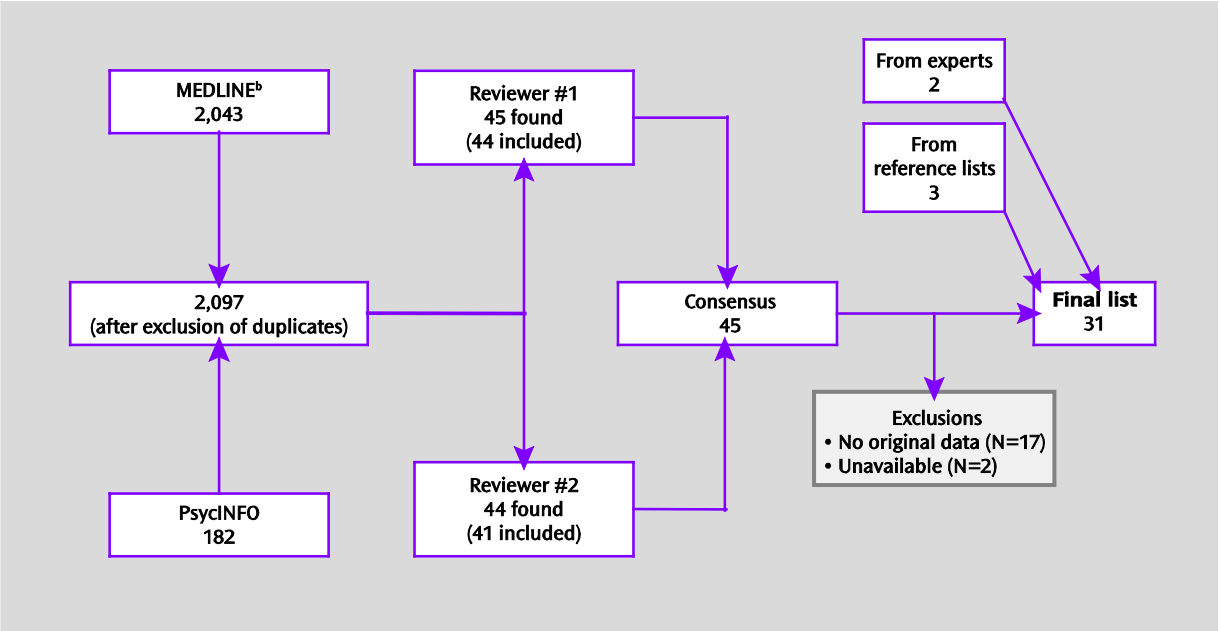
FIGURE S1. Search Strategy for Identifying Studies on the Age at Onset of Attention Deficit Hyperactivity Disorder (ADHD)[a]



[a]No time or language limits were imposed. The search string used was "(ADHD OR ADD OR attention-deficit* OR hyperactiv* OR overactiv* OR innatent* OR hyperkinetic disorder OR minimal brain dysfunction) AND (age at onset* OR age of onset* OR age factors*)."

[b]MEDLINE exhibited a significant number of references outside the mental health field (e.g., overactive bladder).

TABLE S1. Studies Reporting Original Data on the Age at Onset of Attention Deficit Hyperactivity Disorder (ADHD)

STUDY	OBJECTIVES	SOURCE	ONSET VARIABLE	CRITERIA	GROUPS	RESULTS	COMMENTS
Angold 1996	To investigate children's and parents' abilities to report the date of onset of symptoms	• Child or parent	• Age at onset of symptoms (AOS)	• DSM-III-R	• 103 children and adolescents (referred outpatients) age 8 to 16 and their parents	• ADHD AOS least precisely reported in comparison to onset of other symptoms	• Low precision of retrospective reports regarding AOS • Measurement only of precision as rated by interviewer, not actual AOS
Applegate 1997	To examine the validity of the DSM-IV criterion B in the field trials sample	• Parent or teacher for symptoms • Parent for onset (asked for impairment only in the presence of 5 or more symptoms)	• Age at onset of symptoms (AOS) • Age at onset of impairment (AOI)	• DSM-IV	• 251 children and adolescents age 4 to 17 who met symptom criteria for any ADHD subtype: combined (C), hyperactive (HY), or inattentive (IA)	• Median AOS 1 year, median AOI 3.5 years • First symptom before age 7: C 96%, HY 100%, IA 85% • Impairment before age 7: C 82%, HY 98%, IA 57% • In subgroup 7 or older, many did not meet ADHD criterion B: C 24%, IA 50% • Clinicians validated 75% of cases with symptom criteria but without criterion B	• AOS and AOI both early • Different AOS and AOI according to subtype (IA with later onset) • Adoption of AOI increased false negatives for comparison with clinical validation diagnoses
Barkley 1990	To prospectively follow-up the adolescent outcome of hyperactive children	• Parent	• Age at onset of symptoms (AOS)	• Diagnosis by research criteria (including problems before age 6) • Symptoms and onset by DSM-III-R	Children age 4-12 • 123 "hyperactive" • 66 controls	• AOS parental report: 3.7 years	• Early onset of ADHD in sample of children • Presence of "behavioral problems" before age 6 was inclusion criterion

Barkley 2006	To examine behavioral and neuropsychological correlates of three candidate genes in hyperactive and normal children followed to adulthood	• Parent	• Age at onset of symptoms (AOS)	• Diagnosis by research criteria (including problems before age 6) • Symptoms and onset by DSM-III-R	Adolescents in follow-up • 80 "hyperactive" • 52 controls	• In adolescence, DAT1 9/10 genotype was associated with later AOS among hyperactive group and controls (d=0.54)	• Evidence for genetic underpinnings of age-related ADHD symptom emergence irrespective of diagnosis • AOS was not primary outcome
Barkley 2008, U-Mass. study	To determine the necessity or diagnostic utility of specifying an age at onset of symptoms producing impairment by 7 years	• Patient	• Age at onset of symptoms (AOS) • Age at onset of impairment (AOI)	• DSM-IV	• 146 ADHD adults with onset before age 21 • 97 clinic-referred non-ADHD control group	• ADHD group had earlier AOS than clinical control group: age 7.3 (unimodal peak) versus 12.1 (bimodal) • Earlier onset of impairment at home and school (but not social, community, occupational, or marriage) in ADHD • Onset before age 7 for 53% of ADHD and 29% of control groups; 98% and 78% had onset before age 14 • Comparison of early onset (EO) and late onset revealed one more symptom as adult and two as child for EO, but no other differences in psychopathology or impairment	• Symptoms start earlier in ADHD patients than in those with other psychiatric diagnoses • Criterion B would leave a substantial proportion of patients without diagnosis; the 14-year cutoff would include almost all subjects with high symptom levels • Some evidence for increased severity in EO group • Some information previously published, remaining not peer-reviewed
Barkley 2008, Milwaukee study	To determine the necessity or diagnostic utility of specifying an age at onset of symptoms producing impairment by 7 years	• Parent and patient	• Age at onset of symptoms (AOS) • Age at onset of impairment (AOI)	• Diagnosis by research criteria (including problems before age 6)	• "Hyperactive" adults, diagnosed as having been hyperactive in childhood (baseline N=158) • Matched community control group (baseline N=81)	• Baseline AOS: 34 years • Teen follow-up: AOS 3.8 years • Age 27 follow-up: AOS 8 years, with 96% before age 14 and 55% before age 7 among current ADHD group • No differences in AOS or AOI regarding adult ADHD status	• Low precision of reports: even among children diagnosed at age 6, 45% would not endorse age-at-onset criterion at age 27 • Some information previously published, remaining not peer-reviewed

Biederman, 2006	To conduct an open label trial of osmotically released methylphenidate in adults with late-onset ADHD	• Patient	• Age at onset of impairment (AOI) • Late onset (LO): no criterion B	• DSM-IV	• 36 adults age 19-60 with LO ADHD	• Osmotically released methylphenidate at doses up to 1.3 mg/kg/day produced significant improvement in ADHD symptoms	• Evidence for treatment response among LO adults • Small sample, open trial
Cuffe 2001	To study the prevalence of ADHD in a community sample	• Adolescent and parent or spouse	• N.A.	• DSM-III-R	• 490 adolescents in a second wave, mean age 18.65	• ADHD prevalence with age-at-onset criterion (AOC): 1.5% (males 2.6%, females 0.5%) • ADHD prevalence with 8 or more symptoms but no AOC: 1.9% (males 0.3%, females 3.2%)	• Inclusion of individuals with high number of symptoms but no AOC would substantially increase ADHD prevalence
Faraone 1998	To assess the validity of DSM-IV subtypes of ADHD	• Mother	• Age at onset of symptoms (AOS)	• DSM-III-R and DSM-IV	Children and adolescents consecutively referred to pediatric psychopharmacology clinic • Combined (N=182) • Hyperactive (N=28) • Inattentive (N=92) • Controls (N=135)	• Inattentive group had later AOS than combined type	• Evidence for different onset among different subtypes

Faraone 2006a	To assess validity of late onset and subthreshold ADHD by using neuropsychological test scores as external validators	• Best estimate	Age at onset defined as first emergence of impairing symptoms • Full ADHD (FULL): before age 7 • Late onset (LO): at or after age 7 • Subthreshold (ST): at least 3 chronic ADHD symptoms but no ADHD diagnosis	• DSM-IV	Adults • FULL (N=127) • LO (N=79) • ST (N=41) • No ADHD (N=123)	• LO and FULL had similar patterns of neuropsychological dysfunction • ST showed fewer neuropsychological differences than group with no ADHD	• LO resembles full ADHD in neuropsychological performance • Same sample used in other studies
Faraone 2006b	To assess validity of late onset and subthreshold ADHD comparing four groups of adults					• LO and FULL had similar patterns of comorbidity, impairment, and familial transmission • Most of LO group (83%) had onset before age 12 • ST was milder and showed a different pattern of familial transmission	• LO resembles full ADHD in psychopathology and familiar transmission • Same sample used in other studies
Faraone 2007	To assess validity of late onset and subthreshold ADHD through evaluation of substance use and its complications					• LO and FULL more likely to have problems with cigarettes, alcohol, marijuana and more trouble resisting drug use	• LO resembles FULL in substance use patterns • Same sample used in other studies

Faraone 2009	To assess validity of late onset and subthreshold ADHD by using personality traits as validation criterion					• LO and FULL showed similar personality profiles, with deviations in score on 5 of 7 scales of Temperament and Character Inventory (TCI) • ST cases showed deviations in only two TCI scales	• LO resembles full ADHD in personality profile • Same sample used in other studies
Green 1991	To assess the stability of parent recall of age at onset of ADHD behaviors	• Mother	• Age at onset of symptoms (AOS)	• DSM-III and DSM-III-R	177 boys referred for disruptive behaviors, age 7-12 at baseline and followed 1 year later	• Mean AOS for year 1 (5.8 years) was not different from year 2 (5.9 years) • Stability of diagnosis was much lower than stability of AOS	• Impact of AOS variability on diagnosis can be more important than on AOS means • Short follow-up period
Hesslinger 2003	To compare early- versus late-onset ADHD patients in a retrospective study	• Patient	• Early onset (EO): Wender Utah Rating Scale (WURS) score 36 or higher at age 6-10 • Late onset (LO): WURS score 36 or higher after age 10	• DSM-IV	50 ADHD patients, mean age 35.3 • EO (N=36) • LO (N=14)	• Severity differences between groups were seen only before age 15 • No other difference between groups in terms of psychopathology or psychiatric comorbidity	• No difference between EO and LO in adulthood
Karam 2009	To investigate characteristics of adult, late-onset ADHD	• Patient	• Early onset (EO): impairment before age 7 • Late onset (LO): impairment at age 7-12	• DSM-IV	349 referred adults • EO (N=174) • LO (N=175)	• LO adults were diagnosed later and had fewer problems with authority/discipline, lower scores on Barkley's scale for problems in life activities, more comorbid generalized anxiety disorder (GAD), lower SNAP-IV scores • Similar in other characteristics	• Although milder than EO, LO was associated with measures of dysfunction • More comorbid GAD in the LO group • Referred sample

Kessler 2005	To estimate lifetime prevalence and age at onset of DSM-IV diagnoses in the National Comorbidity Survey Replication	• Subject	• Age at onset of syndrome (AO)	• DSM-IV	• 9,282 respondents age 18 or older	• ADHD prevalence 8.1% • AO percentile 50: 7 years • AO percentile 99: 16 years	• In large sample, 7-year cutoff would exclude 50% of subjects; 16-year cutoff would include nearly all cases
Kuperman 2001	To describe the relationship between disruptive behavior and substance use	• Child and parent	• Age at onset of symptoms	• DSM-III-R	• 54 adolescents with alcohol dependence	• ADHD typically occurred before other diagnoses (no age provided)	• Disruptive behavior precedes substance-related problems
Lasky-Su 2007	To test the association between candidate genes and age at onset	• Mother	• Age at presence of two symptoms (AOS)	• DSM-III-R for one subgroup and DSM-IV for another	• 229 families with at least one affected offspring	• Seven consecutive single nucleotide polymorphisms surrounding DRD5 gene were associated with AOS • No associations with SLC6A3, HTR1B, SNAP25, DRD4	• Evidence for genetic underpinnings of age-related symptom development • Adopted presence of two symptoms as basis for age at onset
Loeber 1992	To describe developmental sequences in the age at onset of disruptive behaviors	• Parents	• Age at onset of problematic behavior	• DSM-III and DSM-III-R	• 177 boys age 7-12 referred to three university clinics	• Descriptive presentation of age at onset for externalizing behaviors • Most ADHD behaviors started before age 6 for boys age 7-9 but after age 6 for boys age 10-12	• ADHD symptoms emerged over long period • Median age at onset was markedly higher for older boys than for younger boys
McGee 1992	To examine the impact of age at onset on problem behavior	• Parent	• Age at onset of problem behaviors (AO)	• DSM-III	• 12 boys AO 3 years • 13 boys AO 5-6 years • 15 boys AO 7 years • 369 non-ADHD boys	• By age 15, those with onset at or before age 6 differed in problem behavior scores from non-ADHD boys, which was not the case for those with AO at 7 years	• Possibly decreased severity for individuals with later onset • Small ADHD sample
Neuman 2005	To estimate the prevalence of DSM-IV and latent class subtypes in a twin population	• Parent	• Age at onset (AO) of DSM problems or subtypes and severe latent classes	• Latent classes and DSM-IV	• 213 twins with DSM-IV ADHD	• AO for DSM problems was 3.5 years • AO for DSM subtypes did not differ overall or by sex • AO for severe latent classes was later and differed among themselves for males	• Early onset and no difference among DSM subtypes • Later, but still preschool, onset for severe latent classes cases • Twin sample

Reinhardt 2007	To compare response to methylphenidate in patients with full ADHD and those without age-at-onset criterion	• Children and adolescents: parent • Adults: patient	• Early onset (EO): impairment before age 7 • Late onset (LO): impairment at age 7 or later	• DSM-IV	180 children and adolescents • EO (N=145) • LO (N=35) 123 adults • EO (N=54) • LO (N=57)	• In both samples, EO did not respond better than LO • In adults, LO was associated with better response	• Children, adolescents, and adults: similar responses to methylphenidate in EO and LO (adult LO even better) • Naturalistic design
Rohde 2000	To explore the age-at-onset criterion (AOC) in a school sample of young Brazilian adolescents	• Adolescent and parents	• Early onset (EO): impairment before age 7 • Late onset (LO): impairment at age 7 or later	• DSM-IV	191 students age 12-14 • EO (N=30) • LO (N=27) • Non-ADHD adolescents (N=134)	• Both ADHD groups had higher Child Behavior Checklist scores and lower Child Global Assessment Scale score than non-ADHD group • ADHD groups did not differ significantly in any measure	• Adolescents with and without AOC exhibited similar clinical characteristics • Small ADHD groups
Rucklidge 2002	To examine clinical significance of age at onset by comparing cognitive functioning	• Adolescent and parents	• N.A.	• DSM-IV	Adolescents age 13-16 • 6 adolescent-onset ADHD • 6 childhood-onset, persisting ADHD • 6 ADHD in remission • 6 non-ADHD	• All three clinical groups differed from controls • Remission group did not differ from childhood-onset group • Childhood-onset worse than adolescent-onset ADHD	• Remission group, and not adolescent-onset group, similar to full ADHD group • Small groups, limited statistical analyses
Sullivan 1990	To assess mothers' perceptions of age at onset of childhood disorders	• Parent	• Age at onset of first symptom, problem, and referral	• DSM-III-R	• 96 boys, mean age 9.1; ADHD N=16 • 24 girls, mean age 9.3; ADHD N=1	Boys • First symptom at age 3.6 years • Parent sure of problem at age 6.5 • First referral at age 6.3	• Early onset of ADHD symptoms • young sample
Tillman 2003	To study rates and ages at onset of bipolar comorbid diagnoses	• Parent and child	• Age at onset of syndrome (AO)	• DSM-IV	• 93 pediatric bipolar patients, mean age 10.9; 87% with comorbid ADHD • 81 ADHD patients, mean age 9.7	• Mean ADHD AO 4.8 in bipolar group	• Onset of ADHD before mania

Todd 2008	To assess if criterion B complicates identification of cases later in life	• Parent and self	• Age at onset of symptoms (AOS) • Age at onset of impairment (AOI)	• DSM-IV	• Birth records cohort of twins age 7-19 (N=620)	• Later AOS and AOI reported at second wave • 46% (N=13) of ADHD cases persisting with 6 or more symptoms at second wave lacked criterion B	• Poor stability of reports 5 years later • Use of criterion B results in underidentification of affected individuals • Twin sample
Waschbusch 2007	To examine age at onset of ADHD symptoms in a sample of elementary school students	• Parent questionnaire (oldest age reported by mother or father)	• Age at onset of symptoms (AOS)	• DSM-IV	835 children age 5-12 • Full ADHD (N=63) • ADHD minus age-at-onset criterion (AOC) (N=14) • Control children	• Hyperactive symptoms appeared before inattentive symptoms within combined type • ADHD with and without AOC did not differ in number of symptoms or impairment • Both ADHD groups differed from controls	• Onset varied according to symptom dimension • AOS not related to severity of disorder • Included only children; reduced number of eligible included
Willoughby 2000	To assess implications of the age at onset of ADHD symptoms	• Parent	• Early onset (EO): symptoms before age 7 • Late onset (LO): symptoms at age 7 or later	• DSM-IV	1,419 children from Great Smoky Mountain Study, age 9-16 • EO (N=85) • LO (N=17)	• EO was associated with worse clinical outcomes in combined group but not in inattentive subtype • Regardless of age at symptom onset, a higher number of symptoms was associated with negative outcomes	• Supported inclusion of criterion B only for combined subtype, not for inattentive • Used only 15 of 17 DSM symptoms
Wisniewski 2007	To investigate the developmental sequence of delinquency, academic underachievement, and ADHD	• Parent and teacher	• N.A.	• DSM-based score	• Longitudinal sample of 503 boys (211 with ADHD)	• Analysis of median age at onset uncovered pathway: ADHD $\rightarrow$ academic underachievement $\rightarrow$ delinquency • median ADHD age at onset 9 years	• Average onset at 9 years in large ADHD sample • Study designed for other purposes
Yang 2004	To describe ADHD subtypes in a Chinese outpatient sample	• Parent	• N.A.	• DSM-IV	308 children (85.4% boys) • Combined (N=130) • Inattentive (N=159) • Hyperactive (N=19)	• Inattentive group was older and had a higher age at onset (AO) than hyperactive and combined groups	• Differences in AO among subtypes • Descriptive data only

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