ORIGINAL CONTRIBUTION

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Predictive utility of childhood diagnosis of ICD-10 hyperkinetic disorder: adult outcomes in the MTA and effect of comorbidity

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Abstract
Diagnostic guidelines differ between DSM attention-deficit/hyperactivity disorder (ADHD) and ICD hyperkinetic disorder (HKD). Only 145 of 579 children age 7–9 in the Multimodal Treatment Study of ADHD (the MTA) with combined-type DSM-IV ADHD met criteria for ICD-10 HKD, because major internalizing comorbidities and more stringent symptom count/pervasiveness requirements excluded most. The 145 HKD had significantly better 14-month medication response than the rest. We explored whether HKD had greater adult symptom persistence and/or impairment than other ADHD. Multi-informant assessments were done for 16 years. We used the 12/14/16-year assessments, in young adulthood. The post-attrition 109 with baseline HKD had no greater adult persistence of ADHD symptoms/impairment than 367 without HKD, but had more cumulative stimulant use, more job losses, lower emotional lability, and fewer car crashes. However, those excluded for internalizing comorbidity but otherwise meeting HKD criteria had significantly more persistence. Only 6 of the 109 (5.5%) with baseline HKD met ICD-10 criteria for HKD in adulthood, compared to 25 of 367 (6.8%) without a childhood HKD diagnosis. Despite greater initial symptom severity, HKD had no worse 16-year young adult outcome than others, except for job losses, balanced by less emotional lability and fewer crashes. Comorbid internalizing disorder seems to have worse prognosis than initial severity/pervasiveness of ADHD symptoms.

Keywords International classification of diseases (ICD) · Diagnostic and statistical manual of mental disorders (DSM) · Adult outcomes · Attention-deficit/hyperactivity disorder (ADHD) · Hyperkinetic disorder

Introduction

Attention-deficit/hyperactivity disorder (ADHD), historically called hyperkinetic reaction in the Diagnostic and Statistical Manual of Mental Disorders-Edition II

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(DSM-II), is characterized by excess activity and deficits in attention, behavior regulation, and impulse control. The two major schemes of psychiatric classification, the American Psychiatric Association's DSM and the World Health Organization's International Classification of Diseases (ICD) [1–3], define this condition differently. The ICD-10 term is "hyperkinetic disorder" (HKD); the DSM-IV and DSM-5 terms are "attention-deficit/hyperactivity disorder" (ADHD). The lifespan courses of these two expressions are not well mapped.

Both ICD-10 and DSM-IV/5 use similar behavioral criteria, but the diagnostic decision rules differ. In contrast to DSM-IV or DSM-5, ICD-10 requires greater symptom pervasiveness and the absence of major internalizing disorders of anxiety or depression [4]. Both systems require impairing symptoms in at least two settings, but ICD-10 requires full symptom count in both settings. Further, DSM allows diagnosis with a partial presentation (inattentive or hyperactive/impulsive), while ICD-10 requires both hyperactivity–impulsiveness and inattention in both school and home. As a result, HKD is a narrower disorder with a considerably lower prevalence than ADHD [5]. Studies comparing the two suggest greater severity in HKD rather than qualitative differences [6, 7].

The ICD-10 is under revision and the new criteria for HKD may resemble the DSM-5. Any revision may have treatment implications: treatment guidelines for the UK and Europe call for earlier recourse to medication in severely affected groups (corresponding to HKD) than in other types of ADHD [8, 9]. A previous report from the Multimodal Treatment Study of Children with ADHD (the MTA; see below) indicated that those who met criteria for ICD-10 HKD, compared to other ADHD cases, enjoyed more benefit from carefully managed stimulant medication [10].

Here we examine the long-term outcomes of children with a baseline ICD-10 diagnosis of HKD in the MTA cohort. This subgroup is of interest because, compared to the rest of the MTA sample, it started with greater mean symptom severity and had a significantly better response to stimulant medication compared to intensive behavior therapy [10]. We hypothesize that, by adulthood, children originally meeting diagnostic criteria for ICD-10 HKD, compared to children meeting only DSM-IV ADHD criteria, would have: (a) higher symptom persistence and impairment; (b) greater medication use; and (c) poorer functional life outcomes, such as more motor accidents, justice involvement, occupational difficulties, sexual risk taking, emotional functioning problems, substance use disorders, height suppression, and lower socioeconomic status. We also explore the effects of the ICD-10 HKD exclusionary criterion for anxiety and depression.

Method

Original design, measures, and procedures of the MTA are described in [11–15], and the long-term follow-up (16 years) results are presented in [16–18]; see [18] for a detailed CONSORT chart. Briefly, 579 children aged 7–9 years with DSM-IV combined-type ADHD were randomly assigned to systematic medication management (MedMgt), comprehensive multicomponent behavioral treatment (Beh), the combination of both (Comb) or referral for community comparison treatment-as-usual (CC). Study-provided treatment lasted 14 months and thereafter assessment occurred at 24 months, 36 months, and 6, 8, 10, 12, 14, and 16 years after baseline. Of the original 579 children, 476 (82.2%) had adult assessments (12, 14, and/or 16 years).

The most prominent of a 19-measure outcome assessment battery was parent- and teacher-rated ADHD symptoms on the Swanson, Nolan, and Pelham (SNAP) scale [19]. On these, MedMgt and Comb showed a highly significant ($p = .001$) advantage over Beh and CC, (the Medication Algorithm comparison), even though 66% of the CC group received medication in the community. For academic, social, and emotional outcomes, Comb did best, followed by MedMgt, Beh, and then CC [13]. The medication superiority continued significantly at 24 months although attenuated by half as participants received self-selected treatment in the community [15]. At 36 months, the advantage had vanished while the proportions medicated in the four groups converged.

The 16-year follow-up of the MTA showed symptom persistence to age 25 for 40–60%, depending on whether DSM-IV, DSM-5, or a norm-based symptom count threshold was used [18, 20]. The follow-up also documented significant adult functional impairments in education, work/employment, sexual behavior, emotional stability, and substance use compared to a local normative comparison group [21]. Neither original treatment assignment nor current adult medication status was associated with adult symptom severity or persistence.

Measures

The main diagnostic instrument at baseline was the Diagnostic Interview Schedule for Children (DISC) [22]. The parent version was administered at all assessments and the child or youth version, age 11 onwards. After participants turned 18, the young adult version was used (DISC-YA) by youth and parents.

HYPESCHEME

The ICD-10 research criteria for HKD were implemented by applying HYPESCHEME to baseline DISC-Parent interview and SNAP Teacher ratings. HYPESCHEME is a published

algorithm for coding information from a variety of instruments and records [23]. It can generate an explicit category of HKD as well as ADHD [24]. As described by Santosh et al. [10], each of the operations below provided a 'filter' defined by HKD criteria:

Comorbidity filter	If a DISC diagnosis of generalized anxiety disorder or major depression was present, the HKD diagnosis was excluded based on the ICD-10 decision rule that these internalizing disorders should be considered primary. As used in the MTA sample [10], other anxiety disorders and dysthymia were not exclusionary
Symptom domain filter	If the full ICD-10 symptom count was not met for any of the three domains (inattentiveness, hyperactivity, and impulsiveness), this was considered subthreshold manifestation and HKD was excluded
Pervasiveness filter	If the symptom counts were met in only one of the two settings (school and home), the cases were assigned to 'home-predominant' or 'school-predominant' subthreshold groups and HKD was excluded
Impairment filter	If overall impairment was not endorsed on the DISC interview, then the HKD diagnosis was excluded even if some impairment in two settings could be inferred through collateral information (often at the clinical interview that was the last step of the MTA assessment)

Adult ADHD (DSM-5)

The Conners Adult ADHD Rating Scale (CAARS) [25, 26] rated by youth and parent or significant other was used to determine *adult ADHD symptomatology* at 12-, 14-, and 16-year follow-ups in 476 participants. A symptom was considered present if the respondent rated ≥ 2 on the 4-point CAARS scale (0 = Not at all, 1 = Just a little, 2 = Pretty much, 3 = Very much).

ADHD in adulthood was operationalized in two ways. Mean scores from both self-rated and parent-rated CAARS at the last available time-point (12, 14, or 16 years) provided severity measures. Categorical diagnoses of adult

ADHD were based on DSM-IV (six symptoms from either list), and DSM-5 (five symptoms) plus impairment on the Impairment Rating Scale overall rating. We used the "or" item-level symptom rule, which counted a symptom present if endorsed by either source, providing measures from both sources (subject and parent) were available.

In addition to CAARS-based ADHD symptoms, we also examined adult diagnosis of ADHD as reported by self or parent on the DISC-YA at the last available time-point of 12, 14 or 16 years. However, due to missing DISC-YAs for some participants and to maintain comparability with previous symptom persistence papers from the MTA, the CAARS symptom-based classification of adult ADHD persistence was the primary outcome.

Adult functional outcomes

Comorbidity: we used the Diagnostic Interview Schedule for Children-Parent version (DISC-P) and Young Adult version (DISC-YA) to assess parent- and self-endorsed ADHD, and externalizing problems at 12-, 14- and 16-year follow-ups [22]. Internalizing problems were assessed with DISC-YA only.

Substance use problems were assessed with DISC-P and DISC-YA reports and defined as the presence or absence of alcohol use problems, marijuana use problems, nicotine dependence, or other substance use problems. We also assessed current smoking status (daily or not) using the Substance Use Questionnaire [27, 28].

Educational outcome was operationalized as whether or not a bachelor's degree was obtained.

Occupational functioning was measured by self-reports on total number of job losses.

Socioeconomic functioning was operationalized as whether the participant had received public assistance.

Emotional functioning was operationalized as emotional lability and neuroticism, assessed by self- and observer-reported CAARS and the NEO-Five-Factor Inventory [29], respectively. To partial out impulsivity from emotional lability, we adjusted for CAARS-rated hyperactive/impulsive symptoms as in Hechtman et al. [21].

Sexual behavior was operationalized as self-reported age at first sexual contact.

Justice involvement was assessed as self-reports on total incidents of police contact.

Information on *Medication* use between end-of-treatment at 14 months and 10-year follow-up was available from the Services for Children & Adolescents-Parent Interview (SCAPI) [30] and for 12–16-year follow-ups from the health information questionnaire.

Impairment in adulthood was operationalized as ≥ 3 on the Impairment Rating Scale (IRS) summary item endorsed by either self or observer [20].

Height was taken from health assessment questionnaires.

Car crashes were operationalized as total self-reported car accidents, regardless of whether they were judged at fault, since the time they were licensed. This variable includes information from both adolescent and adult follow-ups.

Adult HKD (ICD-10)

Self- and parent-reported DISC-YA were used to determine adult hyperkinetic disorder. DISC-YA diagnoses of GAD or MDD were counted if reported by either source. Using the last available time-point of 12, 14 or 16 years, we combined item-level scores on inattention, hyperactivity and impulsivity from self and parent reports using the 'or' rule: a symptom was considered present if either source endorsed it. The pervasiveness filter was problematic because ICD-10 requires the symptoms for each domain present in at least two settings, but the DISC does not distinguish symptom domains and a single item measures whether symptoms are present in two settings. Therefore, pervasiveness and impairment were considered positive if endorsed by either self or parent on the DISC. We reapplied the HYPESCHEME filters (described above) such that cases passing all four filters were considered to have HKD in adulthood. The length of follow-up varied slightly based on the fact that the last observation for each case was used, but only if it occurred at one of the three adult assessments (age 21–26). Thus, the length of follow-up was 12–16 years.

Statistical analysis

Adult ADHD symptoms

We counted the number and percentage of participants with and without ICD-10 baseline diagnosis of HKD (based on the DISC) who later met DSM ADHD symptom count criteria in adulthood based on the CAARS. Second, as an exploration of comorbidity effects, we expanded the ICD-10 HKD group to include participants with comorbid anxiety or depression. For this, the HYPESCHEME filters were reapplied such that cases passing symptom domain, pervasiveness, and impairment filters, but not the comorbidity filter, were included. This added an additional 33 participants to the HKD group. We then recalculated the number and percentage of participants with expanded hyperkinetic disorder who met ADHD symptom count in adulthood. Third, we determined differences in adult ADHD symptom count between participants with comorbidity (that is, HKD plus either an oppositional defiant, conduct, anxiety, or depressive disorder) and those without comorbidity (only "pure" HKD). Fourth, we assessed differences in adult ADHD symptom count between participants with either only

anxious/depressed comorbidity or only oppositional-defiant/conduct comorbidity. Chi-square tests were used to assess group differences.

Functional outcomes

Adult functional outcomes, medication use, and hospitalizations were compared between participants with and without HKD at baseline. Medication use was operationalized as the mean dosage of stimulants used (milligrams/day) between end-of-treatment and the 10-year follow-up. We calculated medication use scores for participants who had at least one observation in adulthood (as defined by Swanson et al. [18]). Further, information on lifetime stimulant medication was used to determine participant groups who received medications either consistently, inconsistently or negligibly [18]. Adult outcomes were regressed on HKD/non-HKD groups adjusting for baseline socioeconomic status (total household income) and age at follow-up. We also assessed differences in functional adult outcomes using an expanded definition for hyperkinetic disorder (see below for details on the "expanded definition"). For these exploratory analyses with small numbers, an alpha of 0.05 was used. All analyses were performed using SPSS v. 22.0.0 (IBM Corp., Armonk, NY).

Results

Results are described for an "original HKD subsample" and an "expanded HKD subsample". Figure 1 shows the genesis of the subsamples and attrition for each.

Baseline characteristics showed no significant differences between participants with and without original HKD (Table 1), but attrition from the original HKD subsample was 24.8% compared to 15.4% from the rest of the MTA original sample ($p = .012$). Table 1 presents a comparison of baseline demographic and psychological characteristics between the original HKD participants and the rest of the MTA sample.

Of the 145 participants diagnosed with HKD at baseline by Santosh et al. [10], 109 had at least one adult assessment ("original HKD subsample"). Supplementary Table 1 compares baseline demographic characteristics between the 109 HKD participants followed into adulthood and those lost to follow-up. Of the 109, 52 (37.6%) had baseline comorbid externalizing disorder (HKD + Ext: 38 CD, 14 ODD), and 31 (28.4%) had a baseline anxiety disorder other than the generalized anxiety disorder (GAD) that Santosh et al. [10] excluded.

Next, the HKD subsample was expanded by the 33 that Santosh et al. [10] had excluded for GAD/depression (26 of these 33 were followed into adulthood, of whom 11 also had baseline ODD/CD). This increased the number in the HKD
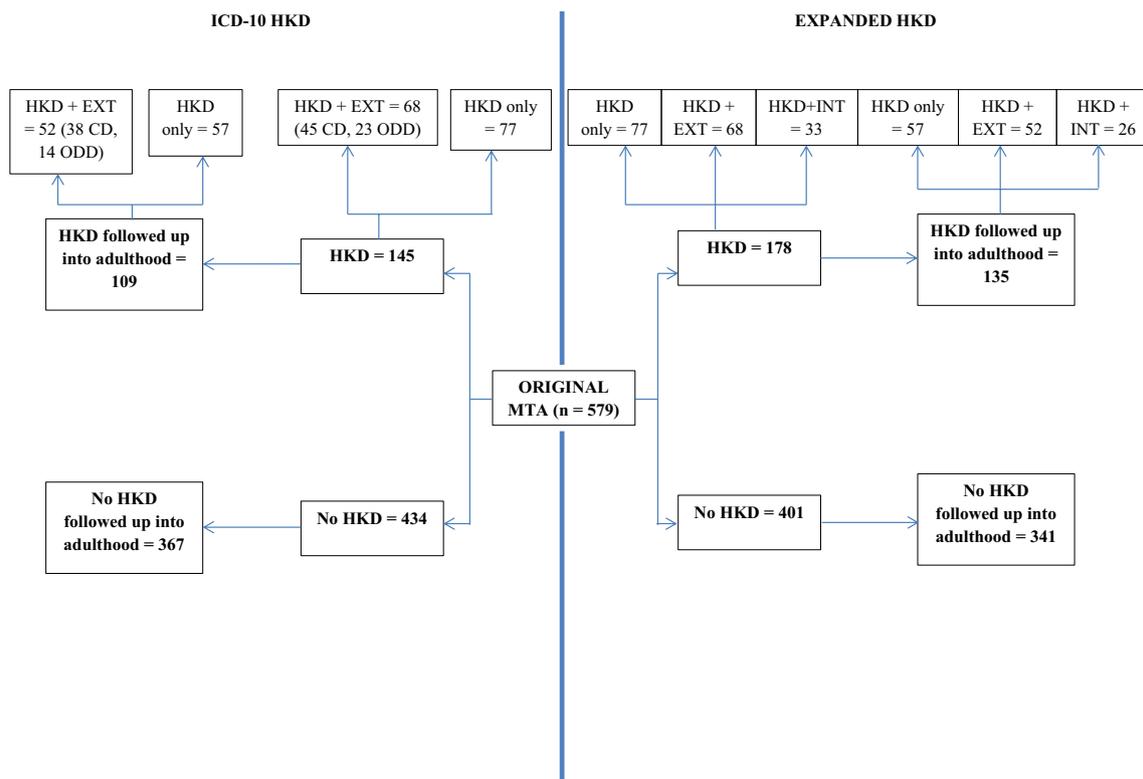
Fig. 1 NB: 'HKD only' included internalizing problems other than GAD and MDD. HKD + INT represented cases with either a generalized anxiety disorder or major depressive disorder in addition to HKD. HKD + EXT includes participants with comorbid opposi-tional defiant and conduct disorder. The additional participants in the expanded group are those who have GAD/MDD, i.e., included in the HKD + INT group

group at baseline from 145 to 178. Of these 178, 135 were followed into adulthood and are referred to as the "expanded subsample" or "expanded HKD". Baseline comorbidity status of these 135 can be classified thus: 26 had HKD with comorbid internalizing disorder ("HKD + Int", GAD 25, major depression 1); 52 others had HKD with ODD/CD; and 57 had "pure" HKD.

Table 2 compares the 109 original HKD Santosh et al. [10] diagnosed at baseline versus the rest (367) of the follow-up MTA sample. No differences in adult symptom severity or rates of DSM-5 and DSM-IV adult ADHD persistence were significant. The 135 expanded HKD versus the rest of the MTA also showed no significant differences in adult severity or rates of DSM-5 ADHD persistence. Thus, hypothesis 1 was not upheld: neither the original nor expanded HKD group differed significantly from the non-HKD majority in adult persistence or severity of ADHD symptoms despite initially greater severity. Because those with HKD responded better to stimulants [10], we checked if long-term medication use may explain why adult symptoms in the HKD group were comparable to the other MTA participants. We found, though, that less than 10% of the MTA participants were still medicated in adulthood. Although

9.1% of the HKD group compared to 6.8% of those without HKD reported consistent medication use, the difference was not significant ($\chi^2 = 3.24$, $p = .19$). Total stimulant use rates were also comparable (Mean$_{HKD}$ = 20.30 mg/day, Mean$_{non-HKD}$ = 16.05 mg/day, $p = .08$; see Table 5).

However, an interesting exploratory finding was based on the observation that those with comorbid HKD (HKD + Int and HKD + Ext) tended to have higher symptom persistence than those with pure HKD (with no comorbidity), although these differences were not statistically significant (See supplementary Table 2 for details). To explore this, we compared participants with baseline HKD + Int versus baseline HKD + Ext. The HKD + Int group had greater adult ADHD persistence rates. Thus, the differences seem to be driven by comorbid anxiety/depression rather than ODD/CD (Table 3). Children with HKD + Int were more likely than those with only pure HKD to qualify eventually for adult ADHD by DSM-IV ($\chi^2_{(1)} = 6.47$, $p = .011$), DSM-5 ($\chi^2_{(1)} = 6.05$, $p = .014$), and NB ($\chi^2_{(1)} = 4.47$, $p = .034$) diagnostic symptom count criteria and impairment. Next, we compared the HKD + Int group to the rest of the HKD expanded group. Results again showed that the HKD + Int group had higher rates of adult ADHD (Table 4). To check whether the

Table 1 Baseline demographic and psychological characteristics in participants with and without ICD-10 hyperkinetic disorder (HKD)

Baseline characteristics	HKD at baseline (ICD-10)		*p*
	Yes *n*=145 *n* (%)	No *n*=434 *n* (%)	
Gender (female)	23 (15.86)	91 (20.96)	.18
MTA treatment group			
Community care	33 (22.75)	113 (26.03)	.69
Medication only	36 (24.82)	108 (24.88)	
Combined treatment	35 (24.13)	110 (25.34)	
Psychosocial only	41 (28.27)	103 (23.73)	
Ethnicity			
Caucasian	92 (63.44)	260 (59.90)	.52
Black	31 (21.37)	84 (19.35)	
Hispanic	10 (6.89)	39 (8.98)	
Other	12 (8.27)	51 (11.75)	
Maternal education level			
Eight grade or less	1 (0.68)	3 (0.69)	.86
Some high school	5 (3.44)	24 (5.52)	
High school graduate or GED	31 (21.37)	89 (20.50)	
Some college or post-high school	53 (36.55)	158 (36.40)	
College graduate	29 (20.00)	95 (21.88)	
Advanced graduate or professional degree	25 (17.24)	62 (14.28)	
Paternal education level			
Eight grade or less	2 (1.37)	8 (1.84)	.79
Some high school	7 (4.82)	27 (6.22)	
High school graduate or GED	29 (20.00)	84 (19.35)	
Some college or post-high school	28 (19.31)	105 (24.19)	
College graduate	23 (15.86)	57 (13.13)	
Advanced graduate or professional degree	22 (15.17)	60 (13.82)	
Household income			
<$10,000	15 (10.34)	36 (8.29)	.28
$10,000–$20,000	10 (6.89)	58 (13.36)	
$20,000–$30,000	19 (13.10)	67 (15.43)	
$30,000–$40,000	27 (18.62)	56 (12.90)	
$40,000–$50,000	14 (9.65)	53 (12.21)	
$50,000–$60,000	18 (12.41)	42 (9.67)	
$60,000–$70,000	10 (6.89)	39 (8.98)	
$70,000–$75,000	7 (4.82)	17 (3.91)	
>$75,000	22 (15.17)	57 (13.13)	
Public assistance/welfare/social security			
Yes	25 (17.24)	83 (19.12)	.63
No	119 (82.06)	351 (80.87)	
	Mean (SD)	Mean (SD)	*p*
Age (in years)	7.74 (.79)	7.79 (.81)	.48
Mother's age	37.60 (7.47)	37.54 (7.15)	.93
Father's age	39.92 (7.19)	40.11 (7.44)	.81
Psychological characteristics	Mean (SD)	Mean (SD)	*p*
Swanson, Nolan, and Pelham (SNAP) questionnaire[a]			
Inattention	2.33 (.37)	2.00 (.50)	<.001

Table 1 (continued)

Psychological characteristics	Mean (SD)	Mean (SD)	p
Hyperactivity	2.16 (.38)	1.81 (.57)	<.001
Impulsivity	2.26 (.47)	1.84 (.67)	<.001
ODD[b]	1.41 (.63)	1.37 (.65)	.59
Total SNAP	2.26 (.31)	1.91 (.43)	<.001
Child depression inventory (CDI)[c]			
Negative mood	.37 (.37)	.35 (.37)	.72
Interpersonal problems	.30 (.36)	.31 (.41)	.68
Ineffectiveness	.44 (.46)	.39 (.45)	.28
Anhedonia	.52 (.40)	.51 (.38)	.74
Negative self-esteem	.28 (.37)	.30 (.36)	.65
Total CDI	.40 (.30)	.39 (.31)	.78
Child behavior checklist (CBCL)[c]			
Withdrawn	.22 (.20)	.31 (.27)	<.001
Somatic complaints	.15 (.20)	.18 (.20)	.12
Anxious depressed	.35 (.27)	.44 (.30)	.001
Social problems	.61 (.33)	.62 (.33)	.76
Thought problems	.18 (.22)	.18 (.20)	.83
Attention problems	.90 (.25)	.87 (.28)	.19
Delinquent behavior	.30 (.23)	.27 (.19)	.14
Aggressive behavior	.81 (.35)	.82 (.35)	.81
Sexual behavior problems	.06 (.14)	.06 (.14)	.95
Total internalizing	.26 (.19)	.33 (.21)	<.001
Total externalizing	.61 (.28)	.60 (.27)	.76
Total CBCL	.42 (.17)	.43 (.17)	.35

[a]Mean scores from parent and teacher reports were used

[b]Oppositional defiant disorder

[c]Parent reports

association of ADHD persistence with comorbid anxiety/depression was peculiar to expanded HKD, we also compared adult ADHD rates of the residue without expanded HKD with versus without anxiety/depression (Table 4). Results from this analysis show a similar pattern: children with comorbid anxiety/depression were more likely to have adult ADHD symptom persistence.

Adult functional outcomes (Table 5) were generally comparable for the original HKD and non-HKD groups except that car crashes and emotional lability problems were higher in the non-HKD group while job losses were higher in HKD. No height differences were found in adulthood despite greater stimulant use by the HKD group. The expanded HKD group (Table 6) also showed a lower risk for car crashes and emotional lability than the non-HKD group, but the difference in job losses and stimulant use was not significant.

No differences were found in medication use patterns (negligible, inconsistent, consistent) through adolescence, but total medication used was higher with baseline original HKD (not the expanded HKD definition). We found

no significant differences in adult ADHD symptom severity by the three naturalistic stimulant-exposure groups between those with HKD (using both the regular and expanded definition) and the rest of the sample (supplementary Table 3). Of 94 participants with baseline HKD and adult medication data, 4 reported occasional stimulant use, 7 frequent stimulant use, and 83 no stimulant use. Of the 295 without HKD, 10 reported occasional stimulant use, 25 frequent stimulant use, and 260 no stimulants. Adult stimulant use did not differ significantly between the HKD groups. Thus, our hypothesis that adult outcomes differ between individuals with and without baseline HKD diagnosis was not well supported.

Supplementary Table 4 presents the number of participants excluded in adulthood from HKD diagnosis with each HYPESCHEME filter, and consequent rates of adult ICD-10 HKD and "expanded" HKD. Of the 109 participants with HKD at baseline, only six (5.5%) could be classified as having HKD in adulthood based on ICD-10 criteria, compared

Table 2 DSM ADHD diagnoses (with impairment) at adult follow-up for children with hyperkinetic disorder (HKD) at baseline and the rest of the MTA sample

ADHD at follow-up (criteria used)	HKD at baseline by strict ICD-10 Dx (original HKD)					HKD at baseline regardless of comorbidity[a] (expanded HKD)				
	Yes $n=109$ mean (SD)	No $n=367$ mean (SD)	d	p	CI	Yes $n=135$ mean (SD)	No $n=341$ mean (SD)	d	p	CI
Adult symptom severity[b]	.98 (.45)	.97 (.45)	.02	.87	− .10 to .09	1.00 (.46)	.96 (.45)	.08	.36	− .13 to .04
	n (%)	n (%)	RR	p	CI	n (%)	n (%)	RR	p	CI
Symptom count using item-level 'OR' rule on self- and observer-reported CAARS[c]										
DSM-5 + impairment										
Yes (34.5%)	32 (30.7%)	125 (35.7%)	.86	.35	.62 to 1.18	46 (35.9%)	111 (34.0%)	1.05	.70	.80 to 1.39
No (65.4%)	72 (69.2%)	225 (64.2%)				82 (64.0%)	215 (65.9%)			
DSM-4 + impairment										
Yes (28.1%)	23 (22.1%)	105 (30.0%)	.73	.11	.49 to 1.09	35 (27.3%)	93 (28.5%)	.95	.80	.68 to 1.33
No (71.8%)	81 (77.8%)	245 (70.0%)				93 (72.6%)	233 (71.4%)			
DISC-YA diagnosis of ADHD										
Yes (20.7%)	26 (24.1%)	71 (19.7%)	1.22	.32	.82 to 1.81	31 (23.1%)	66 (19.7%)	1.17	.41	.80 to 1.70
No (79.2%)	82 (75.9%)	289 (80.2%)				103 (76.8%)	268 (80.3%)			

[a]HKD at baseline regardless of comorbidity = internalizing comorbidity filter not applied; no exclusion for depression or anxiety

[b]Adult symptom severity = symptom rating on CAARS by parent or self (more severe of the two) at last adult assessment age 21–26

[c]Symptom count using item-level 'OR' rule on self- and observer-reported CAARS = symptom was counted as present if endorsed at the level 2 or 3 on the 0–3 scale by either self or other observer, usually parent

Table 3 Comparison of adult ADHD in participants with HKD plus comorbid anxiety/depression versus HKD plus ODD/CD

ADHD at follow-up	HKD with anxiety or depression $n=26$ mean (SD)	HKD with ODD or CD $n=52$ mean (SD)	d	p	CI
ADHD symptom severity[a]	1.10 (.48)	1.02 (.45)	.17	.52	− .29 to .15
	n (%)	n (%)	RR	p	CI
Using item-level 'OR' rule on self- and observer-reported CAARS[b]					
DSM-5 + impairment					
Yes (38.1%)	14 (58.3%)	15 (28.8%)	.49	.01	.28 to .85
No (61.8%)	10 (41.6%)	37 (71.1%)			
DSM-4 + impairment					
Yes (30.2%)	12 (50.0%)	11 (21.1%)	.42	.01	.21 to .81
No (69.7%)	12 (50.0%)	41 (78.8%)			
DISC-YA diagnosis of ADHD					
Yes (26.9%)	5 (19.2%)	16 (30.7%)	.62	.27	.25 to 1.51
No (73.1%)	21 (80.7%)	36 (69.2%)			

[a]Observer and self-rated CAARS from 12-, 14-, and 16-year follow-ups

[b]Ratings from both sources needed to be present

Table 4 Adult ADHD in participants with or without baseline comorbid anxiety/depression in expanded HKD and non-HKD groups

Follow-up ADHD Dx (criteria used)	HKD at baseline (ICD-10 Dx), $n=135$					No ICD-10 HKD at baseline, $n=341$				
	With anxiety or depression $n=26$	Without anxiety or depression $n=109$	d	p	CI	With anxiety or depression $n=95$	Without anxiety or depression $n=246$	d	p	CI
	mean (SD)	mean (SD)				mean (SD)	mean (SD)			
ADHD Sx severity[a]	1.10 (.48)	.97 (.45)	.27	.22	−.07 to .32	1.04 (.41)	.92 (.46)	.27	.033	.01 to .22
	n (%)	n (%)	RR	p	CI	n (%)	n (%)	RR	p	CI
Using item-level 'OR' rule on self- and observer-reported CAARS[b]										
DSM-5 + impairment										
Yes (35.9%)	14 (58.3%)	32 (30.8%)	1.89	.011	1.21 to 2.95	Yes (35.7%) 42 (45.1%)	69 (29.6%)	1.52	.005	1.13 to 2.05
No (64.1%)	10 (41.6%)	72 (69.2%)				No (64.2%) 51 (54.8%)	164 (70.3%)			
DSM-4 + impairment										
Yes (27.3%)	12 (50.0%)	23 (22.1%)	2.26	.006	1.31 to 3.87	Yes (30.0%) 38 (40.8%)	55 (23.6%)	1.73	.001	1.23 to 2.42
No (72.7%)	12 (50.0%)	81 (77.9%)				No (70.0%) 55 (59.1%)	178 (76.3%)			
DISC diagnosis of ADHD										
Yes (23.1S %)	5 (19.2%)	26 (24.1%)	.79	.59	.33 to 1.88	Yes (19.7%) 21 (22.3%)	45 (18.7%)	1.19	.45	.75 to 1.88
No (76.8%)	21 (80.7%)	82 (75.9%)				No (80.2%) 73 (77.7%)	195 (81.2%)			

[a] Observer and self-rated CAARS from 12-, 14-, and 16-year follow-ups

[b] Ratings from both sources needed to be present

to 25 of the 367 (6.8%) without childhood HKD diagnosis. Of the 135 with expanded HKD at baseline, 12 (8.9%) had expanded-definition HKD in adulthood, compared to 26 of 341 (7.8%) without childhood HKD diagnosis.

Discussion

We explored whether ICD-10-defined HKD is a subgroup of DSM-IV ADHD with greater adult symptom and/or impairment persistence. Although this subgroup started with greater severity, their adult severity and persistence were similar to the rest of the MTA sample. It is curious that those with greater severity in childhood did not also have greater severity and persistence in adulthood, in contrast to other literature reporting early severity as predictor of later severity. In exploratory analyses, participants with anxiety or depression (who otherwise would have met HKD criteria, but were excluded by the anxiety/depression filter) showed greater persistence and severity than those diagnosed strictly by HKD criteria, with p values < 0.01 in a few instances. This is reminiscent of Jensen et al's [31] findings in the complete MTA sample at 14 months: those with both internalizing and externalizing comorbidity had worse outcomes and showed the largest relative benefit of combined treatment. It is also compatible with Caye et al's

[32] meta-analysis showing depressive comorbidity was a significant predictor of ADHD persistence. Since anxiety and depression tend to occur together, it is possible that the effect they found for depression was partly driven by anxiety. Most of the baseline internalizing comorbidity in the MTA sample was anxiety (34%, not counting simple phobias) rather than mood disorders (5.4%, including 3.8% major depression, 0.7% hypomania, and 2.6% dysthymia, with overlap). The low rate of baseline depression in the MTA is not surprising given the sample age (7–9 years). In any event, the paradox of strictly diagnosed HKD having greater baseline severity but not greater adult severity is apparently explained by the lack of internalizing comorbidity, which appears extremely important for the persistent severity of ADHD symptoms.

Taken together with the previous report of outcome in the RCT phase of the MTA [10] and the meta-analysis by Caye et al. [32], the findings reported here may be informative for treatment planning and prognostication. These collective findings suggest that the more stringent ICD-10 diagnosis defines a group that has greater severity of symptoms at baseline, and responds better to stimulant medication initially in childhood, but does not show elevated symptoms in adulthood compared to the non-HKD cases that were less severe at baseline. Furthermore, the HKD cases had slightly better symptomatic outcome, even when externalizing

Table 5 Comparison of adult functional outcomes in participants with and without baseline hyperkinetic disorder adjusting for age at follow-up and baseline socioeconomic status

Outcomes at follow-up	HKD at baseline (ICD-10)		OR	p
	Yes n = 109	No n = 367		
	n (%)	n (%)		
Internalizing comorbidity[a]				
0	83 (78.30)	276 (77.96)	.98	.95
≥ 1	23 (21.69)	78 (22.03)		
Externalizing comorbidity[b]				
0	58 (53.21)	190 (52.77)	1.004	.98
≥ 1	51 (46.78)	170 (47.22)		
Car accidents				
0	79 (61.24)	181 (46.41)	1.62	.032
≥ 1	50 (38.75)	209 (53.58)		
Education (obtained bachelor's degree)				
No	57 (52.77)	190 (52.19)	1.07	.75
Yes	51 (47.22)	174 (47.80)		
Receives public assistance				
No	83 (75.45)	275 (75.54)	.93	.79
Yes	27 (24.54)	89 (24.45)		
Justice involvement (any police contact)				
0	97 (89.80)	300 (82.41)	1.94	.06
≥ 1	11 (10.20)	64 (17.58)		
Nicotine dependence				
No	27 (24.77)	85 (23.74)	.90	.70
Yes	82 (75.22)	273 (76.25)		
Alcohol abuse				
No	64 (58.71)	235 (65.27)	.70	.12
Yes	45 (41.28)	125 (34.72)		
Marijuana abuse				
No	74 (67.88)	263 (73.05)	.77	.29
Yes	35 (32.11)	97 (26.94)		
Other substance use				
No	104 (95.41)	344 (95.55)	.89	.83
Yes	5 (4.58)	16 (4.44)		
Current daily smoker				
No	43 (55.84)	133 (51.35)	1.11	.68
Yes	34 (44.15)	126 (48.64)		
Medication use[c]				
Negligible	19 (17.43)	93 (25.34)	2.19[d]	.09
Inconsistent[d]	80 (73.39)	249 (67.84)	1.30[d]	.51
Consistent	10 (9.17)	25 (6.81)		
Adult stimulant use				
No	83 (88.29)	260 (88.13)	.98	.96
Yes	11 (11.70)	35 (11.86)		
	Mean (SD)	Mean (SD)	B	p
Height (in cms)	175.01 (9.02)	175.20 (9.30)	− .36	.74
Mean impairment[e]	1.66 (0.88)	1.80 (0.96)	− .11	.28
Job losses	1.28 (1.68)	1.09 (1.40)	.43	.010
Age at first sexual contact (in years)	16.22 (2.36)	16.22 (2.63)	− .05	.84

Table 5 (continued)

	Mean (SD)	Mean (SD)	B	p
Emotional lability[f]	0.86 (0.47)	0.94 (0.57)	− .12	.005
Neuroticism	1.50 (0.65)	1.44 (0.64)	− .03	.65
Total stimulant medication used per capita (mg/day)	20.30 (21.21)	16.05 (18.95)	3.90	.08

Comorbid group included children with HKD plus anxiety/depression

[a]Any internalizing comorbidity as per DISC-YA reports at 12-, 14- and 16-year follow-ups

[b]Any externalizing comorbidity as per DISC-YA and DISC-P reports at 12-, 14-, and 16-year follow-ups

[c]From baseline to late adolescence

[d]Compared to inconsistent use

[e]Mean self- and parent/observer-reported scores on the Impairment Rating Scales at 12-, 14-, and 16-year follow-ups

[f]Additionally controlled for hyperactive/impulsive symptomatology

(ODD/CD) comorbidity was present, than cases with internalizing comorbidities (anxiety or depression). It may seem counterintuitive, but applying the strict ICD criteria in childhood may exclude those destined to have poorer outcomes (and thus the most in need of treatment). This suggests a possible subcategory of HKD that allows for the specification of internalizing comorbidity analogous to the extant subcategory with externalizing comorbidity.

We found in the whole MTA sample that baseline severity predicted adult symptom persistence [33]. It is thus surprising that the HKD subgroup, with higher baseline severity than the rest of the MTA, did not show greater persistence or severity of ADHD symptoms. This incongruity may be an artifact of the small HKD subsample size, but we did not observe any trend of greater adult severity (Table 1). Perhaps, greater adult severity and persistence require a combination of initial severity and internalizing comorbidity.

Although Caye et al. [32] and Roy et al. [33] report that both internalizing comorbidity and initial symptom severity predict persistence of ADHD, we found only internalizing comorbidity to predict persistence for those with HKD. The initial symptom count/severity may be less important than comorbid anxiety/depression. Those with an internalizing disorder (anxiety or depression) seem to have worse outcomes than those without. It is also possible that some of the comorbid cases had only internalizing disorders and were misdiagnosed as ADHD despite the rigorous diagnostic algorithm used in sample recruitment. Even though MTA entry criteria excluded those with severe depression (i.e., with suicidal ideation or missing over a fourth of school days in the previous 2 months), internalizing comorbidity still showed a significant effect on follow-up outcomes, which might have been more dramatic if those with the most severe depression had been included.

Assessments of adult HKD rates showed that < 6% of children with baseline HKD also met the ICD-10 criteria in adulthood. This is in contrast to the DSM criteria, where about half of all children with a DSM-diagnosed ADHD

continue to have the diagnosis in adulthood [20]. The low rates of adult HKD persistence could be related to the stringent ICD-10 criteria, which require symptoms to be present in all three domains of ADHD. Hyperactive symptoms attenuate with age and ADHD largely persists as inattentive problems. Thus, requiring symptom presence in the hyperactive and impulsive domains may reduce the number of adult cases. It should be mentioned that we could only partly assess the presence of HKD in adulthood as we did not have information on symptom presence in different settings and, therefore, could not apply the pervasiveness filter. However, inclusion of this filter would likely have further reduced, not increased, the number with adult HKD. Interestingly, we also found that 6.8% of participants with no childhood HKD had HKD in adulthood. This seems to confirm HKD as a subgroup of ADHD and shows in another way that childhood HKD does not predict adult outcome any better than non-HKD ADHD.

ICD-11, released this year, does not provide operational criteria anymore as ICD-10 did and abandons the name "hyperkinetic disorder," switching to the DSM name "ADHD." Although the analyses that we conducted will not be possible in the future, our findings are relevant to inform the field on the developmental trajectory of ADHD if more conservative severity criteria are applied to define the disorder and if comorbidities such as anxiety disorder affect the trajectory. Moreover, it justifies and supports the ICD-11 committee's decision to have a prototype definition closer to the ADHD criteria in DSM-5 and to use the name ADHD rather than hyperkinetic disorder (note that the data in the manuscript were shared with the committee in the past).

A limitation of this study is that those with baseline HKD had a higher rate of attrition (almost 25%) than those without a baseline hyperkinetic diagnosis (15.4%). If the most severe cases were lost to follow-up, it would artificially improve the apparent outcome of HKD relative to ADHD without HKD. However, the retained participants with baseline HKD were

Table 6 Comparison of adult functional outcomes in participants with and without expanded hyperkinetic disorder, adjusted for age at follow-up and baseline socioeconomic status[a]

Outcomes at follow-up	HKD/HKCD at baseline (ICD-10)		OR	p
	Yes n = 135	No n = 341		
	n (%)	n (%)		
Internalizing comorbidity[a]				
0	102 (77.3)	257 (78.4)	.95	.84
≥ 1	30 (22.7)	71 (21.6)		
Externalizing comorbidity[a]				
0	68 (50.4)	180 (53.9)	.87	.52
≥ 1	67 (49.6)	154 (46.1)		
Car accidents				
0	96 (61.5)	164 (45.2)	1.78	.006
≥ 1	60 (38.5)	199 (54.8)		
Education (obtained bachelor's degree)				
No	74 (55.2)	173 (51.2)	1.28	.38
Yes	60 (44.7)	165 (48.8)		
Receives public assistance				
No	102 (75.0)	256 (75.7)	.95	.84
Yes	34 (25.0)	82 (24.3)		
Justice involvement (any police contact)				
0	118 (88.1)	279 (82.5)	1.55	.15
≥ 1	16 (11.9)	59 (17.5)		
Nicotine dependence				
No	99 (73.3)	256 (77.1)	.82	.41
Yes	36 (26.7)	76 (22.9)		
Alcohol abuse				
No	79 (58.5)	220 (65.9)	.68	.07
Yes	56 (41.5)	114 (34.1)		
Marijuana abuse				
No	92 (68.1)	245 (73.4)	.80	.33
Yes	43 (31.9)	89 (26.6)		
Other substance use				
No	128 (94.8)	320 (95.8)	.87	.92
Yes	7 (5.2)	14 (4.2)		
Current daily smoker				
No	57 (57.6)	119 (50.2)	1.22	.41
Yes	42 (42.4)	118 (49.8)		
Medication use				
Negligible	29 (21.5)	83 (24.3)	1.87[i]	.14
Inconsistent	93 (68.9)	236 (69.2)	1.63[i]	.20
Consistent	13 (9.6)	22 (6.5)		
	Mean (SD)	Mean (SD)	B	p
Height (in cms)	175.24 (8.75)	175.12 (9.43)	− .01	.99
Mean impairment	1.71 (.89)	1.79 (.97)	− .08	.39
Job losses	1.19 (1.60)	1.11 (1.43)	.26	.09
Age at first sexual contact (in years)	16.19 (2.41)	16.24 (2.63)	− .07	.79
Emotional lability	.89 (.49)	.93 (.57)	− .12	.003
Neuroticism	1.44 (.62)	1.50 (.66)	− .04	.54
Total stimulant medication used	19.30 (20.63)	16.10 (19.04)	2.84	.17

[a]Additionally controlled for hyperactive/impulsive symptomatology

not significantly different sociodemographically from those lost to follow-up (Supplementary Table 3).

To conclude, despite greater initial severity and pervasiveness, those with an ICD-10 HKD at baseline had no worse young adult outcome than those who did not meet criteria for HKD. Internalizing comorbidity seems more important for persistence of ADHD symptoms, and this comorbid subgroup should be recognized in screening/diagnosis as most in need of treatment.

Compliance with ethical standards

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