitoring retention during bi-monthly meetings [16].

Effect sizes: what to expect. As outlined in a recent paper [65], large sample sizes are necessary to examine the earliest markers and mechanisms of disease processes, as these markers are likely to be more subtle early in the course of illness. An opportunity that also presents a challenge is these large data sets enable the detection of very subtle effects not generally detectable in smaller sample studies. The challenge of detecting small effects is determining whether very small effects (i.e., <1% of variance explained) are practically meaningful [65]. Large well-powered samples enable the detection of the earliest subtle associations between predictor and outcome of small effect, prior to larger effect size associations that may emerge later in the disease process. For example, estimating the prevalence of major depressive disorder at 2% in middle childhood [66], the ABCD Study's power = .90 to detect small effect (Cohen's $d = .30$) differences between individuals with major depressive disorder and controls.

Additionally, it is entirely expected that many of these analyses will produce small effects. First, baseline ABCD Study analyses are examining early risk factors of negative mental and physical health outcomes in a generally high functioning non-clinical sample prior to entering the age range of highest risk for a number of negative outcomes (e.g., psychosis spectrum symptoms) [67]. Furthermore, since the ABCD Study is an epidemiologically informed study with a demographically diverse sample [14], rather than a convenience or clinical sample, it is expected that effect sizes will be more "diluted" as they are being examined in the context of a complex set of contextual and background variables. Further, our expectations for effect sizes are likely biased, as it is known that underpowered studies overestimate effect sizes [68, 69]. Thus, the field is in need of well-powered studies, especially in neuroimaging analyses, to better understand the expected effect sizes for these associations in the general population.

Robust exploratory analyses. Another opportunity that the large sample size of the ABCD Study offers is the possibility of conducting exploratory analyses for questions with no strong a priori hypotheses. As the NIMH has recently advocated [70, 71], it will be critical to implement robust and rigorous practices for conducting exploratory analyses. First, we suggest utilizing discovery and replication datasets. Researchers conducting exploratory analyses can conduct analyses on the discovery dataset, and examine whether results replicate in the replication dataset, a technique used to improve the replicability of GWAS studies [72]. Researchers can match these datasets on demographic variables, including sex, race, ethnicity, and age. Given that exploratory analyses are prone to false positives, first examining analyses in a discovery dataset and then testing any findings in a replication dataset reduces the possibility of Type I error. Furthermore, to the extent that it is possible, researchers should specify hypotheses prior to conducting analyses. Ideally, researchers would create a pre-registration or even a registered report detailing hypotheses and analyses prior to conducting analyses (https://cos.io/rr/). Specifying even general hypotheses helps frame the results and can put unexpected results into context. Further, preregistering analysis approaches even in the absence of specific hypotheses helps to avoid problematic analytic approaches resulting in enhanced false positives [73, 74]. Correcting for multiple comparisons is also critical when conducting exploratory analyses. It is important to account for experiment-wide increased false discovery rates, even when conducting multilevel modeling. Further, especially for researchers conducting complicated interaction or genetic analyses, power analyses should be conducted in order to determine whether the analysis is sufficiently powered in the ABCD Study sample [75]. Lastly, researchers should always use best practices in model specification (e.g., nesting ABCD Study site and family) [76].

The importance of replication. The importance of replication is increasingly highlighted as a part of robust research practices [71, 77]. Accordingly, another opportunity that a large study such as the ABCD Study affords is within sample replication. The opportunity to conduct a within sample replication can come in several forms. One possibility is researchers can examine the first data release (Data Release 1.0.1; $N = 4524$) and then replicate findings on the remainder of the baseline sample (Data Release 2.0; remainder sample $N = 7351$). This was recently done examining associations with PLEs [41]. In subsequent data releases, researchers will be able to replicate results across waves, paying close attention to expected developmental alterations that may influence results. Second, as previously mentioned in the exploratory analyses paragraph, researchers can divide the sample into discovery and replication datasets. Third, researchers can also conduct k-fold (e.g., 10-fold) cross-replication [78]. K-fold cross validation is used in predictive modeling to test a model's ability to predict new data not used to create the original model.

However, the gold standard in replication is to use an independent sample with differing methods and sampling techniques in order to ensure that effects are replicable and generalize across samples. As mentioned in the "Overview of the ABCD Study" section, there are a number of large-scale studies that would be ideal for such a replication. For example, the Generation R study is a prospective longitudinal study following individuals from prenatally to young adulthood (Table 2). As with the ABCD Study, the Generation R study is collecting a wide range of outcomes, including physical, behavioral, cognitive, biospecimens, and MRI [5]. In addition, the HCP-D study is collecting data from children ranging from age 5 to 21 (Table 2) [34]. Although the focus of the HCP-D study is on the development of the brain, the study also collects data on puberty, physical activity, health, genetics, and other relevant mental health correlates such as stress [34, 79]. Other studies that may be relevant for replication efforts can be found in Table 2.

Developmental specificity and evolution of risk. The ABCD Study will provide one of the first opportunities to examine a wealth of neuroimaging, genetics, cognition, psychopathological, and

psychosocial factors in the same youth in middle childhood, adolescence, and early adulthood. It will be important for researchers to consider the developmental period in question in order to properly formulate hypotheses regarding risk in each age group, as each period is defined by a unique set of psychosocial and neurobiological alterations. For example, middle childhood is associated with several changes, including continued neuromaturational processes that began in childhood, such as increases in both gray and white matter [80]. Adolescence is a period of often dramatic changes, including hormonal fluctuations and substantial pruning processes [80–83]. Lastly, young adulthood is associated with another set of changes, including in role functioning [84]. In terms of the development of risk, each stage has its own unique set of risk-related factors and developmental changes. For example, adolescence is associated with a spiked increase in risk-taking behaviors, including substance use [8, 13]. Researchers interested in examining ABCD Study data should carefully tune their questions depending on the developmental period from which they are drawing their sample. For example, researchers interested in understanding the progression of risk-taking behaviors, such as the initiation of cannabis use, would likely examine future waves of the ABCD Study (e.g., at year 4 youth = 13-14-years-old) to identify outcome measures and to evaluate response to substance use, but maybe using predictors from an earlier developmental stage. The developmental period in question will also be critical in terms of the covariates of interest in analyses. Pubertal status will be an important covariate in later middle childhood/early adolescence. Likewise, substance use will be an important covariate for many analyses in later adolescence/early adulthood.

The ABCD Study also will provide the opportunity to examine the evolution of risk, including how risk factors change across development and to determine whether there are important variations in the most relevant risk factors at different phases of development. In terms of defining factors that predict variation in developmental trajectories, life course [85] and developmental psychopathology [86] theories suggest that early negative experiences can alter a youth's developmental trajectory [87, 88] and the accomplishment of developmental milestones. However, research has not elucidated whether the consequences of negative life events in terms of mental health are stronger during different development periods, such as in middle childhood versus adulthood. This would have critical treatment and policy implications.

It is also possible that the factors associated with risk may be qualitatively different during different developmental periods. For example, factors associated with risk for depressive symptoms in middle childhood, such as lower physical activity [89], may not be associated with risk for depressive symptoms in young adulthood, as these factors become more normative. In contrast, other risk factors, such as chronic stress and poor social support, may be consistently associated with risk for depression across development [90, 91], although the degree of severity may be different in different development periods. Thus, it is possible that some risk factors first emerge, and then accumulate over time, versus others are only associated with risk during "critical periods" that may correspond with certain maturational changes.

Balancing large-scale studies with deep phenotyping. Research is increasingly moving towards precision medicine efforts, aiming to tailor interventions for psychopathology to the individual [92, 93]. Thus, one potential criticism of large-scale population neuroscience efforts is the value and utility of massive research efforts for precision medicine. It is possible that in advancing our understanding of the etiology of mental and physical illness, we could obscure the trees for the forest by examining large-scale efforts as opposed to deep phenotyping. Deep phenotyping refers to gathering details about disorder manifestations in a fine-grained manner to more precisely define phenotypes [94], as many phenotypes currently fall short of fully capturing the diverse manifestations of the disorder (e.g., schizophrenia, ASD). However, deep phenotyping is typically only possible with smaller samples, due to the large amount of resources required.

The ABCD Study varies in the depth of assessment across phenotypes. For alcohol and substance use, the ABCD Study uses deeper phenotyping, with finer-grained data on patterns of use, including biospecimen collection, youth and parent interviews of use, as well as reports of peer use, expectancies, and consequences of use. Combined with collection of neuroimaging and genetic data, the ABCD Study poses the opportunity to create a nuanced phenotype of alcohol and substance use across adolescence and young adulthood. In contrast, other phenotypes assessed in the ABCD Study, including psychosis, are assessed with less fine-grained detail. Nonetheless, the insights gained from the ABCD Study can be used to spur subsequent deep phenotyping studies that can examine promising risk factors and mechanisms identified in the ABCD Study data in a more fine-grained fashion in more tailored populations.

Future directions

Longitudinal analyses. Given that the ABCD Study is following youth from age 9 to 10 into adulthood, one of the most important future directions is conducting longitudinal analyses. The fields of psychology and psychiatry have made few reliable advances in understanding causal mechanisms underlying the development of negative mental health outcomes, including substance use disorders and psychosis [95]. Following a cohort of youth through a period of significant risk will provide important information about what trajectories of risk factors significantly predict transition to negative mental and physical health outcomes. Through examining trajectories of neural, cognitive, social, emotional, school, and hormonal functioning, the ABCD Study will be able to isolate factors reliably predicting typical versus atypical development from middle childhood into young adulthood [3].

This ten-year study sets the stage for several potential avenues for longitudinal research, helping to answer fundamental questions about the effects of the onset and progression of symptoms of psychopathology [8]. A major aim of the ABCD Study is to longitudinally examine the neurodevelopmental and behavioral effects of substance use. By analyzing development both pre-exposure and post-exposure, researchers will be able to clarify associations between substance use and outcomes, including neurodevelopmental, neural, behavioral, and cognitive correlates [3, 7, 8]. Another aim of the ABCD Study is to longitudinally examine factors, including social and neurobiological, that might contribute to resiliency either from engaging in substance use or from negative outcomes after initiation [3]. This information will be critical for intervention development, including offering potential avenues to mitigate risk. Thus, longitudinal analyses in the ABCD Study will enable the examination of trajectories associated with the onset and progression of, as well as resiliency from, psychopathology and substance use.

Passive data sampling. Several passive data collection methods, or data collection methods that do not require active responses from participants but instead collect data from the participant, will become available in future ABCD Study assessment waves [96]. Passive data collection can be a critical tool for large-scale studies, as it enables additional data without additional burden. The ABCD Study is conducting passive data collection from mobile devices and wearables (i.e., Fitbits). Mobile and wearable technologies can capture information about participants that is unable to be adequately captured through self-report, including precision regarding social interactions, sleep quality, and activity levels.

One exciting avenue for passive data sampling is understanding the role of social media usage as either risk or resilience markers for physical and mental health outcomes, including substance use. Social media use has been linked to psychopathology in adolescents, including higher symptoms of depression and anxiety [97]. However, previous research has not established screen time as a causal factor in the development of mental health outcomes, or whether altered social media use and screen time are a correlate or consequence of the development of psychopathology [98].

As noted above, starting at year 2, the ABCD Study is also using accelerometers (i.e., Fitbits) to examine sleep quality and activity levels. A wealth of research links poor sleep quality to negative physical and mental health outcomes [99, 100]. The examination of variables such as sleep quality over time will begin to disentangle causality, such as whether poor sleep is a cause or a consequence of negative mental and physical health outcomes. Likewise, increased physical activity is a protective factor for a number of positive physical and mental health outcomes, including maintaining a healthy weight and lessened risk of depressive symptoms [89, 101]. Starting in year 4 of data collection, the ABCD Study will also be using an app to assess phone and app usage with youth and parent permission. Using passive data sampling, the ABCD Study will begin to understand the contributions of physical activity level, sleep quality, and social media use to the development and maintenance of negative physical and mental health outcomes.

Examining complex patterns of interactions. Another future direction for ABCD Study data is examining complex interactions. These examinations will likely take several forms, so the current review will focus on two: modeling moderating influences and examining gene × environment interactions. For the first example of complex interactions, researchers will be able to examine the moderating influences of a multitude of factors including mental health (e.g., internalizing and externalizing symptoms [102]); and psychosocial (e.g., parental influences, social support) factors on the initiation of substance abuse. Further, questions remain about how different types of substance use, such as drugs, alcohol, and nicotine use interact, including their interactive effects on cognition and neurobiology [3]. Research using the ABCD Study will also be able to examine how patterns of use interact with psychopathology and psychosocial variables to predict trajectories. For example, it is possible that substance use interacts with poor social support to predict impairments in social and occupational functioning [103]. The ABCD Study sets to stage the begin to uncover the complex patterns of interactions among psychopathology, psychosocial factors, and neurobiology, as well as their interactive effects on long-range outcomes.

Further, the ABCD Study has oversampled for twins (i.e., the study has approximately 860 twin pairs at baseline). This will allow researchers to leverage this data to examine gene × environmental interactions. Briefly, bivariate twin models can be used in order to examine gene × environment interactions [104, 105], including parsing out how variance associated with additive genetic (heritable) and individual-specific environmental factors contribute to the covariance between indices of interest. Discordant twin study designs can be used to examine whether one twin who was exposed to a certain environment (e.g., an adverse childhood event) has a different trajectory of psychopathology (e.g., PLEs) compared to the twin who was not exposed to this environment. This would provide evidence that in the context of certain genetic constitutions, the exposure to negative environments may alter one's trajectory. Further, researchers will be able to examine polygenic risk scores, scores created to reflect the weighted effect of individual single nucleotide polymorphisms associated with risk for an outcome, to examine how heightened the genetic risk for disorders interacts with environmental factors to predict development of disorders [106]. For example, researchers will be able to examine how schizophrenia polygenic risk interacts with factors such as cannabis use to predict the development of schizophrenia spectrum symptoms. Thus, researchers can use the ABCD Study to begin to tease apart complex genetic versus environmental contributions to psychopathology.

Summary and conclusions

The current review provided an overview of the goals, methods, initial results, and future directions for the ABCD Study for understanding the development of risk. The ABCD Study is a historic study following youth from ages 9 into early adulthood and is currently in its fourth year of data collection. The study operates under an open science framework and therefore annually releases data to the public. It is a large-scale population neuroscience study examining a heterogenous population recruited to reflect U.S. national sociodemographic proportions. The study is collecting data across a spectrum of domains, including mental and physical health, culture and environment, biospecimens, and neuroimaging. Emerging cross-sectional results published from this study have already contributed to novel insights regarding psychopathology and brain and behavior correlates in middle childhood. The ABCD Study aims to better understand both normative and non-normative trajectories of development, examining risk for the development of many mental and physical health outcomes, including substance use.

The characteristics of the ABCD Study, including a large heterogeneous sample longitudinally following youth across development, pose unique opportunities for understanding the development of risk. The heterogenous sample combined with examining a middle childhood sample, years prior to the period of greatest risk for many disorders, often results in finding small-moderate effects. Further, researchers have the opportunity to conduct exploratory analyses that incorporate rigorous best practices for data analysis including conducting power analyses. It will be crucial for researchers to replicate findings either using the ABCD Study sample (i.e., using discovery and replication samples or using additional data collection waves) or using an independent sample (Table 2). As the ABCD Study makes advances in our understanding of risk and resiliency factors associated with psychopathology, it will be critical for researchers to begin to translate these findings into screening and intervention advances.

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AUTHOR CONTRIBUTIONS

NRK and DMB jointly developed an outline. NRK drafted the paper and DMB provided critical revisions and table information. All authors approved the final version of the paper for submission.

ADDITIONAL INFORMATION

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