Further Evidence of Morbidity and Dysfunction Associated With Subsyndromal ADHD in Clinically Referred Children

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ABSTRACT

Background: While the diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) have evolved over the years, some children with impairing ADHD symptoms fail to meet the full diagnostic threshold for the disorder. The main aim of this study was to evaluate the morbidity and dysfunction of subsyndromal ADHD in the clinical setting.

Methods: Subthreshold and full ADHD subjects were derived from consecutive referrals (n = 2,947) to a pediatric psychopharmacology program at a major academic center. Subjects were diagnosed with subthreshold ADHD if they met at least 1 of the following criteria: (1) their age at onset for ADHD was ≥ 7 years; (2) they had ≥ 5 but < 8 ADHD symptoms using the *DSM-III-R* or ≥ 4 but < 6 ADHD inattentive or hyperactive/impulsive symptoms using the *DSM-IV*. Healthy controls were derived from 2 identically designed longitudinal case-control studies of youth with and without ADHD. Psychiatric assessments relied on clinical structured interviews and measures of psychopathology, social functioning, cognitive ability, and academic achievement.

Results: Of the 1,931 children diagnosed with ADHD, 140 (7%) were diagnosed with subthreshold ADHD. 48% of subthreshold ADHD subjects had an age at onset ≥ 7 years, and 73% had insufficient symptoms. Reanalysis of findings using *DSM-5* criteria showed that only 21% of our subthreshold ADHD subjects would have met *DSM-5* criteria based on age at onset of < 12 years, while 79% would have maintained their subthreshold diagnoses. Subjects with subthreshold ADHD differed from controls in the mean number of comorbid disorders; rates of mood, anxiety, and elimination disorders (all $P < .001$) and substance use disorders ($P < .05$); scores on all Child Behavior Checklist clinical and social functioning scales; scores on 7 of the 10 Social Adjustment Inventory for Children and Adolescents scales; rates of requiring extra help in school and being placed in a special class; and scores on 4 of the 5 Wechsler Intelligence Scale for Children–Revised Version subscales (excluding Digit Span) as well as in Freedom from Distractibility Index score ($P < .001$). Subthreshold and full ADHD subjects had similarly elevated Global Assessment of Functioning scores versus controls ($P < .001$), but subjects with subthreshold ADHD had fewer perinatal complications and better family functioning scores and were more likely to be female and older and to come from families of higher socioeconomic status than subjects with full ADHD.

Conclusions: Clinically referred children failing to meet full-threshold diagnosis for ADHD due to either insufficient symptoms or later age at onset have patterns of clinical features highly similar to those with the full syndrome. These results extend to previously reported findings in nonreferred samples documenting the high morbidity and disability associated with subthreshold ADHD.

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While the diagnostic criteria for ADHD have evolved over the years, some children with impairing ADHD symptoms fail to meet full diagnostic threshold for the disorder. This is not surprising considering that ADHD symptoms tend to emerge over time as the complexity of cognitive and educational demands increase. This developmental progression predicts that some children will manifest subsyndromal symptoms of ADHD before they meet full diagnostic criteria. Yet, little is known about subsyndromal ADHD.

Using data from a large twin data set, Larsson et al[1] found comparable group heritability estimates and clinical correlates for both the full and the subthreshold variants of ADHD. Likewise, population studies in Korea,[2] France,[3] the United States,[4,5] and Sweden[6] found that subthreshold ADHD was morbid and predicted onset of the full diagnosis during follow-up. Whether similar findings extend to clinical samples remains unknown.

In addition to insufficient number of symptoms, subthreshold ADHD can also stem from an atypical age at onset. This issue is particularly relevant for children with strong intellectual abilities and those living in supportive, well-structured childhood environments that can help affected children compensate in early life for their ADHD symptoms. This state of affairs supports the need for further evaluation of the clinical significance of subthreshold ADHD in clinical samples addressing the issue of atypical age at onset.

Whether subthreshold ADHD is associated with morbidity and dysfunction has important implications. Such knowledge can alert clinicians to consider appropriate interventions for children with subsyndromal symptoms of ADHD to avert the well-documented compromised outcomes associated with the disorder.[7] This knowledge can also improve public health by allowing for the development of methods to detect subthreshold ADHD before it emerges as full ADHD.

The main aim of the present study was to evaluate the morbidity and dysfunction of

Clinical Points

- Although some children with impairing ADHD symptoms seen in clinical practice fail to meet full diagnostic threshold for the disorder, insights about such children are lacking
- A sizable minority of clinically referred children fail to meet full criteria for ADHD due to either insufficient symptoms or later age at onset, and these children have clinical features and impairments highly similar to those with the full ADHD syndrome.
- Children failing to meet full-threshold diagnosis for ADHD are more likely to be female, to be older, to come from higher social class families, to have less family conflict, and to have had fewer perinatal complications.

subsyndromal ADHD in the clinical setting, attending to symptom threshold and atypical age at onset. On the basis of the literature, we hypothesized that subsyndromal ADHD would be an impairing, clinically significant condition.

METHODS

Subjects

Subthreshold and full ADHD subjects were derived from consecutive referrals (n = 2,947) to a pediatric psychopharmacology program at a major academic center from 1991 to 2008. There was no selection bias based on social class or insurance restrictions. Healthy control subjects were derived from 2 identically designed longitudinal case-control family studies of youth of both sexes with and without ADHD.[8,9] These studies received institutional review board approval to review, analyze, and report anonymously on these subjects. The Partners Human Research Committee approved the review and analysis of deidentified information on these subjects.

Assessment Procedures

Psychiatric assessments of subjects were made with the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version.[10] Indirect interviews were conducted with the subject's parent or guardian for children younger than 12 years of age. In addition, for the healthy control subjects from the case-control family studies, direct interviews were also conducted with subjects who were older than 12 years of age. Because the clinical data set spanned many years, *DSM-III-R* criteria for ADHD were used before the advent of *DSM-IV*, and *DSM-IV* criteria for ADHD were used thereafter. The diagnostic approach was non-hierarchical in that each module evaluated the presence or absence of a disorder independently of any other module.

All assessments were conducted by highly trained and supervised psychometricians with bachelor's or master's degrees in psychology or a related field. Interviewers were blind as to the diagnostic or referral status of the subjects. To assess the reliability of our overall diagnostic procedures, we computed κ coefficients of agreement by having experienced, blinded, board-certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median κ coefficient was 0.98.

We assessed dimensional measures of psychopathology with the Child Behavior Checklist (CBCL).[11] CBCL-Dysregulation profiles were created from the combined T-scores of the Anxiety/Depression, Aggression, and Attention subscales.[12] Deficient emotional self-regulation was defined as a combined T-score of ≥ 180 and < 210; severe emotional dysregulation (SED) was defined as a combined T-score ≥ 210.[13]

Social functioning was assessed using the Global Assessment of Functioning Scale (GAF),[14] CBCL social functioning scales (Activities, Social, and School),[15] and the Social Adjustment Inventory for Children and Adolescents (SAICA).[16] Cognitive ability was assessed using the Wechsler Intelligence Scale for Children–Revised Version (WISC-R).[17] Per the methods of Sattler,[18] full-scale IQ was estimated from the Vocabulary and Block Design subtests of the WISC-R. The Freedom From Distractibility (FFD) factor was derived from the Coding, Arithmetic, and Digit Span subtests of the WISC-R. Academic achievement using the Wide Range Achievement Test (WRAT).[19]

Parents provided information regarding their child's history of school problems (ie, grade retention, placement in special classes, and remedial assistance). Additionally, mothers provided information regarding their history of pregnancy and delivery. Family functioning was assessed using the Moos Family Environment Scale (FES).[20] Socioeconomic status (SES) was measured using the 5-point Hollingshead scale.[21]

Definition of Subthreshold ADHD

Subjects were diagnosed with subthreshold ADHD if they met at least 1 of the following criteria: (1) their age at onset for ADHD was ≥ 7 years; (2) they had ≥ 5 but < 8 ADHD symptoms using the *DSM-III-R* or ≥ 4 but < 6 ADHD inattentive or hyperactive/impulsive symptoms using the *DSM-IV*.

Statistical Analysis

We compared psychopathology and clinical correlates among subjects without ADHD (healthy controls), with subthreshold ADHD, and with full ADHD. We used Wilcoxon rank sum tests to compare ADHD characteristics between the subthreshold and full ADHD groups. The 3-group unadjusted analyses were performed using Poisson regression to analyze count outcomes, Pearson χ^2 and Fisher exact tests to analyze binary outcomes, and 1-way analysis of variance and Kruskal-Wallis plus Dunn tests for continuous outcomes. In addition to the unadjusted analyses, we performed analyses adjusting for demographic characteristic that significantly differed across the 3 groups using linear, logistic, ordered logistic, exact logistic, or Poisson regression models. All tests were 2-tailed and performed at the .05 α level using Stata (Version 14; StataCorp LLC).

Table 1. Demographic Characteristics[a]

Characteristic	Healthy Controls	Subthreshold ADHD	Full ADHD	Test Statistic	*P* Value
Age[b]	11.9 ± 3.3	11.8 ± 3.4	10.4 ± 3.5[c***, d***]	$F_{2,2155} = 27.74$	< .001
Socioeconomic status[e]	1.6 ± 0.8	1.2 ± 0.5[c**]	1.9 ± 1.1[c***, d***]	$\chi^2_2 = 28.57$	< .001
IQ[f]	114.1 ± 11.5	104.3 ± 15.8[c***]	103.1 ± 15.7[c***]	$F_{2,1041} = 50.71$	< .001
Male, n (%)[g]	120 (50)	95 (68)[c**]	1,381 (77)[c***, d*]	$\chi^2_2 = 85.90$	< .001

[a]Values shown as mean ± SD unless otherwise noted. Sample sizes vary by characteristic as shown in subsequent footnotes.
[b]No. of subjects: healthy controls, n = 242; subthreshold ADHD, n = 138; full ADHD, n = 1,778.
[c]Compared to healthy controls.
[d]Compared to subthreshold ADHD.
[e]No. of subjects: healthy controls, n = 241; subthreshold ADHD, n = 40; full ADHD, n = 1,239. The Hollingshead scale ranges from 1 to 5, with higher score indicating lower socioeconomic status.
[f]No. of subjects: healthy controls, n = 242; subthreshold ADHD, n = 63; full ADHD, n = 739.
[g]No. of subjects: healthy controls, n = 242; subthreshold ADHD, n = 140; full ADHD, n = 1,789.
*$P < .05$.
**$P < .005$.
***$P < .001$.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

RESULTS

The clinic sample consisted of 1,931 children with a diagnosis of ADHD. Of these, 1,734 (90%) had a *DSM-III-R* diagnosis of ADHD and 197 (10%) had a *DSM-IV* diagnosis. Based on the criteria used to define subthreshold ADHD described in the Methods section, 140 subjects (7%) were diagnosed with subthreshold ADHD. The comparison sample consisted of 242 healthy controls without ADHD. Thus, comparisons were made between 1,791 subjects with full ADHD, 140 subjects with subthreshold ADHD, and 242 healthy controls without ADHD.

Sociodemographic Characteristics

There were small but significant differences among groups in age, SES, IQ, and sex (Table 1). Subjects with subthreshold ADHD had a significantly higher proportion of females, were older, and were of higher SES compared to full ADHD subjects. There were no differences in IQ between subthreshold and full ADHD subjects, and both groups had significantly lower IQs compared to the healthy controls.

ADHD Characteristics

Almost half of subjects with subthreshold ADHD (n = 140) had an age at onset ≥ 7 years, and 73% had insufficient symptoms (< 8 symptoms for those diagnosed using the *DSM-III-R* and < 6 symptoms for those diagnosed using the *DSM-IV*). The mean ± SD age at late-onset ADHD was 9.5 ± 2.0 years, and the mean ± SD number of ADHD symptoms for those with insufficient symptoms was 5.8 ± 1.0. Subjects with subthreshold ADHD were a mean of 3.2 years older at ADHD onset and had a mean of 4.6 fewer ADHD symptoms compared to subjects with full ADHD.

DSM-5 Considerations

Given that the *DSM-5* uses the age at onset criteria of < 12 years, we reexamined how many of our subthreshold ADHD subjects would be considered to have full ADHD based on the *DSM-5* age at onset criteria. This reanalysis showed that 21% of subthreshold ADHD subjects (n = 30) would have met *DSM-5*, while 79% (n = 110) would have maintained their subthreshold diagnoses.

Patterns of Psychiatric Comorbidity

There were significant differences in the mean number of comorbid psychiatric disorders across the 3 groups ($\chi^2_2 = 615.53$, $P < .001$; Figure 1). There were no significant differences in the mean number of psychiatric disorders between subjects with subthreshold and full ADHD, and both ADHD groups had significantly more comorbid psychiatric disorders than healthy controls (Figure 1A). Significant differences across the groups were seen in rates of disruptive disorders ($\chi^2_2 = 315.34$, $P < .001$), mood disorders ($\chi^2_2 = 172.28$, $P < .001$), multiple (≥ 2) anxiety disorders ($\chi^2_2 = 107.37$, $P < .001$), language disorders ($\chi^2_2 = 58.02$, $P < .001$), elimination disorders ($\chi^2_2 = 55.68$, $P < .001$), and substance use disorders ($\chi^2_2 = 6.97$, $P = .03$). With the exception of disruptive behavior and language disorders (rates of which were both higher in full ADHD subjects compared to subthreshold ADHD subjects), there were no other significant differences between the 2 ADHD groups (Figure 1B). Both ADHD groups had significantly higher rates of all disorders.

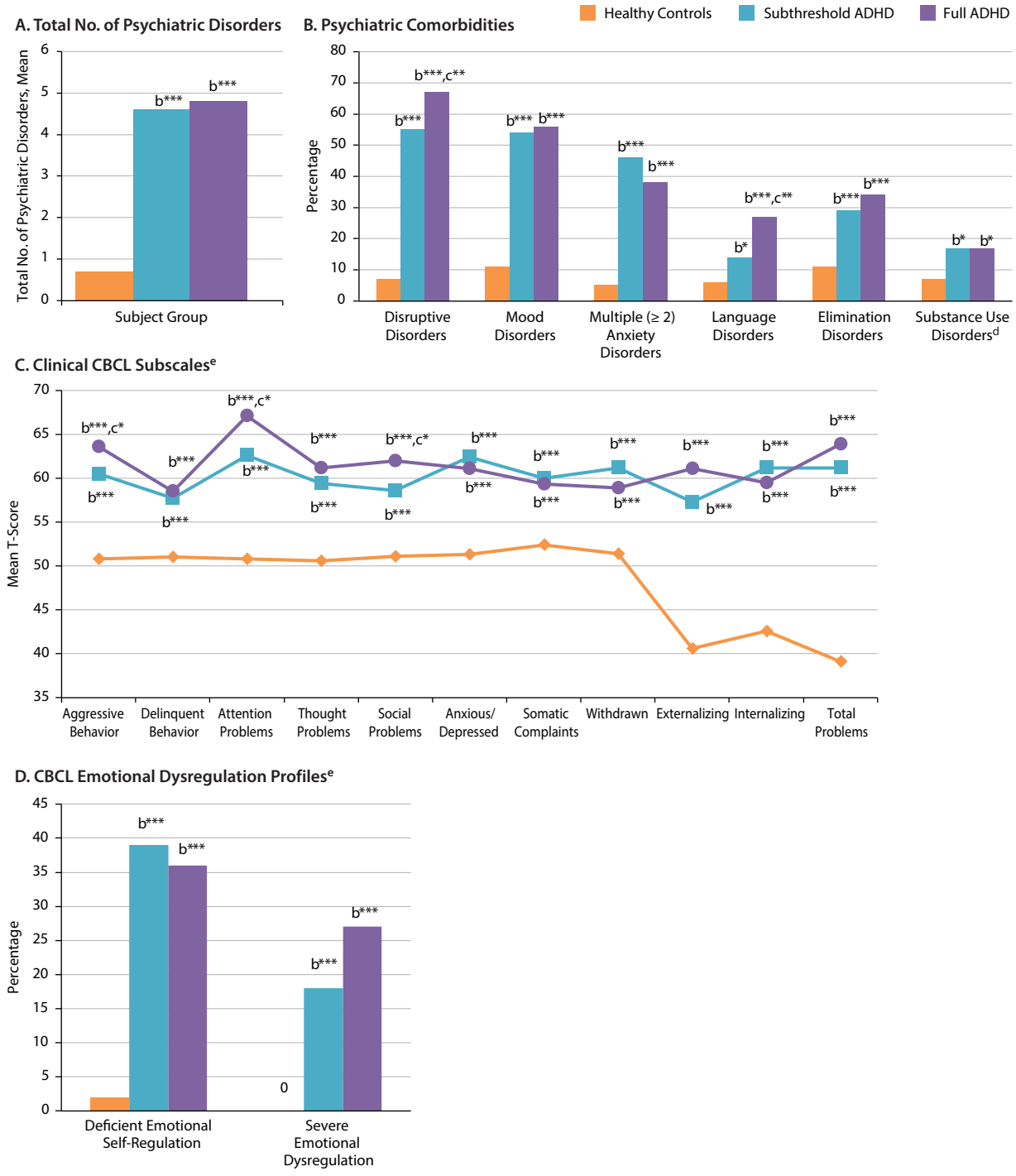
CBCL Findings

Both ADHD groups had significantly higher T-scores on all CBCL clinical subscales versus controls (all $P < .001$). With the exception of higher Aggression, Attention, and Social Problems scale scores in subjects with full versus subthreshold ADHD, there were no other individual or aggregate CBCL scale differences (Figure 1C) between the ADHD groups. Subthreshold and full ADHD subjects had similarly elevated rates of emotional dysregulation that significantly differed from those of healthy controls (deficient emotional self-regulation: $\chi^2_2 = 85.90$, $P < .001$; SED: Fisher exact, $P < .001$) (Figure 1D).

Social Functioning

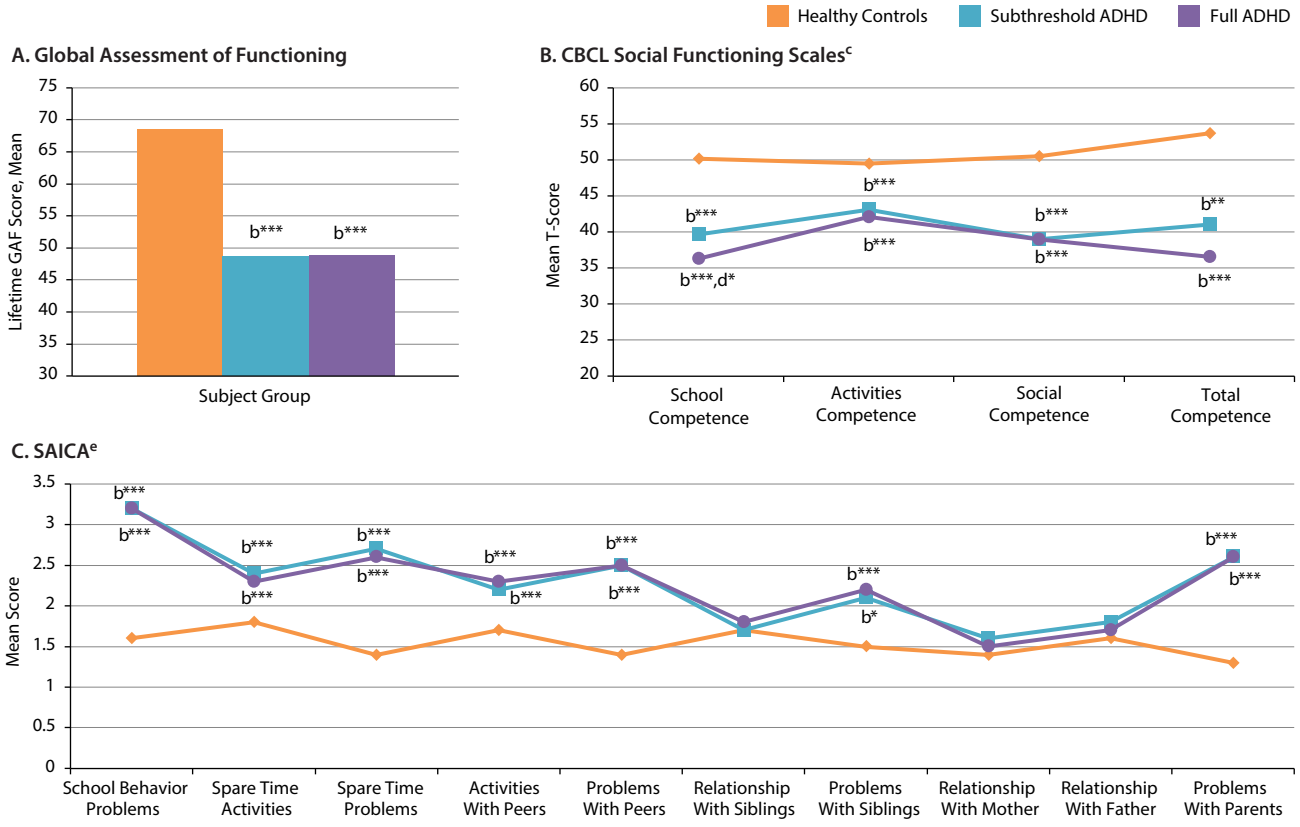
Although GAF scores significantly differed across the 3 groups ($F_{2,2168} = 651.24$, $P < .001$), there were no differences between subjects with subthreshold and full ADHD, and both

Figure 1. Patterns of Psychiatric Comorbidity and Psychopathology[a]



[a]No. of subjects, unless otherwise noted: healthy controls, n = 242; subthreshold ADHD, n = 140; full ADHD, n = 1,791.
[b]Compared to healthy controls.
[c]Compared to subthreshold ADHD.
[d]Age restricted to > 12 years. No. of subjects: healthy controls, n = 103; subthreshold ADHD, n = 60; full ADHD, n = 474.
[e]No. of subjects: healthy controls, n = 229; subthreshold ADHD, n = 49; full ADHD, n = 183.
*$P < .05$.
**$P < .005$.
***$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CBCL = Child Behavior Checklist.

Figure 2. Social Functioning Measured by the GAF, CBCL Social Functioning Scales, and SAICA[a]



[a]No. of subjects, unless otherwise noted: healthy controls, n = 242; subthreshold ADHD, n = 140; full ADHD, n = 1,791.
[b]Compared to healthy controls.
[c]No. of subjects: healthy controls, n = 202–222; subthreshold ADHD, n = 10–46; full ADHD: n = 65–168.
[d]Compared to subthreshold ADHD.
[e]No. of subjects: healthy controls, n = 209–234; subthreshold ADHD, n = 53–66; full ADHD: n = 698–838.
*$P < .05$.
**$P < .005$.
***$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CBCL = Child Behavior Checklist, GAF = Global Assessment of Functioning, SAICA = Social Adjustment Inventory for Children and Adolescents.

ADHD groups had significantly lower GAF scores versus healthy controls (Figure 2).

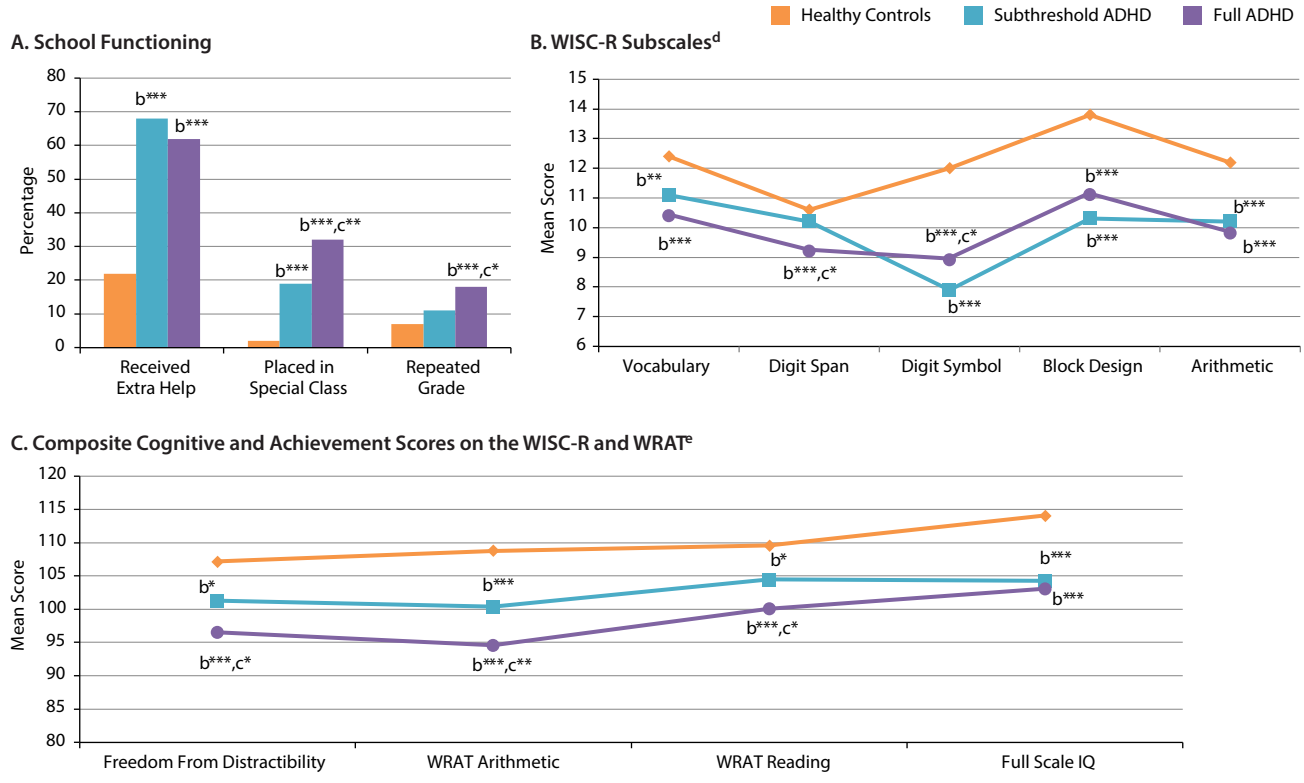
Significant differences in mean T-scores were observed in all 4 individual and aggregate social function scales (all $P < .001$) (Figure 2B). Both the subthreshold and full ADHD subjects had significantly more impaired scores on all individual and aggregate social scales versus controls. Except for the scores on the School Competence scale indicating more impairment in subjects with full ADHD, there were no other significant differences in any of the other individual or aggregate social scales scores between the 2 ADHD groups.

Likewise, scores on 7 of the 10 SAICA scales significantly differed across the 3 groups (Figure 2C). Subthreshold and full ADHD subjects did not significantly differ on any of these items, and both ADHD groups did have significantly worse scores than the controls.

School and Neurocognitive Functioning

We found significant overall differences among groups in the rates of requiring extra help in school ($\chi^2_2 = 141.34$, $P < .001$), being placed in a special class ($\chi^2_2 = 101.48$, $P < .001$), and repeating a grade ($\chi^2_2 = 20.98$, $P < .001$; Figure 3). Subjects with subthreshold ADHD had significantly lower rates of being placed in special classes and repeating a grade versus those with full ADHD (Figure 3A). There were no differences between the 2 ADHD groups in rates of receiving extra help in school. Both ADHD groups received significantly more extra help and were placed more often in special classes versus controls. Cognitive scores significantly differed across the groups on all 5 of the WISC-R subscales (all $P < .001$). Subthreshold ADHD subjects had significantly higher Digit Span and lower Digit Symbol scores than full ADHD subjects (Figure 3B). The 2 ADHD groups did not differ on any of the other cognitive subscales assessed. Compared to controls, subthreshold ADHD subjects had significantly lower scores on 4 of the 5 subscales (excluding Digit Span). There were significant differences across the groups in FFD index scores ($\chi^2_2 = 33.35$, $P < .001$), WRAT Arithmetic scores ($\chi^2_2 = 110.08$, $P < .001$), and WRAT Reading scores ($\chi^2_2 = 37.17$, $P < .001$). Subjects with subthreshold

Figure 3. School and Neurocognitive Functioning[a]



[a]No. of subjects, unless otherwise noted: healthy controls, n = 242; subthreshold ADHD, n = 140; full ADHD, n = 1,791.
[b]Compared to healthy controls.
[c]Compared to subthreshold ADHD.
[d]No. of subjects: healthy controls, n = 242; subthreshold ADHD, n = 39–66; full ADHD, n = 660–752.
[e]No. of subjects: healthy controls, n = 90–242; subthreshold ADHD, n = 40–65; full ADHD, n = 466–739.
*$P < .05$.
**$P < .005$.
***$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, WISC-R = Wechsler Intelligence Scale for Children–Revised, WRAT = Wide Range Achievement Test.

ADHD scored significantly better than subjects with full ADHD on all 3 measures, and both ADHD groups scored significantly worse than the healthy controls (Figure 3C).

Family Environment and Pregnancy and Delivery Complications

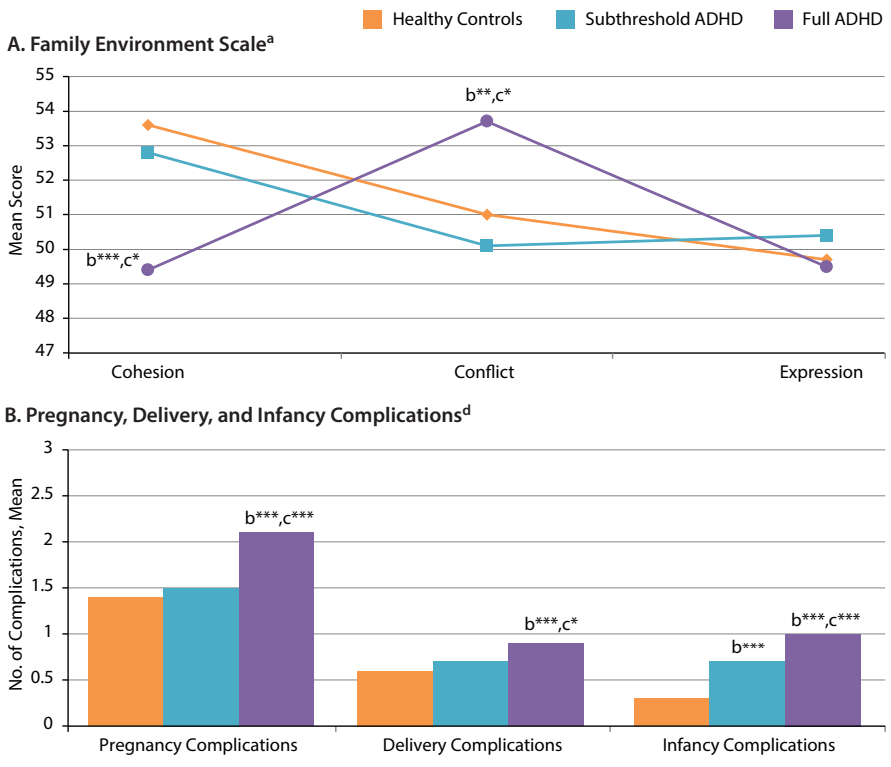
The 3 groups significantly differed on the Cohesion ($\chi^2_2 = 13.45$, $P = .001$) and Conflict ($\chi^2_2 = 11.12$, $P = .004$) subscales of the Family Environment Scale (Figure 4). Subthreshold ADHD subjects and controls had significantly better Cohesion and Conflict scores compared to full ADHD subjects.

The mean number of pregnancy, delivery, and infancy complications significantly differed across the groups (pregnancy complications: $\chi^2_2 = 50.57$, $P < .001$; delivery complications: $\chi^2_2 = 16.68$, $P < .001$; infancy complications: $\chi^2_2 = 90.73$, $P < .001$). Subthreshold ADHD subjects and controls had significantly fewer pregnancy, delivery, and infancy complications compared to full ADHD subjects (Figure 4B). Additionally, subjects with subthreshold ADHD had significantly more infancy complications than controls.

Results From Adjusted Analyses

With few exceptions, follow-up adjusted analyses controlling individually for age, sex, SES, and IQ revealed that all significant outcomes from the unadjusted analysis remained significant after correcting for age and sex. We found differences in 3 SAICA items, which gained significance after controlling for age: relationship with siblings ($\chi^2_2 = 11.22$, $P = .004$), relationship with mother ($\chi^2_2 = 10.59$, $P = .005$), and relationship with father ($\chi^2_2 = 15.63$, $P < .001$) (Figure 2C). Subthreshold ADHD and full ADHD subjects did not significantly differ on any of these 3 items. Both ADHD groups had significantly worse relationships with their mothers and fathers versus controls, and full ADHD subjects also had worse relationships with their siblings versus controls. When analyses were controlled for sex, the only outcome that gained significance was the SAICA item regarding relationships with fathers ($\chi^2_2 = 15.63$, $P = .046$). Both ADHD groups had worse relationships with their fathers versus controls. Substance use disorders (Figure 1B) and delivery complications (Figure 4B) lost significance when we controlled for SES ($P = .07$ and $P = .06$, respectively),

Figure 4. Family Functioning and Mean Number of Pregnancy, Delivery, and Infancy Complications



[a]No. of subjects: healthy controls, n = 238; subthreshold ADHD, n = 60; full ADHD, n = 787–792.
[b]Compared to healthy controls.
[c]Compared to subthreshold ADHD.
[d]No. of subjects: healthy controls, n = 238; subthreshold ADHD; n = 102; full ADHD, n = 520–533.
*$P < .05$.
**$P < .005$.
***$P < .001$.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

and the Cohesion subscale of the FES (Figure 4A) lost significance when we controlled for IQ ($P = .07$). We were unable to analyze scores for FFD Iindex, WRAT Reading, and WISC-R Block Design in the SES-adjusted analysis and the CBCL Total Competence subscale because there were too few subjects in the subthreshold ADHD group. The results for all other outcomes remained the same after performing SES-adjusted and IQ-adjusted analyses (all $P < .05$). Likewise, results remained largely unchanged when subject who would have met *DSM-5* criteria were excluded from the analysis.

DISCUSSION

Clinically referred children failing to meet full-threshold diagnosis for ADHD due to either insufficient symptoms or later age at onset had patterns of correlates highly similar to those with the full syndrome, including high rates of comorbid psychopathology and cognitive, interpersonal, and school functioning deficits. These results extend previously reported findings[2,5,22,23] in nonreferred samples documenting high morbidity and disability associated with subthreshold ADHD.

Our finding of a more even sex distribution in subsyndromal ADHD subjects than in full ADHD subjects is consistent with previous epidemiologic studies documenting a higher male predominance in full versus subthreshold cases.

Our results showing that subthreshold ADHD subjects come from families with higher social class status and higher Cohesion and lower Conflict scores than full ADHD subjects are consistent with the idea that better socioeconomic resources and lower family conflict can help some ADHD children compensate early in life for the disorder, delaying its full manifestation until adulthood.[24]

The findings of high rates of comorbid psychiatric disorders and the highly similar findings in all CBCL individual and composite scale scores between subthreshold and full ADHD subjects are consistent with results from epidemiologic samples,[2,25] providing further support of the morbidity and dysfunction associated with subthreshold ADHD.

The finding of significant differences in the rates of disruptive and language disorders between subjects with full and subsyndromal ADHD in our clinical sample differs from findings in epidemiologic samples that reported differences

only in the rates of anxiety disorders. Our findings, however, are consistent with the idea that disruptive and language disorders drive referral status.

Further evidence of the morbidity associated with subthreshold ADHD can be gleaned from the school and cognitive findings. Both full and subthreshold ADHD subjects differed from controls in the rates of extra help in school, being placed in a special class, and repeating grades as well as in overall estimated IQ and scores on all 5 of the WISC-R subscales, the WRAT-R, and the FFD index, a proxy for working memory deficits. However, the finding that measures of working memory deficits (FFDI), digit span, and arithmetic scores showed less impairment in subthreshold ADHD are consistent with the idea that better intellectual abilities may allow such children with ADHD to compensate for their disorder.[24]

Our perinatal findings showing a stronger association with full ADHD are consistent with those of Kim et al[26] suggesting that perinatal factors are more closely related to full than to subthreshold ADHD. These findings support the idea that perinatal complication may mediate the development of the full syndrome in children at genetic risk for the disorder.

The finding that a sizable minority of subjects with subthreshold ADHD in our pre–*DSM-5* dataset had an age at onset of ADHD symptoms that would have allowed them to meet *DSM-5* criteria for ADHD is noteworthy. It stresses the arbitrariness of age at onset in our nosology. Elsewhere,[24] we posited that the etiology of ADHD leads to a wide variability in ages at onset of initial symptoms, symptoms exceeding diagnostic threshold, and impairment arising from those symptoms. Those with lower levels of risk at birth will take longer to accumulate sufficient risk factors and have a longer time to onset with symptoms and impairment. This multifactorial perspective of ADHD allows for different risk factors to exert effects at different ages, thereby influencing age at onset. Because these effects are multifactorial, there is no clean separation of etiologic factors in people above and below the arbitrary ages at onset set forth in the *DSM*. Such a scenario suggests that ADHD may be a disorder with a continuum of ages at onsets, with some subjects starting their symptoms earlier while others later.

Our findings need to be viewed against some methodological limitations. Although the sample size of subthreshold ADHD subjects was relatively modest, we could document statistically significant findings against controls in most outcomes assessed. Although the data were collected before the publication of *DSM-IV*, reanalysis of findings using age at onset of < 12 years showed that only 21% of our subthreshold ADHD subjects would have met *DSM-5* criteria, whereas 79% would have maintained their subthreshold diagnoses. Because children with subthreshold ADHD had higher ratings of internalizing disorders than controls, these children might have had primary disturbances of mood and anxiety disorders. However, the diagnostic approach used was non-hierarchical in that each module evaluated the presence or absence of a disorder independently of any other module, making it difficult to determine which disorder was primary or secondary. Moreover, the rates of mood and anxiety disorders in subthreshold ADHD subjects were the same as in those with a full-threshold diagnosis. Because the GAF scores used to assess impairment assessed overall (global) impairment, we cannot determine the extent to which impairment is related to ADHD or to problems attributable to comorbid pathology. Yet, it is noteworthy that GAF scores were similar between subthreshold and full ADHD subjects. Since the sample was largely white, our findings may not generalize to other ethnic groups.

Despite these considerations, our results show that clinically referred children failing to meet full-threshold diagnosis for ADHD due to either insufficient symptoms or later age at onset have patterns of correlates highly similar to those with the full syndrome, including high rates of comorbid psychopathology and interpersonal, cognitive, and school functioning deficits. Female sex, higher SES, less family conflict, and fewer perinatal complications distinguished subthreshold from full ADHD cases. These results extend, to referred samples, previously reported findings in nonreferred samples documenting the high morbidity and disability associated with subthreshold ADHD.

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Potential conflicts of interest: **Dr Biederman** is currently receiving research support from the following sources: American Academy of Child and Adolescent Psychiatry, US Department of Defense, US Food and Drug Administration, Headspace, Lundbeck, Neurocentria, National Institute on Drug Abuse, PamLab, Pfizer, Shire, Sunovion, and National Institutes of Health (NIH). Dr Biederman has a financial interest in Avekshan LLC, a company that develops treatments for attention-deficit/hyperactivity disorder (ADHD). His interests were reviewed and are managed by Massachusetts General Hospital (MGH) and Partners HealthCare in accordance with their conflict of interest policies. Dr Biederman's program has received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Ingenix, Prophase, Shire, Bracket Global, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. In 2017, Dr Biederman was a consultant for Akili, Guidepoint, and Medgenics. He was on the scientific advisory board for Alcobra and Shire. He received honoraria from the MGH Psychiatry Academy for tuition-funded Continuing Medical Education courses. Through MGH corporate licensing, he has a US Patent (#14/027,676) for a non-stimulant treatment for ADHD and a patent pending (#61/233,686) on a method to prevent stimulant abuse. In the past year, **Dr Faraone** received income, potential income, travel expenses, and/or research support from Lundbeck, Rhodes, Arbor, KenPharm, Ironshore, Shire, Akili Interactive Laboratories, CogCubed, Alcobra, VAYA Pharma, and National Association for Continuing Education. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received income or research support from Shire, Neurovance, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer ,and Eli Lilly. Dr Faraone receives royalties from books published by Guilford Press (*Straight Talk about Your Child's Mental Health*, Oxford University Press (*Schizophrenia: The Facts*, and Elsevier (*ADHD: Non-Pharmacologic Interventions*. He is principal investigator of www.adhdinadults.com. **Mss Fitzgerald**, **Kirova**, and **Woodworth** and **Mr Biederman** have no conflicts of interest.

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