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The Preschool Attention-Deficit/Hyperactivity Disorder Treatment Study (PATs) 6-Year Follow-up

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This article is discussed in an editorial by Dr. Mary Margaret Gleason on page xxx.

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Abstract

Objective—To describe the clinical course of attention-deficit/hyperactivity disorder (ADHD) symptom severity and diagnosis from ages 3–5 to 9–12 years during a 6-year follow-up after the original Preschool ADHD Treatment Study (PATS).

Method—207 participants (75% male) from the original PATS, assessed at Baseline (mean age 4.4 years, when all met criteria for ADHD) and 3-months later (prior to medication treatment), were re-evaluated in three follow-up assessment visits (Year 3, mean age 7.4 years; Year 4, 8.3 years and Year 6, 10.4 years). Parents and teachers rated symptom severity and clinicians established psychiatric diagnoses. Analyses examined longitudinal changes in symptom severity and ADHD diagnosis.

Results—Parent- and teacher-rated symptom severity decreased from Baseline to Year 3 but remained relatively stable and in the moderate-to-severe clinical range through Year 6. Girls showed generally steeper decreases in symptom T-scores. At Year 6, 89% (160/180) of remaining participants met ADHD symptom and impairment diagnostic criteria. Comorbidity of oppositional defiant disorder and/or conduct disorder was associated with a 30% higher risk of having an ADHD diagnosis at Year 6 in the multiple logistic model. Medication status during follow-up, on vs. off, did not predict symptom severity change from Year 3 to Year 6 after adjustment for other variables.

Conclusions—ADHD in preschoolers is a relatively stable diagnosis over a 6-year period. The course is generally chronic, with high symptom severity and impairment, in very young children with moderate-to-severe ADHD, despite treatment with medication. Development of more effective ADHD intervention strategies is needed for this age group.

Keywords

attention-deficit/hyperactivity disorder (ADHD); follow-up; pre-schoolers; development

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common, impairing and chronic childhood-onset condition with an estimated world-wide prevalence in children and adolescents of about 5.3%.¹ In the U.S., the most recent estimate for 4–17-year-olds, based on parent surveys, is 9.5% (ever) and 7.2% (current).² ADHD can impact virtually every area of a child's development and functioning, including learning, behavior, family, peer relationships, physical safety, and emotional development.³

In the U.S., the core symptom clusters of ADHD—inattention, hyperactivity and impulsivity—have remained essentially unchanged since they were operationalized over 30 years ago with the publication of the American Psychiatric Association's *Diagnostic and Statistical Manual, Version III*.⁴ Although the *DSM-5* workgroup is considering some changes in the criteria and subtypes of ADHD, many of the 18 core symptoms in the current *DSM-IV*—9 for inattention, 6 for hyperactivity and 3 for impulsivity—appear likely to be included in this next major revision of the *DSM* (www.dsm5.org).⁵

ADHD onsets in childhood and follows a chronic course, with severity of symptoms, especially hyperactivity and impulsivity, decreasing with increasing age.^{6–13} Over the past 25 years, longitudinal studies of ADHD have primarily followed school-aged or older children and mainly focused on boys.^{8,14–25} These studies have shown a wide range of outcomes, with approximately 35 to 80% of children who were initially diagnosed with ADHD at elementary school-age retaining the diagnosis in adolescence, and with about 50 to 65% of these same children manifesting a full ADHD diagnosis or clinically significant symptoms in adulthood (for a review, see Faraone et al.²⁶).

However, behavior problems often start well before elementary school, as seen in community samples and as evidenced by preschool-age children being referred, assessed and treated for ADHD.^{27–30} Notably, only a few research studies have been conducted to evaluate the course of ADHD when the onset and identification are in the preschool years (ages 3–5). An early longitudinal study of preschoolers with “hyperactivity” (but not with a diagnosis of ADHD) found general persistence of symptoms over time, from age 3 to 6.³¹ In another study of 21 preschoolers with “pervasive hyperactivity” followed from age 3 to 15, only 25% “recovered” and 33% met *DSM-III* attention-deficit disorder (ADD) criteria at follow-up.³² The first longitudinal study of ADHD in young children, 4–7 years old³³ found that 79% of the children who met “full” criteria for ADHD at study entry received the diagnosis on at least two out of three assessments over the next 3 years. These children also continued to show associated functional impairment, especially in academic and social domains. Although this study had many methodological strengths, the diagnoses were made by lay interviewers and only about a third (36%) of the 96 participants with “full” ADHD were preschoolers at study entry; the others were in kindergarten (43%) or first (21%) or second (1%) grade.³⁴ Also, the sample included clinic-referred and community children with only mild to moderate functional impairment, as indicated by the mean Children's Global Assessment Scale (CGAS) score range of 64 to 73, and only moderate exposure to medication treatments during the follow-up period.

The limited knowledge of the course of moderate-to-severe ADHD in youth diagnosed at a very young age is an important gap in the field. As more preschool-age children are identified as having ADHD and treated for it, knowing the long-term trajectory of this disorder is vital for establishing optimal interventions early on for these children and their families. The Preschool ADHD Treatment Follow-up Study (PATs F/U) provides a unique opportunity to examine the trajectory of symptom severity and diagnosis over 6 years, when first identified in preschoolers with moderate-to-severe symptoms at original diagnosis.

PATS (Preschoolers with ADHD Treatment Study) was a National Institute of Mental Health–sponsored, multisite, randomized efficacy/effectiveness trial designed to evaluate the short-term efficacy and long-term (40 weeks) safety of methylphenidate (MPH) in preschoolers, ages 3.0 to 5.5 years, with *DSM-IV* ADHD (Combined or Predominantly Hyperactive/Impulsive Type) in the moderate-to-severe range with mean 47.3 (SD=4.07) CGAS scores at baseline. Three hundred and four participants enrolled in PATS; 261 completed parent training; 169 completed open-label safety lead-in; 147 completed the double-blind medication phase; and 140 enrolled in open label maintenance. Among the methodological strengths of the PATS was a rigorous diagnostic process involving cross-site clinician consensus and collection of symptom severity data from both parents and teachers. The rationale, design and results of the PATS have been reported previously.³⁵⁻³⁸

This paper describes the longitudinal course of ADHD symptoms and diagnosis in preschoolers during a six-year follow-up period, from an average age of 4.4 years to 10.4 years. The report focuses on ADHD stability across several outcomes: parent-rated and teacher-rated symptom severity and research clinician-rated ADHD diagnosis. We also examined the persistence of a categorical diagnosis of ADHD, taking into consideration gender and medication status. Although these analyses were primarily descriptive, we expected: substantial continuity in ADHD diagnosis and symptom severity over time, some differences between boys and girls in trajectory of symptom severity, and an association between medication treatment and ADHD diagnosis.

METHOD

Overview

Families of 304 participants enrolled in the original PATS³⁶ were contacted by phone or mail and invited to return for an observational follow-up. The children were assessed in three follow-up visits (Year 3, 4, and 6). Year 3, 4, and 6 visits occurred on average 3.1 (SD=0.64), 4.0 (SD=0.65), and 6.0 (SD= 0.67) years, respectively, after the initial diagnostic evaluation in the original PATS. Children were, on average, 4.4 years old at the time of the initial evaluation and 7.4, 8.3 and 10.4 years old at follow-up Years 3, 4 and 6 (see Table 1). Some of the variability in the assessment time intervals among the participants was due to a one year gap in funding between the end of the original PATS (August 2003) and the start of the follow-up study (September 2004). Diagnosis was ascertained as a result of a full diagnostic evaluation in Years 3 and 6. Only selected research assessments, including parent and teacher ratings of ADHD symptoms, were administered in Year 4 and a formal diagnosis was not determined (see Table S1, available online, for schedule of assessments). The assessments in the observational follow-up were designed to evaluate longitudinal changes in 5 functional domains: 1) ADHD diagnosis and symptom severity, including co-morbid diagnostic profile and related functioning and impairment; 2) cognitive and academic functioning; 3) mental health service utilization (including information about mental health, educational and medical services); 4) pharmacological treatment received in the community since the original PATS; and 5) physical health and safety related to early and continued medication treatment. This report focuses on ADHD symptom severity and diagnosis (domain #1) and considers the impact of community medication treatment on symptom severity and diagnosis (domain #4) over time.

Participants

All participants screened in the original PATS were eligible to enter the follow-up study. Of the 304 participants enrolled in the original PATS, 207 (68.0%) took part in the follow-up study (see CONSORT Chart; Figure S1, available online). The study was approved by the Institutional Review Board (IRB) at each collaborating site (Columbia University, Duke

University Medical Center, Johns Hopkins University, New York University, University of California–Irvine, and University of California–Los Angeles). A parent or legal guardian of all 207 participants in the follow-up provided written consent, and all children gave verbal assent.

ADHD Symptom Severity and Diagnostic Assessment Process (see Table S1, available online)

The assessment process used in the original PATS was repeated in the follow-up. In Years 3 and 6, an M.D. or Ph.D. clinician-researcher performed a comprehensive clinical evaluation with the caregiver and the child in the clinic to determine the child's current multi-axial *DSM-IV* diagnoses. For ADHD, clinicians considered information from multiple sources when rating presence or absence of 18 ADHD symptoms and associated impairment on the *Clinician's ADHD Checklist* (see below), including the scaled symptom ratings collected on Conners Rating Scales–Revised, Long Version (CPRS-R:L for parents, CTRS-R:L for teachers),^{39–40} Diagnostic Interview Schedule for Children–Parent Version (DISC-IV P)⁴¹ and the *PATS Diagnostic Interview (PDI)*.^{36–37} Of note, T-scores of ≥ 65 (1.5 SDs) on the parent and teacher Hyperactive-Impulsive subscale, and a CGAS rating of ≥ 55 , were required for entry into the original PATS. During the follow-up study, teacher ratings on CTRS-R:L were obtained within 6 months of the parent assessments at Years 3, 4, and 6. For the assessments taking place over the summer, teacher ratings were collected from the fall subsequent to the Year 3, 4 or 6 assessments.

The ADHD section of the Diagnostic Interview Schedule for Children–Parent Version (DISC-IV)⁴¹ was administered to the parent by trained research assistants and served as a diagnostic screen for ADHD. The *PATS Diagnostic Interview (PDI)*, based on the ADHD section of KSADS-PL with prompts modified for pre-schoolers, was administered by the clinician to determine the frequency of each of the 18 symptoms, on a scale from 0 to 5 (e.g., 0 = not at all, 3 = often, 5 = all the time) and 6 areas of associated impairment (i.e., school/academics, home, peers, self-esteem, physical injury/risky behavior, and other). Symptoms rated by the clinician as present on the PDI “often” or more for the last 6 months were endorsed as positive on the *Clinician's ADHD Checklist*.³⁷ This checklist also served as a reference for impairment criteria during consensus diagnostic conference calls.

Consistent with *DSM-IV*, diagnosis was based on the overall frequency of a child's symptoms and typical functioning, regardless of medication status. Thus, ADHD symptoms and impairment were based primarily on behavior observed on medication for medicated participants and, by definition, non-medicated behavior for primarily non-medicated participants. For participants on medication, clinicians also documented presence of ADHD symptoms and associated impairment on the Clinician's ADHD Checklist for Unmedicated Behavior, specifically during off-medication periods over the previous 6 months (i.e., before onset of medication effect, after medications wore off, skipped or missed dosages, weekends, extended drug holidays, and extended periods not treated with medication). These ratings did not affect consensus determination of diagnostic status. Instead, this instrument was used in this report to estimate the rate of ADHD diagnosis in those children who did not meet diagnostic criteria while medicated.

Secondary Axis I diagnoses not covered in The Schedule for Affective Disorders and Schizophrenia for School Age Children–Present and Lifetime Version (KSADS-PL)⁴² were assessed with the DISC-IV P.

Clinicians prepared a case report that summarized relevant rating scale scores and provided medical and psychiatric information, which was discussed on a cross-site teleconference to achieve diagnostic consensus.

Medication Status

For the predictive models, three categories of participation in the original PATS medication trial, based on medication exposure, were created: 1) participated in parent behavior management training but not in medication phases, 2) participated in some or all short-term medication phases (safety, dose optimization, placebo-controlled parallel) and some open-label maintenance, and 3) participated in some or all short-term medication phases and completed open-label maintenance.

For determining whether or not a participant was considered on medication during particular periods of the follow-up study, on-medication status was defined as being on any stimulant, norepinephrine reuptake inhibitor or alpha adrenergic agonist medications for more than 50% of the time in the 6 months preceding a clinical assessment or 1 month preceding a CPRS or CTRS.

Data Analyses

Analyses were conducted to examine longitudinal changes in both symptom severity and categorical diagnosis from the original PATS study to the end of the follow up period.

ADHD Symptom Severity—Four symptom stability outcomes, based on T-scores on the parent and teacher Conners *DSM-IV* scales for Inattention and Hyperactivity-Impulsivity, were examined over five time points: Baseline (n=207) and 3-Months (n=175) in the original PATS study, which were completed prior to randomization³⁶ about 3 months apart, and the 3 follow-up assessments done at Year 3, 4, and 6. First, we determined the statistical significance of change in the severity of symptoms across subjects using paired t-tests (thus limiting the number of pair-wise t-tests selected), with Year 3 of follow-up as the reference point. Since the prevalence of ADHD differs by gender, time-trends were stratified by gender to identify potential differences in stability of the symptoms over time.

Next, linear mixed models⁴³ using PROC MIXED (SAS Version 9.2) were used to model ADHD symptom severity at follow-up as a function of age, severity at baseline, gender, IQ (estimate on the *Differential Abilities Scale*⁴⁴), comorbidity (categorized as oppositional-defiant disorder [ODD]/conduct disorder [CD] or not), medication status (assessed via the Services Use in Children and Adolescents–Parent Interview (SCA-PI)⁴⁵⁻⁴⁶) at follow-up, medication exposure group based on the original PATS study, and parental level of education, all of which may be significantly related to inattention and hyperactivity-impulsivity symptoms. Due to variable entry into the follow-up study, we additionally adjusted for the time between the screening and first follow-up assessment. Clinical site was also controlled for in the models. Random intercept at participant level was used to represent unobserved factors that are common to all scores for a given participant. All of the above-listed predictors were included as fixed effects, while the effect of age was allowed to vary across children (i.e., random slope). Potential nonlinearity in continuous covariates (age, and IQ⁴⁷⁻⁴⁸) was explored. We tested for statistical interaction by gender, by PATS participation category and by site at 5% significance level.

Patterns of missing data on symptom severity were explored, as was the distribution of covariates among children with and without missing data. By using linear mixed models we assumed that the data are missing at random whereby the probability of missingness only depends on previous measurements and other measured covariates (i.e., only on variables included in the model, not on other observed or unobserved factors) and the available data describes each subject's trajectory.⁴⁹ In addition, missing teacher assessment data were imputed using data augmentation Markov Chain Monte Carlo (MCMC) method (PROC MI and MIANALYZE). We used available information on parent assessment to evaluate the

robustness of our conclusions to various strategies of dealing with a total of 128 subjects missing data across the 5 time points (i.e., sensitivity analysis).⁵⁰

ADHD Diagnosis—We assessed the proportion of the sample with a diagnosis of ADHD at Years 3 and 6 and explored the association between categorical diagnosis and medication status using the Chi-square test. Generalized linear model (GLM) with Poisson distribution and robust variance was employed to model the probability of an ADHD diagnosis at Year 6 as a function of ADHD diagnosis and medication status at Year 3 and original PATS participation categories, age, gender, IQ, comorbidity and parent education.⁵¹ Variables significant at 0.1 level in unadjusted analyses were included in the final adjusted model.

RESULTS

Descriptive

Subject flow—As shown in the CONSORT Chart (Figure S1, available online), of the 304 preschoolers who were enrolled in the original PATS, 207 (68.1%) participated in the follow-up study. The 96 original PATS participants who did not participate in the follow-up study dropped at various times in the 8-phase PATS study, most commonly between parent training and initial medication dose finding (n=34), and between completion of open label maintenance and start of the follow-up study (n=39). Of those 207, 206 (99.5%) participated in assessment at Year 3; 189 (91.3%) participated in a brief assessment at Year 4, and 186 (89.9%) took part in assessment at Year 6. The most common reasons for nonparticipation included loss of the family to all tracking efforts (n=15) and refusal to participate (n=4). Children who did not participate in the follow-up did not differ from those who returned for follow up on any of the examined baseline characteristics: sex, IQ, ethnicity, family composition, parental education, public assistance, or age.

Demographics—As shown in Table 1, the composition of the sample remained consistent over time. On average, participants were 75% male and reflective of the ethnic and racial composition of the U.S. population; that is, predominantly White and non-Hispanic, with substantial racial and ethnic diversity. The sample was largely middle and upper-middle class as noted by the low percentage of public assistance and the high percentage of college graduates. About 75% of the children had 2 parental figures in their primary residence. A high level of global impairment is demonstrated by the mean CGAS scores of 53.7 at Year 3 and 56.4 at Year 6.

Medications—From the parent-reported SCA-PI, prescribed medications were organized into 10 classes: 1 = stimulants (i.e., methylphenidate or amphetamine preparations), 2 = norepinephrine reuptake inhibitors (NRIs; i.e., atomoxetine), 3 = alpha-2-adrenergic agonists (i.e., clonidine or guanfacine preparations), 4 = non-selective serotonin reuptake inhibitor (non-SSRI) antidepressants (e.g., bupropion), 5 = antipsychotics, 6 = non-antipsychotic mood stabilizers, 7 = SSRIs, 8 = anxiolytics, 9 = miscellaneous (e.g., propranolol), and 10 = “sleepers” (e.g., melatonin, diphenhydramine). Table S2, available online, indicates medication use by each medication class (irrespective of other classes), anchored to 6-months prior to the clinical evaluation at Years 3 and 6. At Year 3, the most commonly prescribed medication classes were: stimulants (58.7%), NRIs (10.7%) and antipsychotics (8.3%). At Year 6, the most common classes were: stimulants (62.9%), antipsychotics (12.9%), and SSRIs (8.6%).

Parent and Teacher-Rated ADHD Symptom Severity

Effects not adjusted for covariates—Table 2 shows mean T-scores by gender for the CPRS and CTRS 9-item Inattention subscale and 9-item Hyperactivity-Impulsivity subscale

overtime, from Baseline (Time 0), to 3-Months of the original PATS study, and at Years 3, 4, and 6 of the follow up study. The overall trajectories of hyperactivity/impulsivity and inattention did not differ in this sample. Across participants, parent-and teacher-reported inattention and hyperactivity-impulsivity T-scores decreased significantly from both Baseline ($p < 0.0001$) and 3-Months ($p < 0.0001$) to Year 3. However, there was no significant change in T-scores from the first (Year 3) to the last (Year 6) follow-up. In general, throughout the follow-up period, T-scores for hyperactivity-impulsivity remained higher than T-scores for inattention across the sample. However, teacher-reported inattention and hyperactivity-impulsivity T-scores converged at Year 6. On average, girls exhibited higher T-scores and steeper decreases in scores between baseline and follow-up (Table 2). Despite the overall decrease in the symptoms from Baseline to Year 6, across the sample, many of the CPRS mean T-scores remained in the moderate-to-severe clinical range (65), while most of the CTRS mean T-scores did not.

We also compared parent- and teacher-reported symptom severity (CPRS/CTRS) for inattention and hyperactivity/impulsivity by ODD/CD comorbidity status at Year 3 and 6 (data available from the author). Children with comorbid ODD or CD had significantly higher parent- and teacher-reported hyperactivity/impulsivity symptoms at Year 3 and 6 follow-up. Only parent-reported, but not teacher-reported, inattention severity was higher for the ODD/CD group. All differences were significant at $p < 0.005$. For example, for Year 6 parent reports, mean hyperactivity/impulsivity symptom severity T-score was 71.8 ± 11.4 for ODD/CD positive vs. 65.4 ± 12.8 for ODD/CD negative; mean inattention was 67.6 ± 11.4 for ODD/CD positive vs. 61.2 ± 12.7 for ODD/CD negative groups.

The proportion of participants on medication during the follow-up (at Year 3, 4, or 6) with a T-score below the clinical cut-off (< 65) on both the parent inattention and hyperactivity/impulsivity scales ranged from 35% to 38%. For participants not on medication, the proportions ranged from 38% to 42%.

Effects adjusted for covariates (models)—We observed expected heterogeneity in symptom severity trajectories over time (data not shown). The effect of age was not significant in any of the models, except for teacher-rated inattention scores (Table 3) generally suggesting no change in ADHD symptom severity over the follow-up time after adjusting for the demographic, comorbidity, medication, IQ and baseline symptom severity variables. The model of teacher-rated inattention scores predicted that a child who is one year older would have ratings that are estimated to be 0.95 points higher (95%CI: 0.21 to 1.7, p -value = 0.012). Also, there was a significant effect of baseline ADHD symptom severity on parent ratings, but not on teachers' ratings. For example, according to the fitted model a child who had 10-point higher hyperactivity score at baseline is expected to have 4.36 higher hyperactivity severity rating at follow-up after adjusting for other covariates in the model (95%CI: 1.76 to 6.96, p -value = 0.001). The models predicted that girls have higher inattention, but not hyperactivity scores after controlling for the covariates. According to the model of parent-reported scores, girls had on average 4.56 higher inattention T-scores (95%CI: 1.25 to 7.87, p -value = 0.007) after controlling for other covariates. This estimate was similar in the model of teacher-reported inattention scores (i.e., average estimated difference between a girl and a boy = 4.60 (95%CI: 1.43 to 7.78, p -value = 0.005). This relationship was reversed in the model of teacher-reported hyperactivity; a girl on average is predicted to have 3.97 lower score than a boy after adjustment for the covariates (95%CI: -7.12 to -0.83 , p -value = 0.014). The overall effect of PATS participation was significant in both models of parent ratings (chi-square [2 df] = 3.41, p -value = 0.035 for parent-rated inattention and chi-square [2 df] = 3.87, p -value = 0.023 for parent-rated hyperactivity; not shown) and in the teacher-reported hyperactivity model (chi-square [2df] = 4.11, p -value = 0.019). In the models of parents' report, a

participant who only went through short phases of medication, but did not complete maintenance in the original PATS study is expected to have higher average score compared to a participant who completed maintenance. In particular, the model predicted that a child who received short phases of medication had on average 4.84 higher inattention T-score compared to a child who completed 10-month maintenance (95%CI for the difference: 1.08 to 8.61, p -value = 0.012) after controlling for all other variables in the model. This effect was stronger for hyperactivity; the average estimated difference was 5.64 (95%CI for the difference: 1.48 to 9.79, p -value = 0.008). Analogously, participation in PATS maintenance phase resulted in lower hyperactivity scores as rated by the teachers compared to no medication or no maintenance groups (p -values = 0.006 and 0.035, respectively).

Figure 1 shows marginal predictions for parent-reported inattention and hyperactivity by gender, PATS participation and age. The marginal predicted inattention and hyperactivity scores for each child over time were obtained using the fixed-effect parameters of the random-effect models presented in Table 3. Of note, the models did not support different trajectories by PATS participation (p -value for interaction = 0.833 and 0.868 for parent-reported inattention and hyperactivity, respectively).

Stability of ADHD Diagnosis

Effects not adjusted for covariates—The rate of diagnosis of ADHD, based on the overall frequency of behavior and resulting impairment, irrespective of medication status, at Year 3 was 76% and did not differ significantly from that at Year 6 (77.2%). Among children who were medicated during follow up and no longer were diagnosed with ADHD, 18 of 31 children at Year 3 and 19 of 26 children at Year 6 met diagnostic criteria for ADHD based on symptom and impairment ratings for un-medicated behavior, bringing the estimate of ADHD to 84.8% at Year 3 and 89.2% at Year 6 (Table 4).

Effects adjusted for covariates (models)—The results of GLM (Table 4) showed that the probability of ADHD diagnosis at Year 6 was about 30% higher for children receiving community medication treatment for at least 50% of time within 6-months of the diagnostic evaluation at Year 3 in the unadjusted model (95%CI for the Risk ratio: 1.01 to 1.54, p -value = 0.039). This effect was attenuated and did not reach statistical significance after adjusting for covariates (p -value = 0.065).

In the final model, only concurrent comorbid diagnosis of ODD/CD predicted ADHD diagnosis at Year 6. After adjustment for prior ADHD diagnosis, IQ, and medication status, the risk of ADHD is estimated to be 30% higher among patients with comorbid ODD/CD compared to those without comorbid ODD/CD (95%CI: 1.10 to 1.46, p -value = .001).

DISCUSSION

In this 6-year follow-up study, almost 80% of clinic-referred preschoolers initially diagnosed with moderate-to-severe ADHD, who mostly received parent training followed by controlled medication treatment, continued to be diagnosed with ADHD into mid-to-late childhood. Across the sample, severity of symptoms, despite initial decline, remained primarily in the moderate-to-severe clinical range. Comorbid diagnosis of ODD or CD during follow-up was the strongest predictor of diagnostic stability, after accounting for other factors. Medication treatment in the original PATS predicted higher ADHD symptom severity between follow-up Year 3 and 6 in some, but not all, models, while sex (girls) predicted worse hyperactivity/impulsivity (teacher report) and inattention (parent and teacher reports). The main findings with respect to trajectories of symptom severity, stability of diagnosis, and the use of medication are discussed below.

Symptom Severity Patterns and Trajectories

Overall patterns—For parent- and teacher-reported symptoms of inattention and hyperactivity/impulsivity, there was an overall (not accounting for medication status) significant drop from Baseline and 3-Months to Follow-up Year 3. There was no significant change from Year 3 to Year 4 or from Year 3 (mean age 7.4) to Year 6 (mean age 10.4), with the exception of a small, but significant decrease in teacher-reported hyperactivity/impulsivity from Year 3 to Year 4. It should be noted that this does not necessarily indicate that the absolute frequency of symptoms did not decrease, but rather that frequency relative to peers of a similar age and gender did not change, as captured by the normed T-scores.

The overall pattern of symptom severity was essentially identical for inattention and hyperactivity/impulsivity. Thus, unlike in other studies showing a faster rate of remission in hyperactivity/impulsivity from preschool to school-age period^{8, 52} in this study the overall pattern of change for inattention and hyperactivity/impulsivity did not differ. There was no evidence of decline in symptom severity in either domain after age 7. This finding is consistent with results from the *DSM-IV* field trial⁵³ showing preponderance of hyperactive-impulsive symptoms until peak onset of inattentive symptoms at around age 9. There was a statistically significant increase in teacher-rated inattention with age after adjustment for other factors, which most likely represents more opportunities for teachers to observe children being off-task as the demands for sustained attention increase with grade. One would expect hyperactive-impulsive symptoms to then decrease during adolescence.^{7-9, 21}

Parent vs. teacher ratings—Severity of both inattention and hyperactivity/impulsivity symptoms was higher on parent ratings than teacher ratings at all follow-up assessments (Years 3, 4, and 6). Earlier analysis of parent-teacher agreement on symptom ratings in PATS⁵⁴ showed that parents were quite likely to agree with teachers' endorsements of symptoms, but much less likely to agree with teachers' non-endorsement of a symptom, which may translate into inflated parent ratings over time. Possible explanations for these observations include: school behavior is more likely to be positively influenced by medication, parents are more likely to observe a wider sample of behaviors (including information from school); or a halo effect, i.e., changes in teachers over time vs. stability in parental care.

Age—Are the observed age-related decreases in ADHD symptom severity clinically meaningful? The continued elevations in symptoms relative to normal peers above accepted clinical thresholds, especially for parent ratings, the lack of change in CGAS ratings from Year 3 to 6, the preponderance of community stimulant treatment, and increases in most other classes of psychotropic medications suggest little, if any, clinically significant change in the time/age-trends in symptom severity.

Sex—Symptom trajectories differed for boys and girls: girls' symptoms were more severe relative to other girls of similar age than for boys relative to other boys of similar age, especially at baseline, and showed a steeper decline from baseline to follow-up. Without considering the effect of other factors, except for teacher hyperactivity/impulsivity ratings, girls' symptoms remained more severe throughout the study (see Table 2). Because externalizing behaviors are less common in girls than in boys, girls are typically rated as more severe relative to their age- and gender-matched non-impaired peers, which in the current study was reflected in girls' higher Conners T-scores. However, in absolute terms (frequency of behaviors), girls typically have fewer ADHD symptoms relative to the boys (lower raw total scores on the Conners), as seen in higher rates of observed classroom ADHD symptoms in boys than girls.⁵⁵ The absolute frequency of ADHD symptoms was not

analysed in this report. Although *DSM* diagnostic approach to ADHD is not norm-referenced, understanding impairment from developmentally inappropriate behaviors, arguably, requires appreciation of how these behaviors are perceived relative to one's gender.

IQ—Lower IQ was associated with higher teacher-rated inattentive symptoms after adjustment for other covariates. In epidemiological samples, pure inattentive symptoms have been shown to be more closely related to global cognitive development.⁵⁶ While disruptive classroom behavior is the most common cause of treatment referral in childhood, inattentive problems arguably have more deleterious long-term sequelae such as academic failure.⁵⁷⁻⁵⁸ The divergence in correlates of two symptom clusters points to different developmental trajectories in inattention and hyperactivity/impulsivity, possibly with distinct underlying etiologies, outcomes, and necessity for tailored assessment and treatment.

Diagnosis

For the vast majority of children in the study, the initial diagnosis of ADHD persisted throughout the 6 years of follow-up. Most of the children who were no longer diagnosed with ADHD by the study clinician based on how they behaved “most of the time” (whether on or off medications) met symptom and impairment criteria when parents were asked to rate off-medication behavior. This resulted in prevalence rates increasing from 76–77% to 89%.

In the adjusted model, ODD/CD comorbidity predicted ADHD diagnosis at Year 6.⁵⁹⁻⁶² A more detailed treatment of comorbidities and medication will be the topic of future publications.

The effect of medication at the prior visit (Year 3) on diagnosis at Year 6 did not reach statistical significance ($p = .065$).

Medications

Not surprisingly, the most commonly prescribed medications for participants in this study were stimulants (59% and 63% at Years 3 and 6, respectively). Other medications used to treat ADHD were prescribed less frequently: NRIs (11% and 6%) and alpha-adrenergic agonists (5% and 8%). Over time, from Year 3 to Year 6, prescribing decreased for NRIs and increased for SSRIs (3% and 9%) and antipsychotics (8% and 13%). Since SSRIs and antipsychotics are generally used to treat disorders other than ADHD, these increases in prescribing suggest the emergence of other disorders or combination pharmacotherapy in treating more disruptive and chronic forms of pathology.⁶³

We saw a positive effect of completion of the medication maintenance phase in original PATS on both inattention and hyperactivity/impulsivity parental ratings, after adjustment for other comorbidities in the model. We did not see an independent effect of medication (on vs. off during follow-up) on these follow-up scores.

It is noteworthy that most participants who were on medication still met diagnostic criteria for ADHD (Table 2). However, parent and teacher ratings of ADHD symptom severity were not significantly different between children on-medication vs. those who were off-medication during follow-up, after taking into account other relevant factors (Table 3). These finding raises questions that unfortunately cannot be answered from these data. For example, why were the medications—as administered in the community—not sufficiently effective in reducing symptoms to below clinical ranges in most participants? Was

adherence a problem? Alternatively, it is possible that pharmacotherapy practices of community practitioners were not geared to maximize clinical benefit.⁶⁴

Participation in the original PATS—parent training (PT) only, PT plus short and/or partial maintenance medication, or PT plus short and complete maintenance medication—was not associated with presence of ADHD diagnosis at Year 6 (see Table 5). This finding is similar to the finding of no effect of original treatment assignment on 8-year follow-up in the MTA study.⁶⁵ This may be due to the non-random participation in various phases of the original PATS study. Also, it is difficult to demonstrate effects of short term controlled treatment on long-term community treatment.

This study has several limitations. Perhaps most important, there was no comparison group. To compensate for this, children's symptom trajectories were examined using normed instruments (e.g., CPRS/CTRS), which allowed comparison of our sample to a normative one. Also important was the fact that treatment was not controlled during the majority of the 6 year follow up period. More specifically, this was a naturalistic follow-up of subjects who were once enrolled in a randomized controlled trial (RCT); this limits any conclusions regarding the long term effect of the original controlled medication treatment. Another limitation is the relatively long time between the original study and the first follow-up assessment. This was directly related to the lapse in funding from the original to the follow-up study. Also, given the symptom severity and global impairment thresholds of the original PATS, participants in this follow-up study likely had more severe symptoms and impairment than in the general ADHD population. In addition, although some of the demographic characteristics were representative of the US population, e.g., race, ethnicity and gender, others were not, e.g. level of parental education, proportion receiving public assistance and proportion with two parental figures. These demographic characteristics could limit generalizability to other samples, especially poor communities. In addition, there were other limitations not uncommon in clinical follow-up studies: attrition; self-selection bias (i.e., who selects to continue treatment and variability in provider practices/training/experience, etc).

Because ADHD is highly stable in preschoolers with moderate to severe ADHD and because frequent dissatisfaction with ADHD treatment leads to drop out,⁶⁶ especially in younger children, early and intensive interventions are needed. Understandably, most clinicians approach the treatment of preschool ADHD more conservatively, and may attempt to delay the incorporation of pharmacotherapy, with the hope of a more benign course. Given that this treatment-naïve sample received a brief course of group parent training, followed by a controlled trial of MPH for the majority of them, and the majority of children continued to receive community medication and, perhaps, other treatments for several years, and yet most retained their diagnosis, suggest that more comprehensive and/or intensive treatments are needed. This could include more effective use of medication, longer or more intensive parent training (see, for example, Webster Stratton et al.⁶⁷), and/or addition of behavioral interventions at school. Other medications need rigorous evaluation in preschoolers with ADHD in an effort to improve outcomes. At the same time, despite overall persistence of ADHD, individual variability in course was striking, calling for more efforts to identify robust predictors of trajectory, which conceivably could inform clinical decision-making.

In general, studies that follow children with ADHD (without ODD/CD) and that use patient self-report find that less than 10% of individuals diagnosed with ADHD as a child still have the diagnosis as adults.²³ In contrast, studies that include children with ADHD and comorbidities and that use parent informants show that 49%–67% children with ADHD continue to have the disorder in adulthood.¹⁶ Given the very high rate of persistence in the diagnosis of ADHD in this sample, it will be important to examine which specific

characteristics increase the risk of long-term ADHD (e.g., family history of ADHD, psychosocial adversity, comorbidity with conduct, mood, and/or anxiety disorders), as well as characteristics of those children who no longer have symptoms in the clinical range. Also, predictors of functional impairment, the development of other disorders such as autism and bipolar disorder, when and why medications are prescribed, the impact of stimulant medication on growth, and sex differences in the homotypic and heterotypic continuity of the disorder, need to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Inattention Scores

Boys

Girls

Hyperactivity Scores

Boys

Girls

Figure 1.

Marginal predictions from the linear mixed models of parent-reported inattention and hyperactivity scores over time by gender and the Preschool Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS) participation.

Table 1
Preschool Attention-Deficit/Hyperactivity Disorder (ADHD) Treatment Study (PATS)
Follow-up Study Sample Characteristics at Years 3 and 6 (N=207)

	Year 3 (n=206)		Year 6 (n=186)	
Age , mean (SD)	7.4	(0.97) [0]	10.4	(0.98) [0]
Gender , n (%)				
Male	154	(74.8)	138	(74.2)
Female	52	(25.2)	48	(25.8)
Ethnicity , n (%)				
Hispanic or Latino	40	(19.4)	32	(17.2)
Non-Hispanic or -Latino	166	80.6	154	(82.8)
Race , ^a n(%)				
White	159	(77.2)	138	(74.2)
Black or African American	44	(21.4)	39	(21.0)
American Indian/Alaskan Native	14	(6.8)	14	(7.5)
Asian	3	(1.5)	5	(2.7)
Native Hawaiian/Other Pacific Islander	2	(1.0)	1	(0.5)
Other	17	(8.3)	18	(9.7)
Public Assistance , n (%)	23	(11.2)	12	(6.5)
Parent(s) has college or more degree , n (%)	141 [3] ^b	(69.5)	135 [6] ^b	(75.0)
Family composition , n (%) ^c				
2 parental figures	159	(77.2)	137	(73.7)
1 parental figure	45	(21.8)	43	(23.1)
N/A - missing	2	(1.0)	6	(3.2)
C-GAS , mean (SD)	53.7	(10.12) [2]	56.4	(10.10) [2]

Note: CGAS = Children's Global Assessment Scale.

^a add up to >100% because participants could endorse > 1 race

^b [n] = missing

^c The coding of family composition in PATS followed that of the MTA and refers to the presence of mother and father figures in a child's usual living arrangement, which ranged from parental home to shared residence with biologically unrelated adults.

Table 2
Severity of Parent- and Teacher-Reported Inattentive and Hyperactive-Impulsive Symptoms in Girls vs. Boys

		CPRS-R:L T-Scores						CTRS-R:L T-Scores					
		Baseline			Follow-up Year			Baseline			Follow-up Year		
		1	2	3	4	6		1	2	3	4	6	
N		207	175	202	185	180		202	146	182	163	153	
Severity of Inattentive Symptoms, Mean (SD) ^a		74.5 (11.3)	72.2 (13.0)	62.7 (12.0)	62.9 (11.6)	63.3 (12.6)		72.9 (11.2)	68.2 (13.3)	59.4 (11.7)	58.2 (9.3)	60.9 (12.0)	
	Girls	81.7 (10.3)	80.2 (12.3)	66.8 (14.6)	67.6 (14.3)	70.1 (16.2)		83.1 (8.8)	79.1 (15.3)	63.8 (15.2)	59.5 (11.2)	68.2 (13.9)	
	Boys	72.1 (10.6)	69.6 (12.2)	61.3 (10.6)	61.2 (10.1)	60.9 (10.2)		69.4 (9.6)	64.5 (10.3)	58.0 (9.9)	57.8 (8.5)	58.7 (10.4)	
Severity of Hyperactive-Impulsive Symptoms, Mean (SD) ^b		78.6 (7.7)	74.6 (10.7)	67.8 (12.7)	67.0 (12.6)	67.4 (12.7)		77.1 (7.5)	71.3 (11.9)	61.7 (11.0)	59.3 (10.4)	60.4 (11.8)	
	Girls	87.0 (4.9)	83.3 (9.0)	69.0 (14.1)	69.7 (14.2)	71.7 (15.1)		83.4 (7.7)	79.6 (13.6)	59.3 (12.8)	55.2 (9.0)	61.5 (12.5)	
	Boys	75.7 (6.3)	71.9 (9.7)	67.5 (12.3)	66.1 (12.0)	66.0 (11.5)		75.0 (6.2)	68.5 (9.9)	62.4 (10.2)	60.6 (10.6)	60.0 (11.7)	

Note: Baseline 1 = Baseline; Baseline 2 = 3-months; CPRS-R:L = Conners Parent Rating Scales-Revised, Long Version, CTRS-R:L = Conners Teacher Rating Scales-Revised, Long Version.

^a Rater-specific Inattention T-score *p*-values: Parent-rated (Baseline 1 vs. Year 3 *p*<0.0001, *n*=177; Baseline 2 vs. Year 3 *p*<0.0001, *n*=170; Year 4 vs. Year 3 *p*=0.400, *n*=182; Year 6 vs. Year 3 *p*=0.662, *n*=178). Teacher-rated (Baseline 1 vs. Year 3 *p*<0.0001, *n*=177; Baseline 2 vs. Year 3 *p*<0.0001, *n*=129; Year 4 vs. Year 3 *p*=0.139, *n*=152; Year 6 vs. Year 3 *p*=0.216, *n*=136).

^b Rater-specific Hyperactive-Impulsive T-score *p*-values: Parent-rated (Baseline 1 vs. Year 3 *p*<0.0001, *n*=202; Baseline 2 vs. Year 3 *p*<0.0001, *n*=170; Year 4 vs. Year 3 *p*=0.887, *n*=182; Year 6 vs. Year 3 *p*=0.600, *n*=178). Teacher-rated (Baseline 1 vs. Year 3 *p*<0.0001, *n*=177; Baseline 2 vs. Year 3 *p*<0.0001, *n*=129; Year 4 vs. Year 3 *p*=0.251, *n*=136).

Table 3
Results of linear mixed effects models of follow-up attention-deficit/hyperactivity disorder (ADHD) symptom severity T-scores between Year 3 and Year 6

Parent Report									
Covariate	Inattention (L-score)				Hyperactivity (M-score)				
	slope	SE	p-value	95% CI	slope	SE	p-value	95% CI	
Age (per year)	0.18	0.27	0.516	-0.36	0.72	0.27	0.941	-0.56	0.52
T-score at screen (per 10)	1.95	0.68	0.005	0.61	3.28	1.32	0.001	1.76	6.96
Girls vs. boys	4.56	1.68	0.007	1.25	7.87	2.28	0.354	-6.63	2.38
IQ (per 5)	-0.22	0.23	0.333	-0.67	0.23	0.25	0.698	-0.60	0.40
Comorbidity at screen: ODD/CD vs. no ODD/CD	2.57	1.45	0.079	-0.30	5.43	1.61	0.172	-0.97	5.39
Parent education: college and above vs. below	-0.93	1.50	0.537	-3.88	2.03	1.65	0.605	-4.12	2.41
Medication status: on meds vs. off meds	1.01	1.20	0.402	-1.36^	3.37	1.27	0.912	-2.66	2.38
Time between baseline and follow-up (per year)	0.73	1.20	0.542	-1.63	3.09	1.30	0.876	-2.37	2.77
Original PATS participation									
Parent training only	2.26	2.34	0.336	-2.36	6.87	2.54	0.366	-2.71	7.31
Short phases of medication (with or without enrolling in maintenance)	4.84	1.91	0.012	1.08	8.61	2.11	0.008	1.48	9.79
Short phases of medication and completed maintenance (reference)									
Clinical Site									
DU	0.22	2.72	0.936	-5.14	5.58	3.02	0.298	-9.11	2.81
JHU	0.77	2.91	0.792	-4.98	6.52	3.22	0.532	-8.39	4.35
NYPI	1.72	2.73	0.530	-3.67	7.11	3.03	0.941	-6.20	5.75
NYU	1.56	2.76	0.573	-3.89	7.01	3.08	0.912	-6.43	5.75
UCI	1.95	2.53	0.442	-3.05	6.95	2.80	0.579	-7.09	3.97
UCLA (Reference)									

Teacher Report										
Covariate	Inattention (L-score)				Hyperactivity (M-score)					
	slope	SE	p-value	95% CI	slope	SE	p-value	95% CI		
Age (per year)	0.95	0.38	0.012	0.21	1.70	0.08	0.37	0.837	-0.66	0.81
T-score at screen (per 10)	0.51	0.63	0.418	-0.74	1.77	1.18	0.97	0.224	-0.73	3.10
Girls vs. boys	4.60	1.60	0.005	1.43	7.78	-3.97	1.58	0.014	-7.12	-0.83
IQ (per 5)	-0.59	0.20	0.004	-0.99	-0.20	0.00	0.20	0.997	-0.40	0.40
Comorbidity at screen: ODD/CD vs. no ODD/CD	-2.20	1.25	0.082	-4.69	0.28	-1.15	1.28	0.370	-3.68	1.38
Parent education: college and above vs. below	-0.13	1.28	0.918	-2.66	2.40	-2.30	1.31	0.082	-4.89	0.30
Medication status: on meds vs. off meds	0.17	1.29	0.895	-2.39	2.73	-1.07	1.32	0.419	-3.69	1.54
Time between baseline and follow-up (per year)	0.56	1.07	0.603	-1.56	2.67	-1.62	1.12	0.152	-3.85	0.61
Original PATS participation										
Parent training only	0.58	1.99	0.772	-3.38	4.53	5.87	2.09	0.006	1.72	10.03
Short phases of medication (with or without enrolling in maintenance)	1.86	1.66	0.266	-1.44	5.15	3.70	1.74	0.035	0.26	7.15
Short phases of medication and completed maintenance (reference)										
Clinical Site										
DU	1.87	2.34	0.428	-2.79	6.52	-0.24	2.42	0.923	-5.03	4.56
JHU	-0.99	2.58	0.703	-6.11	4.14	-1.80	2.65	0.497	-7.06	3.45
NYPI	1.27	2.37	0.592	-3.42	5.97	-1.31	2.46	0.596	-6.19	3.57
NYU	0.07	2.38	0.976	-4.66	4.80	1.46	2.48	0.556	-3.45	6.37
UCI	0.92	2.18	0.674	-3.40	5.24	-1.13	2.23	0.614	-5.56	3.30
UCLA (Reference)										

Note: CD = conduct disorder; DU = Duke University; JHU = Johns Hopkins University; NYPI = New York Psychiatric Institute; NYU = New York University; PATS = Preschool ADHD Treatment Study; ODD = oppositional-defiant disorder; UCI = University of California-Irvine; UCLA = University of California-Los Angeles.

Table 4
Clinician Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis by Assessment Time

Diagnosis	YEAR 3			YEAR 6				
	Unadjusted Total (%)	On Meds (%)	Off Meds (%)	Adjusted ^a Total (%)	Unadjusted Total (%)	On Meds (%)	Off Meds (%)	Adjusted ^c Total (%)
YES	155 (76.0)	103 (76.9)	52 (74.3)	173 (84.8)	142 (77.2)	100 (79.4)	38 (73.1)	161 (89.2)
NO	49 (24.0)	31 (23.1) ^a	18 (25.7)	31 (15.2)	42 (22.8)	26 (20.6) ^b	14 (26.9)	23 (10.8)

^a At Year 3, 18 out of 31 ADHD-negative cases and, at Year 6, 19 out of 26 of ADHD-negative cases had more than 6 symptoms resulting in impairment on ADHD Checklist for unmedicated behavior.

^b 6 subjects had no medication data, 2 had no ADHD data, 2 did not have a full diagnostic evaluation.

^c 11 subjects had ADHD missing data and 2 did not have a full diagnostic evaluation.

Table 5
Results of Generalized Linear Model of Probability of Attention Deficit/Hyperactivity Disorder (ADHD) Diagnosis at Follow-up Year 6

Covariates	Unadjusted Effects			Adjusted Effects		
	RR	95% CI	p-value	RR	95% CI	p-value
Prior ADHD diagnosis (Follow Up Year 3)	1.2	0.95, 1.51	0.129	1.2	0.94, 1.43	0.178
Age at the visit (per year)	1.1	0.96, 1.17	0.224			
Girls vs. boys	0.9	0.76, 1.14	0.509			
IQ score (per 5)	1.0	0.95, 1.00	0.082	1.0	0.95, 1.01	0.128
Parent's education (college or above vs. less than college)	1.0	0.85, 1.21	0.861			
Medication status at prior visit: on meds vs. off meds	1.3	1.01, 1.54	0.039	1.2	0.99, 1.50	0.065
Original PATS participation						
Parent training only	0.8	0.66, 1.05	0.119			
Short phases of medication (with or without enrolling in maintenance)	1.00	0.83, 1.19	0.928			
Short phases of medication and completed maintenance	1.0					
Comorbidity (ODD/CD vs. no ODD/CD)	1.3	1.15, 1.53	0.0001	1.3	1.10, 1.46	0.001
N	175			175		

Note: CD = conduct disorder; ODD = oppositional defiant disorder; PATS = Preschool ADHD Treatment Study; RR = Risk ratio.