

Data supplement for Sibley et al., Variable Patterns of Remission From ADHD in the Multimodal Treatment Study of ADHD. Am J Psychiatry (doi: 10.1176/appi.ajp.2021.21010032)

## MTA Collaborators

The Multimodal Treatment Study of Children with ADHD (MTA) was a National Institute of Mental Health (NIMH) cooperative agreement randomized clinical trial, continued under an NIMH contract as a follow-up study and finally under a National Institute on Drug Abuse (NIDA) contract. Collaborators from NIMH: Benedetto Vitiello, M.D. (formerly with the Child & Adolescent Treatment and Preventive Interventions Research Branch), Joanne B. Severe, M.S. (formerly with the Clinical Trials Operations and Biostatistics Unit, Division of Services and Intervention Research), Peter S. Jensen, M.D. (formerly with the Office of the Director, NIMH, currently at REACH Institute and the University of Arkansas for Medical Sciences), L. Eugene Arnold, M.D., M.Ed. (currently at Ohio State University), Kimberly Hoagwood, Ph.D. (currently at NYU); previous contributors from NIMH to the early phases: John Richters, Ph.D. (currently at National Institute of Nursing Research); Donald Vereen, M.D. (currently at NIDA). Principal investigators and co-investigators from the sites are: University of California, Berkeley/San Francisco: Stephen P. Hinshaw, Ph.D. (Berkeley), Glen R. Elliott, Ph.D., M.D. (San Francisco); Duke University: Karen C. Wells, Ph.D., Jeffery N. Epstein, Ph.D. (currently at Cincinnati Children's Hospital Medical Center), Desiree W. Murray, Ph.D.; previous Duke contributors to early phases: C. Keith Conners, Ph.D. (former PI); John March, M.D., M.P.H.; University of California, Irvine: James Swanson, Ph.D., Timothy Wigal, Ph.D.; previous contributor from UCLA to the early phases: Dennis P. Cantwell, M.D. (deceased); New York University: Howard B. Abikoff, Ph.D.; Montreal Children's Hospital/McGill University: Lily Hechtman, M.D.; New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center: Laurence L. Greenhill, M.D. (Columbia), Jeffrey H. Newcorn, M.D. (Mount Sinai School of Medicine). University of Pittsburgh: Brooke Molina, Ph.D., Betsy Hoza, Ph.D. (currently at University of Vermont), William E. Pelham, Ph.D. (PI for early phases, currently at Florida International University). Follow-up phase statistical collaborators: Robert D. Gibbons, Ph.D. (University of Illinois, Chicago); Sue Marcus, Ph.D. (Mt. Sinai College of Medicine); Kwan Hur, Ph.D. (University of Illinois, Chicago). Original study statistical and design consultant: Helena C. Kraemer, Ph.D. (Stanford University). Collaborator from the Office of Special Education Programs/US Department of Education: Thomas Hanley, Ed.D. Collaborator from Office of Juvenile Justice and Delinquency Prevention/Department of Justice: Karen Stern, Ph.D.

## **S1. Baseline Characteristics of the MTA Sample (see MTA Cooperative Group, 1999)**

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<b>Variable</b>	<b>Total Across All Treatment Groups</b>
Age <i>M</i> ( <i>SD</i> )	8.5 (0.8)
Male n (%)	465 (80.3)
Ethnicity n (%)	
White	351 (60.6)
African-American	115 (19.9)
Hispanic	48 (8.3)
Full Scale IQ <i>M</i> ( <i>SD</i> )	100.9 (14.8)
Comorbidity (DISC) n (%)	
Anxiety Disorder	194 (33.5)
Conduct Disorder	83 (14.3)
Oppositional-Defiant Disorder	231 (39.9)
Affective Disorder	22 (3.8)

## **S2. Supplemental Columbia Impairment Scale (CIS) and Impairment Rating Scale (IRS) Analyses to determine optimal threshold for “no impairment.”**

- Sample: MTA Local Normative Comparison Group without baseline ADHD diagnoses (N=258).
- Goal:
  - Select “no impairment” thresholds that are consistent with an approximate percentile of 82 or lower, consistent with interpretation of standardized impairment measures (Goldstein & Naglieri, 2016).
- Method: Parent report on the CIS was collected when participants were under the age of 18. Parent and self report on the IRS were collected when participants were 18 and older. Parent and self reports on the IRS were combined using an item-level OR-rule. Percentiles for measures in the LNCG were calculated by year using the following formula:  $[(m + 0.5 k)/N]*100$ , where  $m$  = number of LNCG obtaining a score at or below the threshold,  $k$  = number of LNCG obtaining a score above the threshold, and  $N$  = total sample size (Crawford et al., 2009).
- Results:

## IRS

IRS Item Responses:

0=No Problem, Definitely do not need treatment or special services

1

2

3

4

5

6=Extreme Problem, Definitely need treatment or special services

	10 year	12 year	14 year	16 year	Average
3 or lower on overall item	95.6%	96.4%	95.0%	96.4%	95.85%
2 or lower on overall item	92.9%	94.4%	92.6%	94.3%	93.55%
1 or lower on overall item	88.8%	91.7%	87.2%	91.4%	89.78%
3 or lower on all items	88.1%	89.7%	87.2%	90.0%	88.75%
2 or lower on all items	81.3%	84.1%	80.7%	82.4%	82.13%
1 or lower on all items	72.4%	74.2%	72.7%	74.1%	73.35%

*Note.* The IRS possessed an overall impairment item that we considered in addition to using an “OR rule” across items. In the end, the OR rule was more sensitive to variations in functioning in the normative sample, providing a psychometrically sounder index of impairment.

CIS (administered to participants under 18 at 2-, 3-, 6-, and 8-year assessments)

CIS Item Responses:

0=No Problem

1

2=Some Problem

3

4=A Very Bad Problem

	2 year	3 year	6 year	8 year	Average
3 or lower on any item	98.3%	96.9%	94.1%	96.4%	96.43%
2 or lower on any item	93.0%	92.2%	87.0%	89.6%	90.45%
1 or lower on any item	69.6%	75.8%	67.5%	72.3%	71.30%
0 on all items	55.8%	58.0%	54.1%	56.6%	56.13%

*Note.* Unlike the IRS, the CIS does not possess an overall impairment item. We also considered a limited set of items that removed CIS items that seemed specifically related to internalizing disorders (i.e., having fun, happiness) and less central to ADHD; however, doing so made almost no difference in the percentage of youth at each threshold (see below). Furthermore, the case was made in the MTA Cooperative group phone call (meeting minutes, 08.25.20) that ADHD may also lead to impairments in traditional internalizing domains for some youth.

### highestitem \* highestitemNOINT Crosstabulation

Count

		highestitemNOINT					Total
		.00	1.00	2.00	3.00	4.00	
highestitem	.00	30	0	0	0	0	30
	1.00	1	70	0	0	0	71
	2.00	0	0	121	0	0	121
	3.00	0	0	0	27	0	27
	4.00	0	0	0	0	9	9
	Total	31	70	121	27	9	258

- Conclusions: A cutpoint of “2” on the IRS and “1” on the CIS are the first cutpoints below the empirically-based percentile threshold of “below 82” for no impairment (Goldstein & Naglieri, 2016). These cutpoints are also theoretically consistent with scale interpretation as they correspond with the first item response below the midpoint of the IRS and CIS scales.
- Limitations: We elected to choose easy to use, item-based thresholds, to preserve clinical applicability and our desire to use an “or” rule to require lack of impairment in all domains (rather than mean score-based cutoffs that could allow high impairment in one domain as long as there was no impairment in others). One limitation of this approach is that, due to the categorical nature of our cutpoints, the adolescent criterion based on the CIS represents a moderately stricter threshold (i.e., approximately 71% percentile) compared to the adult cutpoint based on the IRS (i.e., approximately 82% percentile). The fewer number of response options on the CIS, compared to the IRS, created this asynchrony. This limitation will be considered when interpreting the findings of the study.
- References for Impairment Analyses:

Crawford, J. R., Garthwaite, P. H., & Slick, D. J. (2009). On percentile norms in neuropsychology: Proposed reporting standards and methods for quantifying the uncertainty over the percentile ranks of test scores. *The Clinical Neuropsychologist*, 23, 1173–1195. doi:10.1080/13854040902795018

Goldstein, S., & Naglieri, J. A. (2016). Measuring Impairment with the Rating Scale of Impairment. In *Assessing Impairment* (pp. 247-255). Springer, Boston, MA.

### **S3. Details of Full Remission Classification**

At step 1, symptom remission criteria from our ROC analyses were applied to ensure that cases no longer possessed clinically meaningful ADHD symptoms. At the second step, absence of impairment was evaluated to ensure that subthreshold residual symptoms were unassociated with impairment. At the third step, we required symptom remission to be independent of the therapeutic effects of current medication (i.e., medication use in the 30 days prior to the assessment), recent psychosocial therapy for ADHD (i.e., a full course of psychosocial treatment in the past year), or school-based ADHD intervention (i.e., current school services) by requiring that remitted cases were not being treated acutely.

### **S4. Classification of Persistent and Partially Remitted Cases**

We utilized the DSM-5 definition of persistence validated in Sibley et al., 2016 and Hechtman et 2017 that applied the DSM-5 symptom threshold using the CAARS (or SNAP) and impairment threshold of “3 or higher” based on the IRS (or CIS). Partially remitted cases were those who did not meet criteria for Persistence, but also did not meet criteria for Full Remission due to various rule outs.

### **S5. Consideration of Cases below the ADHD symptom remission threshold with continued impairment that may be better accounted for by a comorbidity.**

Because it is possible that impairment may be due to symptoms other than ADHD, we extracted, for a second round of consideration, cases that met the following criteria: (1) not currently treated for ADHD, (2) below the symptom remission threshold, (3) possessed clinically significant impairment, and (4) met criteria for a mental or substance use disorder (other than ADHD) on the DISC interview. The DISC interview assessed mood disorders (major depression, dysthymia, mania), anxiety disorders (agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, separation anxiety disorder, social phobia, selective mutism, post-traumatic stress disorder), disruptive behavior disorders (oppositional defiant disorder, conduct disorder), substance use disorders (abuse and dependence), and eating disorders (anorexia nervosa, bulimia nervosa). Following extraction, a panel of clinical experts (three child and adolescent psychiatrists, four clinical psychologists) were provided with case information that included the domains of impairment experienced by each case along with DISC diagnoses, and the nature of residual ADHD symptoms (below remission threshold). If a majority of panel members voted that the case should be considered fully remitted from ADHD (i.e., the DISC diagnoses likely explained the reported impairments), the case was considered a tentative full remitter at that time point. In the table below we list the number of cases that were considered for secondary remission at each assessment point, along with the number of cases confirmed as secondary remission by the panel. We also display the details of these cases below.

Assessment Point	N Considered for ADHD Remission in presence of another disorder	Confirmed by Panel
2 year	5	1
3 year	7	3
6 year	5	1
8 year	17	4
10 year <sup>a</sup>	--	--
12 year	22	2
14 year	27	5
16 year	11	2

<sup>a</sup>The DISC was not administered to a majority of participants at the 10 year assessment; as a result secondary remission could not be considered during this time point.

### Details of Fully Remitted Cases with Impairment Due to Another Disorder

Age	Impairment Domain	DSM Dx	Endorsed ADHD Symptoms	Votes for ADHD Full Remission?
12.28	feeling nervous behavior at school, getting along with siblings	Separation Anxiety	Careless mistakes	Yes-6, No-0
11.1	getting along with father, feeling	Simple Phobia	none reported	Yes-4, No-2
11.13	nervous getting along with mother, getting along with siblings,	Simple Phobia	none reported	Yes-6, No-0
11	schoolwork	Simple Phobia, Separation Anxiety	none reported	Yes-5, No-1
16.12	schoolwork	Tic Disorder	none reported	Yes-6, No-0
		Alcohol Abuse, Marijuana Dependence, Nicotine Dependence, ODD, CD	none reported	Yes-7, No-0
17.99	behavior at school, getting along with siblings			

		Selective		
17.41	feeling unhappy or sad behavior at school, involvement in activities, schoolwork	Mutism, Alcohol Abuse	None reported	Yes-7, No-0
17.12	getting along with father, getting along with siblings,	Specific Phobia (miscellaneous)	none reported	Yes-6, No-1
15.72	schoolwork academic impairment, overall impairment, impairment with parents, family impairment, impairment with teachers, romantic impairment, social impairment	Separation Anxiety, selective Mutism	none reported	Yes-7, No-0
20.63	impairment with parents	Marijuana Abuse	none reported avoids tasks that require sustained mental effort	Yes-7, No-0
19.91	sibling impairment, impairment in self-esteem	Marijuana Abuse Alcohol Dependence; taking Abillify/Lithobid for "Bipolar disorder (self-reported)"	difficulty playing quietly, on the go/driven by a motor	Yes-5, No-2
23.89	impairment with parents	CD	talks excessively	Yes-4 No-2
23.86	impairment in self-esteem, family impairment, romantic impairment, overall impairment, family impairment, academic impairment, overall impairment	Marijuana Dependence, Nicotine Dependence	on the go/driven by a motor	Yes-5 No-1
24.00	social impairment, impairment with	Alcohol Dependence	none reported	Yes-6, No-0
21.49				

		parents, academic, impairment in self-esteem, family impairment, overall impairment academic impairment, sibling impairment, impairment with parents, social impairment	PTSD, Marijuana Dependence Specific Phobia of Thunder and Lightning	on the go/driven by a motor	Yes-6, No-0
21.11		impairment with parents		none reported	Yes-6, No-1
26.57		social impairment, impairment with parents, vocational impairment, impairment in self-esteem, family impairment, overall impairment			
23.8	impairment		Alcohol Abuse	none reported	Yes-5, No-2

*Note.* Cases above possess ADHD symptoms that are below the empirically-validated threshold for full remission (i.e., three or fewer symptoms of Inattention and/or Hyperactivity/Impulsivity, but elevated impairment. The clinical panel elected to classify these cases and fully remitted because it appeared that impairments were most likely due to a disorder other than ADHD.

#### **Details of Cases with Comorbidities that the Panel Elected to Retain in the Partially Remitted Category**

<b>Age</b>	<b>Impairment Domain</b>	<b>DSM Dx</b>	<b>Endorsed ADHD Symptoms</b>	<b>Votes for ADHD Remission?</b>
12.15	getting along with mother, getting along with father, behavior at school, schoolwork, behavior at home academic impairment	Simple Phobia	None Reported Doesn't seem to Listen, easily distracted, forgetful	No-6
9.85	behavior at home, getting into trouble, getting along with father, feeling	Simple Phobia, Social Phobia, Separation		No-6

	nervous, getting along with siblings, getting into trouble, getting along with father, behavior at school, feeling nervous, getting along with peers	Anxiety Disorder		
9.5	getting along with father, feeling nervous, getting along with peers	Social Phobia	careless mistakes, difficulty organizing tasks/activities	No-6
9.26	getting along with father, feeling unhappy or sad, involvement in activities, schoolwork	Nocturnal Enuresis	None Reported	No-2, Yes-4
12.94	getting along with siblings, behavior at home social impairment	ODD	careless mistakes, careless mistakes, does not follow through on instructions, difficulty organizing tasks/activities, Blurts out answers, Difficulty waiting in lines, interrupts or intrudes	Yes-2, No-4
11.06	behavior at school, Behavior at School	ODD	careless mistakes, on the go/driven by a motor difficulty	No-6
10.91	schoolwork	Nocturnal Enuresis	organizing tasks/activities, easily distracted, talks excessively, interrupts or intrudes	No-6
11.03	getting into trouble, getting along with mother	Simple Phobia	intrudes	No-6

			fidgets, on the go/driven by motor	
16.29	getting along with peers	Marijuana Abuse	talks excessively,	No-6
15.26	feeling unhappy or sad relationship with mother, relationship with father, behavior at school, feeling nervous, peer impairment, schoolwork,	Alcohol Abuse	blurs out	No-6, Yes-1
14.04	behavior at home	Social Phobia	doesn't seem to listen, difficulty organizing tasks/activities, forgetful	No-7
14	involvement in activities	Tic Disorder	difficulty organizing tasks/activities, Easily distracted, fidgets, leaves seat, on the go/driven by motor	No-7
18	getting in trouble, getting along with mother, behavior at home	Marijuana Abuse, ODD Specific Phobia of thunder and lighting, separation anxiety disorder , Marijuana Abuse, CD	talks excessively	No-7
17	getting along with mother, feeling nervous, getting along with siblings, schoolwork		does not follow through on instructions, avoids tasks that require sustained mental effort, easily distracted	No-7
17.05	getting along with father, getting along with siblings, schoolwork	ODD Specific Phobia, Alcohol Dependence,	difficulty sustaining attention, does not follow through on instructions, difficulty organizing tasks/activities	No-7
17.96	behavior at school, schoolwork		does not follow through on instructions	No-7

		Marijuana Abuse, Substance Dependence, Transient Tic Disorder, CD		
17.59	getting in trouble, relationship with mother, feeling unhappy or sad, behavior at school, getting along with adults, feeling nervous, schoolwork, behavior at home relationship with mother, sad, having fun, getting along with adults, peer impairments, getting involved with activities, schoolwork	CD	does not follow through on instructions, easily distracted	No-7
16.89	getting along with father	Substance Abuse, Major Depressive Disorder	careless errors, does not seem to listen, fidgets does not seem to listen, on the go/driven by a motor	No-7
17.06	getting in trouble, getting along with father, getting along with siblings	Nicotine Dependence	avoids tasks that require sustained mental effort, easily distracted	No-7
17.44	getting along with father, getting along with siblings	Specific Phobia of Needles	difficulty sustaining attention, does not seem to listen, easily distracted, on the go/driven by a motor, talks excessively, Interrupts or	No-7
17.15	feeling unhappy or sad, behavior at school, feeling	ODD Specific Phobia of Needles, separation	Intrudes difficulty sustaining attention, loses	No-7
16.87				No-7

	nervous, getting along with siblings, getting along with peers, schoolwork, behavior at home getting in trouble, relationship with mother, relationship with father, sad, school behavior, having fun, getting along with adults, feeling nervous, peer impairment, trouble joining activities, schoolwork,	anxiety disorder	things, fidgets, leaves seat, talks excessively	
16.01	behavior at home getting into trouble, behavior at school,	ODD, CD	careless errors, difficulty sustaining attention, does not seem to listen, leaves seat, difficulty waiting for things	No-7
16.31	schoolwork	CD	leaves seat does not follow through on instructions, avoids tasks that require sustained mental effort, leaves seat, difficulty waiting	No-6, Yes-1
16.07	getting in trouble, getting along with father, behavior at school, getting along with siblings, trouble joining activities, schoolwork,	CD	for things difficulty organizing tasks/activities, easily distracted, fidgets, difficulty waiting ones turn, interrupts/intrudes	No-7
21.84	social impairment, vocational impairment, family impairment, overall impairment social impairment, impairment with parents, academic impairment, vocational impairment, impairment in self-esteem, family impairment, romantic	Alcohol Abuse Major Depressive Disorder, Alcohol Dependence, Marijuana Abuse, Nicotine Dependence	difficulty organizing tasks/activities, easily distracted, runs about or climbs excessively, on the go/driven by a motor	No-7
22.55				No-7

	impairment, overall impairment, academic impairment, impairment with teachers, impairment in self-esteem, romantic impairment, overall impairment			
21.96	academic impairment, overall impairment social impairment, sibling impairment, impairment with parents, family impairment	Marijuana Abuse	fidgets, runs about or climbs excessively, on the go/driven by a motor	NO-7
21.49	social impairment, sibling impairment, impairment with parents, family impairment social impairment, sibling impairment, impairment with parents, vocational impairment, impairment in self- esteem, family impairment, overall impairment, soical, impairment wiht parents, family impairment, co- worker impairment, supervisor impairment, overall impairment	Alcohol Dependence	does not seem to listen, difficulty waiting ones turn	No-7
21.35	academic impairment, impairment wiht parents, academic impairment, impairment in self- esteem, overall impairment	Marijuana Abuse, Nicotine Dependence, ODD, CD	does not follow through on instructions/fails to finish, avoids taks that require sustained mental effort, fidgets	NO-7
21.29	forgetful in daily activities, fidgets, on the go/driven by a motor makes careless errors, avoids taks	CD; missing YA DISC		NO-7
21.6	CD; missing YA DISC	Alcohol Abuse, Marijuana Abuse	makes careless errors, avoids taks that require	No-7

			sustained mental effort, difficulty playing quietly, on the go/driven by a motor	
21.01	social impairment, academic impairment, impairment in self-esteem, romantic impairment, overall impairment, impairment with parents, overall impairment	Alcohol Abuse	avoids tasks that require sustained mental effort, leaves seat , runs about or climbs excessively, on the go/driven by a motor	No-7
21.1	social impairment, romantic impairment, vocational impairment	Marijuana Abuse; Received Therapy for OCD in this interval	sustaining attention, easily distracted, forgetful in daily activities, talks excessively	NO-7
22.05	social impairment, sibling impairment, impairment in self-esteem, family impairment, romantic impairment, overall impairment	Marijuana Abuse, Substance Abuse	does not seem to listen, avoids tasks that require sustained mental effort, on the go/driven by a motor, blurts out, interrupts/intrudes	NO-7
20.87	academic impairment, academic impairment	Alcohol Dependence	does not seem to listen, on the go/driven by a motor	No-7
20.3	vocational impairment, family impairment	OCD, Marijuana Dependence, Nicotine Dependence	difficulty organizing tasks/activities, avoids tasks that require sustained mental effort, on the go/driven by a motor, talks excessively	No-7

	impairment with parents, impairment in self-esteem, family impairment, overall impairment impairment wiht parents, family impairment, impairment in self-esteem	Tic Disorder; No parent Disc Alcohol Abuse, Alcohol Dependence, Marijuana Abuse, Nicotine Dependence	loses things, forgetful in daily activities makes careless errors, fidgets, on the go/driven by a motor, blurts out does not follow through on instructions/fails to finish, avoids tasks that require sustained mental effort, fidgets, on the go/driven by a motor difficulty sustaining attention, does not seem to listen, easily distracted, on the go/driven by a motor	No-7
20.31	academic impairment, overall impairment, academic impairment	Alcohol Abuse, Marijuana Abuse, Nicotine Dependence	taks that require sustained mental effort, fidgets, on the go/driven by a motor	No-7
20.47	sibling impairment, sibling impairment	Dependence; CD	attention, does not seem to listen, easily distracted, on the go/driven by a motor	No-6, Yes-1
19.41	sibling impairment impairment in self-esteem, family impairment, romantic impairment, academic impairment, impairment with teachers, impairment in self-esteem	Alcohol Abuse, Alcohol Abuse	SN, does not seem to listen, avoids tasks that require sustained mental effort, fidgets, on the go/driven by a motor	No-6, Yes-1
20.15	impairment with parents, impairment in self-esteem, family impairment	Alcohol Abuse; No parent DISC	does not follow through on instructions/fails to finish, difficulty	No-7
19.28		CD		No-7

			organizing tasks/activities, difficulty playing quietly, on the go/driven by a motor, talks excessively	
19.17	sibling impairment, academic impairment, impairment in self- esteem, family impairment, overall impairment, sibling impairment, impairment in self- esteem	Selective Mutism	does not follow through on instructions/fails to finish, avoids taks that require sustained mental effort, blurts out does not follow through on instructions/fails to finish, difficulty playing quietly, on the go/driven by a motor, talks excessively	No-7
19.81	academic impairment	Tic Disorder	makes careless errors, difficulty sustaining attention, difficulty organizing tasks/activities,	No-7
25.01	impairment with parents, academic impairment, vocational impairment, impairment in self- esteem, family impairment, overall impairment	Selective Mutism, Alcohol Abuse	blurts out, difficulty waiting ones turn difficulty organizing tasks/activities, avoids taks that require sustained mental effort, on the go/driven by a motor	No-5
24.14	impairment with parents	Alcohol Abuse, Alcohol Dependence, Marijuana Abuse	easily distracted, leaves seat	NO-4, Yes-1
24.28	impairment with parents, academic	Alcohol Abuse, Nicotine		No-5

	impairment, impairment in self-esteem, family impairment, romantic impairment, overall impairment, impairment wiht parents, family impairment, impairment in self-esteem, overall impairment	Dependence; no parent disc		
23.93	family impairment	CD	difficulty sustaining attention, difficulty organizing tasks/activities, on the go/driven by a motor, difficulty waiting ones turn	No-5
23.9	family impairment	Alcohol Abuse	difficulty sustaining attention, difficulty organizing tasks/activities, easily distracted, difficulty playing quietly, talks excessively, blurts out	No-5
23.59	vocational impairment, impairment in self-esteem, social impairment	Alcohol Abuse, Marijuana Abuse, Substance Abuse; no parent DISC	attention, difficulty organizing tasks/activities, forgetful in daily activities, on the go/driven by a motor, blurts out avoids taks that require sustained mental effort,	No-5
23.5	sibling impairment	Marijuana Abuse	loses things, on	No-5

			the go/driven by a motor, blurts out makes careless errors, difficulty organizing tasks/activities, avoids tasks that require sustained mental effort	
24.18	impairment in self-esteem social impairment, sibling impairment, impairment with parents, vocational impairment, impairment in self-esteem, family impairment, romantic impairment, overall impairment	Generalized Anxiety Disorder, Marijuana Dependence, Substance Abuse		No-5
23.15	impairment social impairment, sibling impairment, impairment with parents, academic impairment, family impairment	Alcohol Abuse	difficulty organizing tasks/activities	No-6
23	impairment impairment in self-esteem, Social impairment, supervisor impairment, impairment in self-esteem	Alcohol Dependence	difficulty organizing tasks/activities, avoids tasks that require sustained mental effort	No-6
22.81	impairment social impairment, sibling impairment, impairment with parents, impairment in self-esteem, family impairment, overall impairment, social impairment, vocational impairment	Alcohol Abuse; no parent disc	forgetful in daily activities, fidgets	No-6
22.88	impairment social impairment, impairment with parents, vocational impairment	Selective Mutism; no parent DISC	avoids tasks that require sustained mental effort, fidgets, runs about or climbs excessively	No-6
22.68	impairment,	Alcohol Dependence, Marijuana	does not seem to listen, difficulty organizing	No-6

	impairment in self-esteem, family impairment, overall impairment	Dependence, Nicotine Dependence, Substance Abuse; CD	tasks/activities, avoids tasks that require sustained mental effort, on the go/driven by a motor difficulty	
22.99	social impairment, romantic impairment	CD	organizing tasks/activities, avoids tasks that require sustained mental effort, runs about or climbs excessively, on the go/driven by a motor, talks excessively	No-6
23.99	social impairment, sibling impairment, academic impairment, vocational impairment, family impairment, overall impairment	Substance Dependence	makes careless errors, loses things, easily distracted, interrupts/intrudes	No-6
22.99	impairment with parents, family impairment, romantic impairment, overall impairment	Alcohol Dependence	easily distracted, on the go/driven by a motor	No-6
21.72	social impairment, sibling impairment, impairment with parents, family impairment, romantic impairment, overall impairment	Marijuana Abuse; no parent DISC	makes careless errors, does not seem to listen, easily distracted, talks excessively, blurts out, interrupts/intrudes loses things, fidgets, runs about or climbs excessively, on the go/driven by a motor	No-6
22.72	academic impairment ,co-worker impairment, supervisor impairment	OCD		No-6

	social impairment, sibling impairment, impairment with parents , impairment in self-esteem,family impairment, romantic impairment, overall impairment, social, family impairment, romantic impairment, overall impairment		does not follow through on instructions/fails to finish, avoids taks that require sustained mental effort, fidgets, on the go/driven by a motor, talks excessively	
22.21	22.21 impairment	ODD	does not seem to listen, avoids taks that require sustained mental effort, loses things, fidgets, leaves seat , difficulty waiting ones turn	No-6
22.26	social impairment, overall impairment social impairment, sibling impairment, impairment with parents, vocational impairment, impairment in self- esteem, family impairment, overall impairment, sibling impairment, impairment in self- esteem	Alcohol Abuse; ODD	avoids tasks that require sustained mental effort, talks excessively	No-6
21.35	21.35 impairment with parents, impairment in self-esteem, family impairment, overall impairment, sibling impairment, impairment in self- esteem	Social Phobia	loses things, on the go/driven by a motor	No-6
21.61	21.61 impairment with parents, academic impairment, impairment in self- esteem	Marijuana Abuse	does not seem to listen, avoids taks that require sustained mental effort, easily distracted	No-6
26.16	26.16 impairment with parents, academic impairment, impairment in self- esteem	Alcohol Abuse, Nicotine Dependence		No-6

	academic impairment, sibling impairment, impairment with parents, family impairment, vocational impairment		difficulty organizing tasks/activities, avoids tasks that require sustained mental effort, fidgets	
26	impairment	Alcohol Abuse	fidgets does not follow through on instructions/fails to finish, difficulty organizing	No-6
25.23	social impairment, sibling impairment, impairment with parents, impairment in self-esteem, family impairment, romantic impairment, overall impairment, romantic impairment	Alcohol Abuse, Marijuana Dependence; ODD Alcohol Dependence , Marijuana Dependence, Substance Dependence, Alcohol Abuse	tasks/activities, avoids tasks that require sustained mental effort	No-6
24.91	impairment with parents social impairment, sibling impairment, impairment with parents, academic impairment, vocational impairment, impairment in self-esteem, family impairment, overall impairment, family impairment	Dependence, Alcohol Abuse	loses things, fidgets, runs about or climbs excessively	No-6, Yes-1
24.6	impairment	Nicotine Dependence, Alcohol Abuse	difficulty organizing tasks/activities, easily distracted, forgetful in daily activities	No-7
24.41	romantic impairment sibling impairment, impairment with parents, overall impairment,	Nicotine Dependence	avoids tasks that require sustained mental effort	No-5, Yes-2
24.42	impairment wiht	Substance Abuse, Alcohol Abuse	on the go/driven by a motor, talks excessively	No-5, Yes-2

	parents, family impairment			
23.72	impairment with parents, impairment in self-esteem, family impairment, overall impairment social impairment, sibling impairment, impairment with parents, impairment in self-esteem, family impairment, romantic impairment, overall impairment, sibling impairment, impairment with parents	Alcohol Dependence, Substance Dependence	difficulty organizing tasks/activities, loses things, on the go/driven by a motor	No-7
23.81		Marijuana Dependence, Nicotine Dependence	avoids tasks that require sustained mental effort, on the go/driven by a motor	No-7

## S6. Rationale for Methodological Choices when Defining Cross-sectional and Longitudinal Categories

Our definition building process emphasized avoidance of known diagnostic pitfalls in the ADHD literature. Specifically we focused on: (1) eliminating recovery and remission definitions that would likely produce known methodological artefacts and (2) making choices that are sensible within the context of the MTA's existing design. Through this process, we arrived at definitions that we believe are optimal.

With respect to the lower bound on duration of recovery, it was imperative to avoid the “snapshot” pitfall that besieges much of the extant research on ADHD persistence and remission—that is, if we allow an individual to be classified as recovered based on just a single time point of data, we cannot be sure that the duration of this remission is any longer than a month (i.e., the observational period elicited on the symptom rating scales). At the very least, we feel obligated to honor the DSM-5’s only guidance on defining remission (APA, 2013), which requires six months of symptom absence for partial remission—thus, we decided that six months should be considered the lower bound for duration of recovery—which rules out the one time point + no evidence of recurrence option for defining recovery.

With respect to the upper bound on duration of recovery, another alternative to our two time point + no recurrence definition could be requiring three or more time points + no recurrence. This would be a stricter definition that would impose a criterion of at least four years of full remission from ADHD + no recurrence to be classified as recovered. The disadvantage of this definition is related to the MTA’s design—participants were only followed until approximately age 25—therefore, most recovery that began after age 21 would be disqualified. As a group, we

decided that (a) because there is no real gold standard for determining the expected duration of recovery for ADHD (the current study is the first to estimate this statistic) and (b) because we wanted to take a moderate approach to defining recovery that balanced risk of false positive and false negative classifications—the two time point + no recurrence definition seemed like a pragmatic choice.

Similar issues were addressed when deciding how to define “stable partial remission.” This category was actually created by process of elimination. After sorting participants into the clinically meaningful “stable persistence,” “recovered,” and “fluctuating status” longitudinal classifications, there was one subgroup of participants who remained unclassified—these individuals had in common that they displayed “one classification change from persistent ADHD to partial remission that maintained until study endpoint.” Though one could argue that this category has low clinical utility, for completeness we created this category, which allowed us to sort all of the ADHD participants in the MTA study (except for a handful of outliers who had higher levels of missing data; see Figure 1) into one of four orthogonal longitudinal categories.

## **S7. Final Definitions for Cross-Sectional and Longitudinal Classifications**

<b>Classification</b>	<b>Definition</b>
Cross-sectional Classifications	
Persistent	DSM-5 symptom criteria (5 or 6 symptoms of either Inattention or Hyperactivity/Impulsivity, depending on age) plus clinically significant impairment (3 or higher on IRS or CIS)
Full Remission	Fewer than three symptoms of both Inattention and Hyperactivity/Impulsivity according to all informants, plus the absence of clinically significant impairment, and discontinuation of all ADHD intervention for at least a month prior to the assessment.
Partial Remission	Those who neither met criteria for persistence, nor full remission
<b>Longitudinal Classifications</b>	
Stable Persistence	Persistent ADHD for the entire follow-up period
Recovered	Full remission of ADHD that persisted for at least two consecutive assessments without a subsequent period of recurrence (i.e., full remission until study endpoint)
Fluctuating	At least two changes to classification since baseline diagnosis of ADHD, in the absence of the recovery pattern
Stable Partial Remission	Displaying one classification change from persistent ADHD to partial remission that maintained until study endpoint.

## **S8. Additional discussion of limitations and considerations regarding the influence of medication on persistence.**

The analyses presented herein have some additional limitations that should be considered.

For example, when using a broad diagnostic approach that includes partial remission as a negative outcome (i.e., a milder, but clinically significant, manifestation of ADHD), the results suggest that most childhood-onset cases (~90%) will continue to experience impairment and/or elevated symptoms during the follow-up period. An alternative interpretation could be offered if one applied a narrow diagnostic approach that considers partial remission to be a non-clinical outcome based on its subthreshold nature.

Following this logic, an alternative interpretation of our findings might be that only those with a chronic, persistent longitudinal pattern (10.8% of the sample) continue to demonstrate ADHD by young adulthood. Under this interpretation, sporadic symptom severity might be considered a positive outcome (i.e., relief from ADHD) versus a negative outcome (i.e., residual ADHD symptoms throughout the follow-up period).

Some of the methodological choices we made in this study were empirically selected because we could find no prevailing precedent in the research literature (i.e., CIS and IRS definitions for “lack of impairment,” statistically-derived threshold for “full remission” of ADHD). We also made several methodological choices in this study based on best diagnostic practices and previously validated methodologies found in past research conducted by our colleagues’ or our own team. For example, our methodology relied on multiple rather than single source verification (i.e., relying on self-report alone) based on past research validating combined reports as delivering incremental diagnostic information in the adolescent and young adult developmental periods (i.e., Barkley et al., 2008; Sibley et al., 2012a/b, 2016, 2017). Though we

present varying exclusion criteria for full remission in a stepwise manner (see Table 1), we opted for a restrictive, multi-phase exclusion criteria for full remission (symptom cutoff and impairment rather than impairment alone, requiring ADHD to be untreated). If we had applied a less restrictive definition of “full remission” (i.e., only relying on symptom desistence), our results might suggest higher rates of recovery and lower rates of partial remission. We hope that Table 1 presents sufficient information to allow readers to consider alternative definitions of full and partial remission, as well as aggregate partial and fully remitting cases at each time point, to envision the range of persistence and remission estimates that may be possible when using alternative definitions. Ultimately, we stand by our choices as representing best practices in the measurement of ADHD symptoms and impairment, as well as empirically-validated criteria.

There were also several possible formulas for calculating normative percentiles in the LNCG. These formulas are either theoretical or empirical. We considered multiple options and selected an empirically derived formula based on appropriateness for the distribution of LNCG symptom data. The use of a percentile cutoff (84%) based on positively skewed ratings of symptom severity in the LNCG has some complications that have been discussed elsewhere but have not been fully addressed here.

In the LNCG, the waxing and waning of symptom ratings also occurs (Sibley et al., 2018, *American Journal of Psychiatry*), but to a lesser extent than in the ADHD groups. When validating the full remission threshold against LNCG normative data, we did not directly adjust for this temporal variation in the ADHD group.

The additional remission exclusion criterion that was applied with respect to current treatment suggests that active treatment with medication confers a benefit to symptoms. This assumption may not be true. There were dramatic decreases in medication use over time in the

longitudinal follow-up and some preliminary data from the MTA suggest that dissipation of relative benefit of medication use over time. This trend is partially substantiated by a lack of symptom deterioration when MTA participants discontinue long-term stimulant medications. Therefore, our decision to be conservative, and require remission independent of medication, could be viewed as a mismatch with signals from the MTA data suggesting that medication use that has been sustained for many years likely has a minimal impact on symptoms in those with desistent profiles. Ongoing work in the MTA study will further clarify the relationship between medication and symptom persistence/remission during the long-term follow-up period.

## **S9. Sensitivity Analyses**

### *Analysis 1: Sensitivity analyses for Recovery Definition based on conservative vs. moderate vs. liberal thresholds for duration requirements*

Based on primary analysis methodology, 50 cases were classified as recovered (9.0%) based on the requirement that recovery sustain for two time points with no evidence of recurrence. If we were to apply the more liberal “one time point + no evidence of recurrence” criterion, we would classify 29 new cases as recovered (total recovery n=79), raising the recovery rate from 9.0% to 14.2%. Each of these 29 new cases experienced their episode of full remission at their final MTA assessment. Therefore, there is no evidence of either continued remission or recurrence because the study ended. Alternatively, if we were to utilize the more conservative “three or more time points + no evidence of recurrence” criterion, only 33 cases would be classified as recovered, lowering the recovery rate from 9.0% to 5.9%. Thus the lower and upper bound for recovery estimates might be 5.9% and 14.2%, respectively.

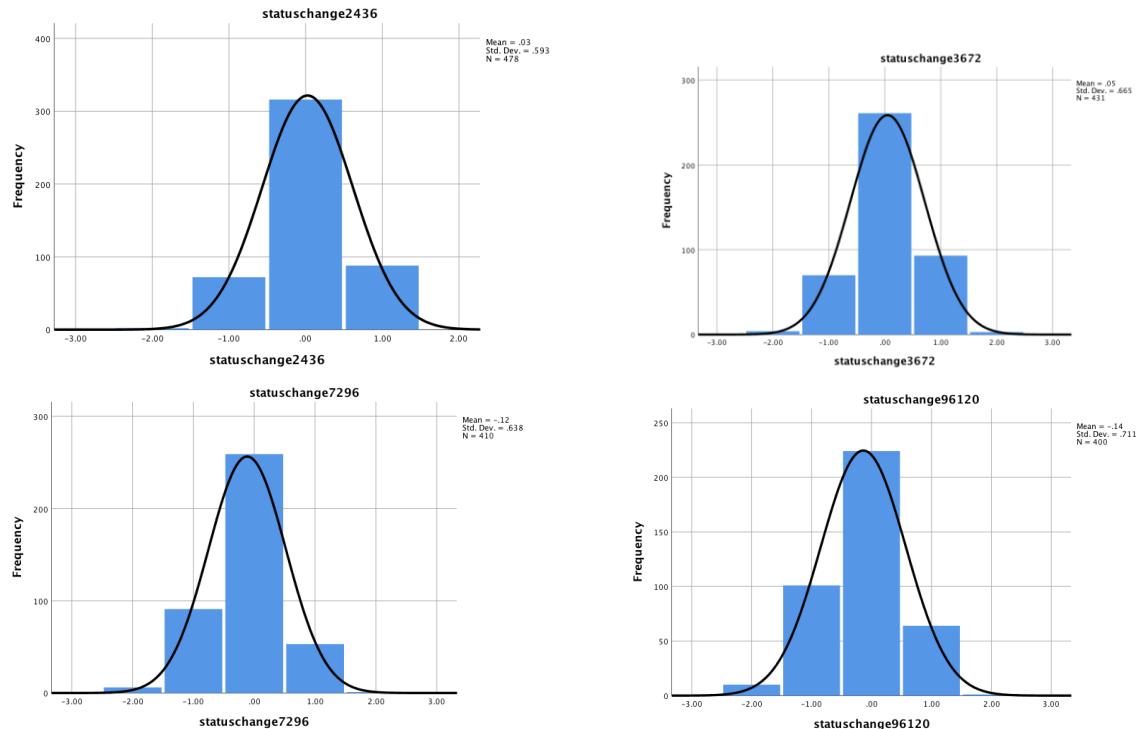
### *Analysis 2: Sensitivity analyses for Longitudinal Classifications based on Varying Missing Data Approaches*

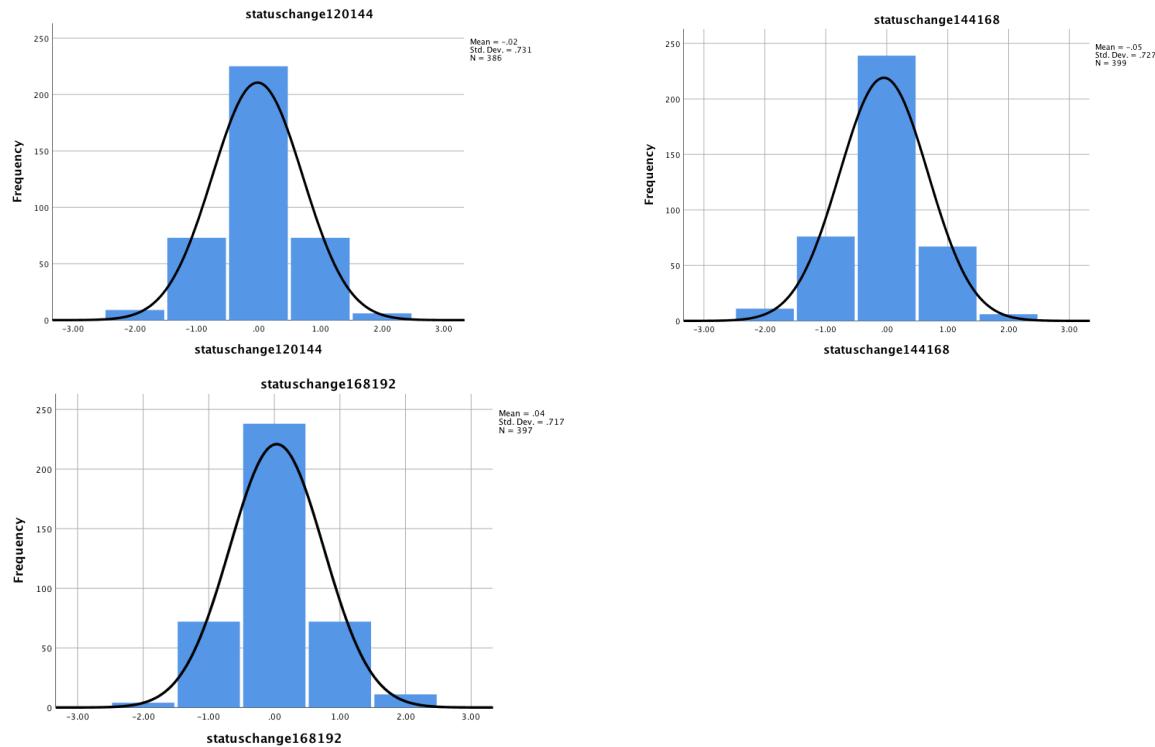
	Primary Analyses (N=558)	Removal of Cases with <3 data points (N=536)	Removal of Cases with any missing data (N=249)
Stable Persistence (%)	10.8	9.3	6.8
Stable Partial Remission (%)	15.6	14.0	4.4
Fluctuating Status (%)	64.0	66.6	75.9
Recovered (%)	9.0	9.3	12.9

*Note.* Sensitivity analyses indicate that the fluctuating pattern may be underestimated based on missing data while the stable partial remission and stable persistence categories may be overestimated.

**Analysis 3: Sensitivity analyses examining the impact of source of information-switching on categorical fluctuations over time.**

To investigate the impact of source of information switching (hereon referred to as “source switching” on categorical fluctuations over time, we first composed variables that represent the direction and magnitude of status changes from each assessment to the following assessment. A score of -2 indicated a two category reduction in status (i.e., from persistent to full remission), -1 a one category reduction in status (i.e., from persistent to partial remission or partial remission to full remission), 0=no change in status, 1 = a one category increase in status (i.e., from full remission to partial remission or partial remission to persistence), 2=a two category increase in status (i.e., from full remission to persistence). Histograms for each of these variables are shown below.





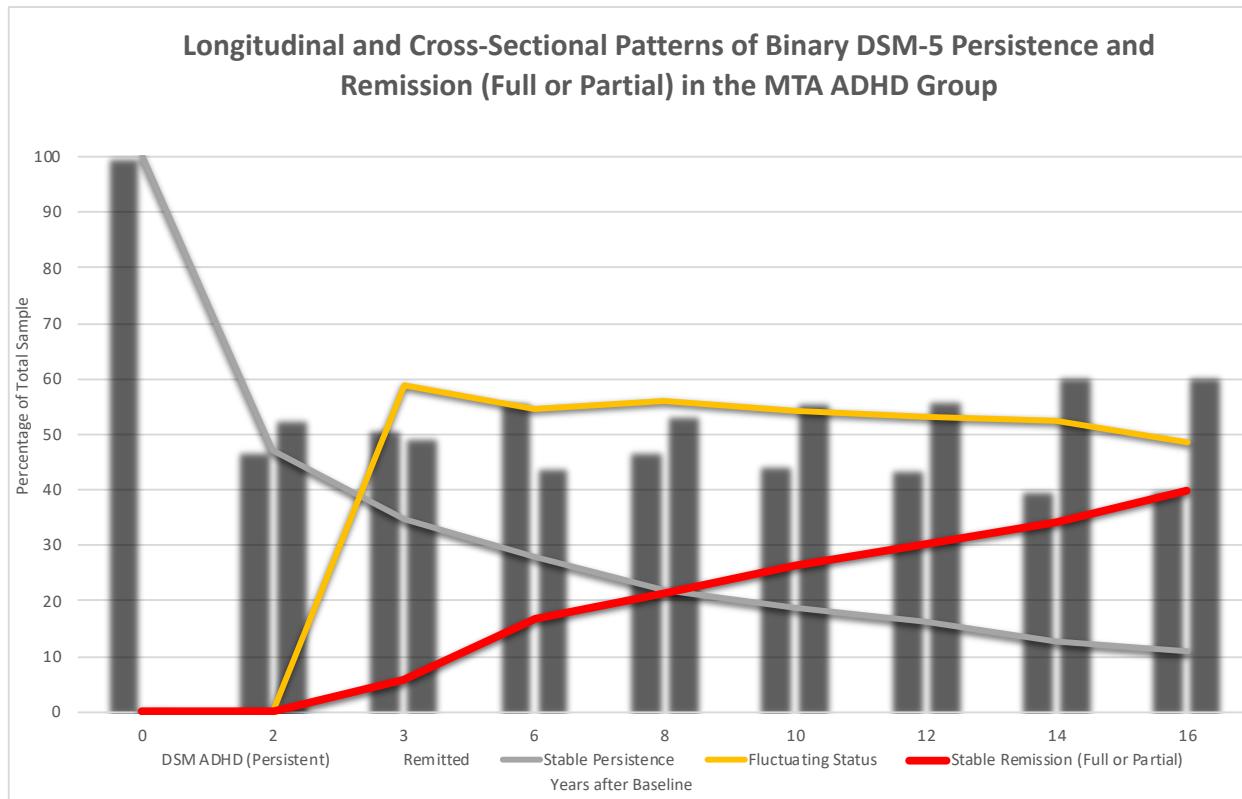
To understand the amount of variance in category changes that may be due to source switching, we created dummy coded variables that represented loss of a rater or gain of a rater between each time point. For assessments with three raters, we created four total dummy codes (loss of two raters, loss of one rater, gain of one rater, gain of two raters). The fluctuation (or status change) variable presented above was regressed upon these dummy codes for each time point. The table below presents the results of these multiple regression models for each time point. Results indicate that as a set of variables, the source-switch predictors accounted for between .07% and 5.1% of the variance in category fluctuations between two time points. While source switching had a significant impact on 5 out of 7 between-timepoint fluctuations, the size of this effect was generally quite modest. Over 95% of the variance in fluctuations was due to a source other than source-switching.

	$R^2$	F	p	b	SE	p
<u>2 year to 3 year</u>	.013	3.14	.044*			
Loss of rater				-.149	.081	.064
Gain of rater				.136	.088	.123
<u>3 year to 6 year</u>	.016	2.34	.073			
Loss of rater				-.155	.089	.081
Gain of 1 rater				.372	.300	.216
Gain of 2 raters				.484	.315	.126

6 year to 8 year	.042	4.44	.002*			
Loss of 1 rater				-.170	.074	.022*
Loss of 2 raters				-.548	.178	.002*
Gain of 1 rater				.073	.117	.532
Gain of 2 raters				1.07	.628	.090
8 year to 10 year	.041	4.27	.002*			
Loss of 1 rater				-.171	.072	.017*
Loss of 2 raters				-.959	.270	<.001*
Gain of 1 rater				.033	.118	.777
Gain of 2 raters				.212	.701	.763
10 year to 12 year	.051	6.78	<.001*			
Loss of 1 rater				-.186	.083	.026*
Loss of 2 raters				-.621	.323	.055
Gain of 1 rater				.724	.219	.001*
12 year to 14 year	.019	3.85	.022*			
Loss of rater				-.229	.128	.073
Gain of rater				.327	.155	.035*
14 year to 16 year	.007	1.36	.259			
Loss of rater				-.101	.111	.362
Gain of rater				.183	.141	.193

Note. \*p<.05, b=unstandardized beta, SE=standard error.

## S10. Longitudinal Patterns of Binary Persistence/Desistence



*Note.* Bar graphs indicate cross-sectional estimates for persistence and remission; line graphs display longitudinal patterns by time point. Individuals were classified as displaying stable persistence if they demonstrated persistent ADHD for all assessments to date in the follow-up period. Therefore, the gray line represents the percentage of participants who continued to demonstrate stable persistence at a given timepoint. Stable remission was defined as displaying one classification change from persistent ADHD to remission (full or partial) that maintained until study endpoint. Therefore, the red line represents the percentage of participants who had experienced onset of stable remission by the corresponding time point. A fluctuating pattern indicated at least two changes to cross-sectional classification since baseline diagnosis of ADHD in the absence of the stable remission pattern. Therefore, the yellow line represents the percentage of participants who meet criteria for fluctuating status at a given time point (which precludes also meeting criteria for stable remission at any future time point).