Comorbidity in Adult Attention-Deficit Hyperactivity Disorder

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Abstract
In cross-sectional studies, attention-deficit hyperactivity disorder (ADHD) in adults has been linked to the presence of several other psychiatric disorders. This diagnostic comorbidity is consistently found for antisocial personality disorder and also substance use disorders. There is great divergence in reports of comorbid anxiety and mood disorders. Quality of designs varies widely, limiting interpretation of conflicting results. Evidence suggests that men and women with ADHD present with similar patterns of comorbidity, regardless of whether they are referred or non-referred individuals. Prospective follow-up studies of children with ADHD into adulthood have generated similar findings of comorbidity: elevated rates of antisocial personality and substance use disorders, and divergent findings with regard to comorbidity of anxiety and mood disorders. There is very limited information about differences in comorbidity between children whose ADHD persists into adulthood and those in whom it remits (prognostic comorbidity). The sparse evidence from prospective longitudinal studies suggests that antisocial personality is predicted by the retention of ADHD into adulthood. Except for nicotine dependence, no other condition has emerged as a significant correlate of persistent ADHD.

In its broadest concept, comorbidity has been defined as ‘any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study’ [1]. This definition includes disorders that are antecedent to, and those that are concurrent with, a specific condition. This broad definition has been refined further by Kaplan and Feinstein [2] in their discussion of comorbidity in internal medicine. They describe prognostic comorbidity as the risk conferred by one disease for another disease. In the population, the relationship between the index and ‘comorbid’ condition is not a random phenomenon. However, in referring to an individual, the term comorbidity is also used to denote the co-occurrence of disorders, whether or not their joint presence exceeds chance expectation in the population. In general medicine, comorbidity refers to the presence of conditions that represent discrete diseases. Even if they are causally related, the two
diseases have distinct pathophysiology, and often require different interventions (as in the example of diabetes and renal disease). The concept of comorbidity has been important in medicine since it has major implications for understanding mechanisms of pathophysiology, for clinical care, and for prevention. However, ambiguities emerge when applying this framework to psychiatric disorders. As noted by Fyer et al. [3], internal medicine provides many instances of different pathologies leading to similar clinical syndromes, e.g. diabetes, but the identification of distinct pathologies enables their differentiation. In contrast, psychiatric disorders are defined by their clinical presentation. Problematically, psychiatric disorders are polythetic. They not only share diagnostic features, but almost never possess uniquely pathognomonic symptoms. In the absence of pathophysiologic data, symptomatic definitions lead to a situation in which similar syndromal presentations have diverse underlying pathology. The heterogeneity inherent in psychiatric disorders may lead to findings of comorbidity that do not apply across the entire clinical population, and may result in ‘pseudocomorbidity’ [4]. Unfortunately, there are no means of identifying phenocopies (syndromes that look alike but have distinct etiologies, be they genetic, environmental, or otherwise influenced). This diagnostic imprecision likely leads to misleading inferences about comorbidity.

Comorbidity in psychiatry is highly prevalent, and has received a great deal of attention, due to its importance for clinical management and research. Knowledge that disorders often co-occur, either concurrently or sequentially, will shape diagnostic and therapeutic practice. For example, if we know that individuals with substance use disorders (SUDs) are relatively more likely to have or have had attention-deficit/hyperactivity disorder (ADHD), inquiry for ADHD will become routine in the assessment of patients with substance disorders, and treatment plans will consider addressing both conditions. As an example, a population study found that adults with ADHD had high rates of comorbid disorders (described below) and that, among the treated individuals, treatment had mostly been for another disorder rather than ADHD.

Research-wise, knowledge of comorbidity justifies efforts to identify common risk factors, causes, and fosters improved diagnostic classification by making distinctions within a disorder when it is comorbid and when it is not. For example, if SUD that is comorbid with ADHD differs from non-comorbid SUD with regard to risk factors, prognosis, treatment response, brain function, the nomenclature might be altered to reflect such distinctions. However, in order for reports of comorbidity to generate meaningful and fruitful findings, its magnitude must exceed chance co-occurrence. If it does not, much effort will be wasted in the investigation of its significance.

**Diagnostic and Methodological Issues**

The influence of symptomatic overlap across disorders has been discussed by many as a potential confounder in the study of psychiatric comorbidity in general, but it may
be especially salient in ADHD. The cardinal symptoms of ADHD, restlessness, inattention and impulsivity, are highly non-specific, and occur in numerous conditions, even if they are not they are not defining clinical criteria. As a result, disorders may be comorbid due to lack of symptomatic specificity across various diagnoses. With regard to ADHD, problems of symptomatic overlap appear likely for depression and bipolar disorder since they explicitly include similar features, such as poor concentration, restlessness and, in the case of bipolar disorder, impulsivity. That symptom overlap is a significant issue is illustrated by a study by Millberger et al. [5], in which 53% of children with comorbid ADHD and bipolar disorder ceased to meet criteria for bipolar disorder when symptoms common to mania and ADHD were removed. Another diagnostic limitation is that, in the DSM [6], diverse symptomatic expressions of a dysfunction are encompassed by a single label. A case in point might be poor concentration. It is probable that the symptom has different clinical features when it occurs in the context of ADHD versus depression, but no information is given on this point, and clinicians are not alerted to distinguish among various forms of inattention. The same applies to other symptoms. This lack of clinical refinement is likely to influence estimates of comorbidity.

Another related methodological issue is the use of non-clinicians to determine psychiatric diagnoses. Individuals without clinical experience and training cannot make symptomatic distinctions, especially since clinical decisions rely on verbal questionnaires. This approach to diagnosis is also likely to inflate comorbidity since the presence of symptoms depends exclusively on the positive endorsement of fixed questions that may be interpreted differently by various people. This dilemma is illustrated by findings of very high rates of anxiety disorders in children with ADHD diagnosed via a structured interview by non-clinicians [7].

In sum, the nature of classification in psychiatry poses major dilemmas in establishing whether disorders represent distinct conditions, thereby complicating true identification of comorbidity. In addition, diagnostic approaches commonly utilized, such as the reliance on lay interviewers, likely lead to overestimates of comorbidity. At the same time, the potential contribution of comorbidity to our understanding of psychopathology is so diverse and potentially informative that it remains a major interest.

In this review, whose focus is on adult ADHD, we report on the broad concept of diagnostic comorbidity, i.e., the co-occurrence of adult ADHD with other diagnoses, and on prognostic comorbidity of childhood ADHD to adult psychopathology.

**Study Designs and Estimates of Comorbidity**

Besides diagnostic issues, differences in study designs also influence and possibly confound estimates of comorbidity. A number of studies have conducted cross-sectional evaluations of self-referred adults, often in adult ADHD clinics, to estimate
prevalence of comorbid disorders. Others have assessed ADHD in adults with other psychiatric disorders (alcoholism, cocaine abuse, major depressive disorder, etc.). In these instances, the establishment of childhood ADHD relies on retrospective recall. It is generally acknowledged that children with ADHD are very poor observers and reporters of their difficulties, and that the diagnosis must rely on informants, typically parents and teachers. Can we expect children with ADHD to become accurate about early history some 20 years later? It is possible that, with age, people develop more objective appreciation of their childhood ADHD symptoms than they had at the time. In a systematic prospective study of recall of childhood ADHD, we found that 78% of 176 adults with confirmed ADHD in childhood, reported childhood symptoms of inattention, hyperactivity and/or impulsivity that qualified for a diagnosis of ADHD in childhood (most had been treated for extended periods, which should have enhanced correct recollection); in turn, 11% of 168 normal comparisons erroneously recalled childhood ADHD [8]. These findings of 0.78 sensitivity and 0.89 specificity appear encouraging. However, sensitivity varies as a function of base rate [9], consequently, the 0.78 sensitivity does not reflect the accuracy to be expected when the base rate of ADHD is low, as is the case in the general population. By applying a sensitivity rate of 0.78 to an adult population in which 5% truly had childhood ADHD, only 27% of those who report childhood ADHD will be accurately identified (positive predictive value). However, 99% of those judged not to have had ADHD would be correctly classified (negative predictive value) [8]. Thus, in a situation where ADHD is infrequent, the great majority of individuals who indicate that they had ADHD in childhood will be wrong. In contrast, accuracy will be much better in cases who do not indicate childhood ADHD.

Because of inherent limitations in retrospective recall, prospective longitudinal studies of children with established ADHD are much preferable. However, prospective studies also pose their own methodological problems. It is virtually impossible for longitudinal studies to gather information from all individuals in the entire original groups. Therefore, selective attrition becomes a major concern since the partial sample successfully followed may differ from the original cohort in ways that affect estimates of comorbidity. Some have found that missing cases had better outcomes [10], others have reported the opposite [11] and yet others find significant differences in childhood between retrieved and missing ADHD subjects [12].

Also limiting features of longitudinal studies may be the failure to have collected informative predictors in childhood, and changes in the diagnostic definition of ADHD over time. These complicate the relevance of prospective studies that span several decades. At the same time, provided that the early information was systematically obtained and comprehensive (e.g., multiple informants and ratings, psychiatric evaluations, etc.), the onset of the disorder in childhood is assured. Another hindrance to meaningful long-term studies is the need for appropriate controls identified at the time the ADHD children were identified. The full complement of optimal design features is scarce in longitudinal studies of children with ADHD into adulthood.
Concurrent Comorbidity

The current nomenclature includes three types of ADHD, combined, predominantly inattentive, and predominantly hyperactive-impulsive types. This convention enhances further the heterogeneity and polythetic nature of ADHD. Our goal is to address comorbidity in ADHD, combined type. Most major studies have restricted their sample to this ADHD type. An exception is the Boston group that reports on the course of combined and predominantly inattentive types, without distinction.

The evidence on comorbidity in adult ADHD stems from cross-sectional clinical studies, and prospective studies that have followed children with ADHD into adulthood. As shown in table 1, these differ in multiple ways such as retrieval rate, blindness, etc. [10, 12–17]. Despite these differences, certain findings regarding mental status have been consistent. For one, all longitudinal studies have found that ADHD persisted into adulthood in a significant proportion of ADHD children. However, the magnitude of estimates of that proportion has varied widely (7% of probands reporting the full or partial syndrome at follow-up in the New York Study [16, 17] to 58% in the Boston study [12]). Possible reasons for these discrepancies are discussed elsewhere [18]. In addition, all prospective studies have shown that children with ADHD, compared to children without the disorder, have elevated rates of antisocial personality disorder (APD) in adulthood [10, 12–17], and three of the five studies report increased risk for SUD (described below) (table 1). Findings for other conditions are inconsistent. In each section, we present clinical reports of adults with ADHD first, followed by prospective longitudinal studies of children/adolescents with ADHD into adulthood.

Antisocial Personality Disorder

As shown in table 2, Downey et al. [19] and Torgersen et al. [20] have reported rates of 13 and 44% of APD in adults with ADHD, respectively. Since these investigations did not include a comparison group of non-ADHD adults, the specific relationship between ADHD and APD is obscure. The great dissimilarity in prevalence of APD between the two studies raises questions about methodological differences in establishing diagnoses, including the equivalence of the ADHD samples. Schubiner et al. [21], who evaluated randomly selected adult inpatients from two substance abuse treatment facilities, found that those with ADHD, compared to those without ADHD, had significantly higher rates of APD (69 vs. 29%, p < 0.001). This finding suggests that, among substance abusers, APD is also related to adult ADHD. In contrast, Murphy et al. [22] failed to find elevated rates of APD among adults attending ADHD clinics relative to adults without ADHD in the community (4 and 0%, respectively). In our prospective study of boys with ADHD (ages 6–12; mean age 8 years) followed into adulthood (mean age 25 years), 17 of 176 (10%) retained ADHD to at least age 18. As indicated in table 1, rates of APD among the 17 adults with ADHD were strikingly more prevalent than among the 168 non-ADHD comparisons (47 vs. 3%, p < 0.001) [23].
Table 1. Prospective, controlled studies of the course and outcome of children with ADHD followed into adulthood

<table>
<thead>
<tr>
<th>Principal investigators</th>
<th>Location of study</th>
<th>Initial sample</th>
<th>n at FU</th>
<th>% child-</th>
<th>Age at FU</th>
<th>FU interviewer</th>
<th>Person interviewed</th>
<th>Major outcome findings of adult mental status (ADHD refers to ongoing, at FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barkley and Fischer(^a)</td>
<td>Milwaukee (USA)</td>
<td>Clinic</td>
<td>147</td>
<td>93</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>1) P&gt;C- ADHD, APD, MDD, PAPD, HPD, BPD</td>
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<td>2) P=C- Alc, SUD, AD</td>
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<td>Biederman(^b)</td>
<td>Boston (USA)</td>
<td>Clinic</td>
<td>112</td>
<td>80</td>
<td>22</td>
<td>No</td>
<td>Yes</td>
<td>1) P&gt;C- ADHD</td>
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<td>2) P&gt;C (1-year rates)- APD, SUD</td>
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<td>3) P&gt;C (lifetime)- APD, Alc, SUD, MDD, BD, AD, etc.</td>
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<td>Rasmussen and Gillberg(^c)</td>
<td>Gothenburg (Sweden)</td>
<td>Community</td>
<td>55</td>
<td>90</td>
<td>22</td>
<td>Yes</td>
<td>Yes</td>
<td>1) P&gt;C- ADHD, APD, Alc</td>
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<td>2) P=C- SUD, MDD, BD, AD</td>
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<tr>
<td>Weiss and Hechtman(^d)</td>
<td>Montreal (Canada)</td>
<td>Clinic</td>
<td>61</td>
<td>59</td>
<td>25</td>
<td>Yes</td>
<td>No</td>
<td>1) P&gt;C- ADHD symptoms, APD</td>
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<td>2) P=C- Alc, SUD, MDD, BD, AD</td>
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<tr>
<td>Mannuzza and Klein(^e)</td>
<td>New York (USA)</td>
<td>Clinic</td>
<td>176</td>
<td>85</td>
<td>25</td>
<td>Yes</td>
<td>Yes</td>
<td>1) P&gt;C- ADHD, APD, SUD</td>
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<td>2) P=C- MDD, BD, AD</td>
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<tr>
<td>Klein and Mannuzza(^f)</td>
<td>New York (USA)</td>
<td>Clinic</td>
<td>17</td>
<td>(P_{168})</td>
<td>25</td>
<td>Yes</td>
<td>Yes</td>
<td>Probands with adult ADHD (P_{168}) vs. controls (C)-</td>
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<td>APD: 47 vs. 3%, (p &lt; 0.001)</td>
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<td>Alc: 29 vs. 29%, ns</td>
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<td>SUD: 53 vs. 29%, (p &lt; 0.04)</td>
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<td>Mood dis.: 35 vs. 24%, ns</td>
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<td>MDD: 29 vs. 24%, ns</td>
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<td>BD: 0 vs. 0%</td>
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<td>AD: 18 vs. 8%, ns</td>
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</tbody>
</table>

\(^a\)Barkley et al. [13] and Fischer et al. [14]; \(^b\)Biederman et al. [12]; \(^c\)Rasmussen and Gillberg [15]; \(^d\)Weiss et al. [10]; \(^e\)Mannuzza et al. [16,17]; \(^f\)Unpublished data: of 176 male probands with ADHD in childhood, 17 (10%) reported that ADHD persisted into adulthood, defined as age 18 or older. Rates of various disorders among these 17 male probands with adult ADHD \(P_{168}\) are compared to rates among 168 non-ADHD male controls \(C\).

FU = Follow-up; P = probands, i.e. had ADHD in childhood; C- = controls, i.e. did not have ADHD in childhood; P>C- = probands had significantly higher rates of [X] than controls, P=C- = no significant difference in rates.

APD = antisocial personality disorder; MDD = major depressive disorder; BD = bipolar disorder; AD = anxiety disorders; Alc = alcohol abuse or dependence; SUD = SUD other than alcohol; BPD = borderline personality disorder; HPD = histrionic personality disorder; PAPD = passive-aggressive personality disorder; ns = \(p > 0.10\).}

FU interviewers: psychological assistant supervised by a neuropsychologist in the Barkley & Fischer studies; individuals with undergraduate degrees in psychology in the Biederman study; clinical psychologist and psychiatric social worker in the Klein & Mannuzza studies; psychiatrist in the Rasmussen & Gillberg and Weiss & Hechtman studies.
<table>
<thead>
<tr>
<th>Principal investigator</th>
<th>Sample</th>
<th>n</th>
<th>Mean age years</th>
<th>Interviewer and diagnostic interview</th>
<th>Major findings regarding comorbid adult mental disorders</th>
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<tr>
<td><strong>Controlled studies</strong></td>
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</table>
| Biederman\textsuperscript{a} | PA: referred adults with ADHD | PA- 84 | PA- 39 | Interviewer not stated | 1) PA > CA: APD, Alc, SUD, MDD, AD  
2) PR > CA: APD, Alc, SUD, MDD, AD  
3) PA = PR: APD, Alc, SUD, MDD, AD |
|                        | PR: non-referred adult relatives w/ADHD | PR- 36 | PR- 39 | Semistructured interview |                                                          |
|                        | PC: referred children with ADHD | PC- 140 | PC- 10 |                                                          |                                                        |
|                        | CA: comparison adults w/o ADHD | CA- 207 | CA- 39 |                                                          |                                                        |
| McGough\textsuperscript{c} | Parents of families with 2 children with ADHD (P), and non-referred parents of control children from family genetic studies of ADHD (C) | P- 79 | P- 43 | ‘Clinical psychologists or highly trained interviewers with extensive experience’ | P > C: (lifetime) APD, Alc dependence, SUD, MDD, BD, OCD, GAD, SoP |
| Murphy\textsuperscript{d} | Individuals referred to an adult ADHD clinic | P- 172 | P- 32 | Clinical psychologist | 1) P > C: Alc  
2) P = C: SUD, MDD, dysthymia, AD |
|                        |                                                                 | C- 30 | C- 36 | Semistructured interview |                                                          |
| Murphy\textsuperscript{e} | Individuals referred to child & adult ADHD clinics, & community controls | P- 96 | P- 21 | Clinical psychologist | 1) P > C: Alc, SUD, dysthymia  
2) P = C: APD, MDD, AD |
|                        |                                                                 | C- 64 | C- 21 | Unstructured interview |                                                          |
| Secnik\textsuperscript{f} | Individuals referred to an adult ADHD as identified from a database of employees of Fortune 200 companies who submitted insurance claims | P- 2,252 | P- 32 | None: all diagnoses determined from codes entered in the medical database | P > C: APD, Alc or SUD, MDD, BD, AD |

| **Uncontrolled studies**  |        |     |                |                                      |                                                        |
| Downey\textsuperscript{g} | Patients treated at an adult ADHD clinic | 78    | 33  | A psychiatrist and a clinical psychologist | 1) 13% had APD  
2) 33% had Alc  
3) 21% had SUD  
4) 37% had MDD, dysthymia, or depr. disord. NOS  
5) 47% had AD or a depressive disorder |

\textsuperscript{a} Individuals referred for treatment of adult ADHD (P), and non-referred parents of control children from family genetic studies of ADHD (C)  
\textsuperscript{b} Individuals with undergraduate degrees in psychology  
\textsuperscript{c} ‘Clinical psychologists or highly trained interviewers with extensive experience’  
\textsuperscript{d} Clinical psychologist  
\textsuperscript{e} Clinical psychologist  
\textsuperscript{f} None: all diagnoses determined from codes entered in the medical database  
\textsuperscript{g} A psychiatrist and a clinical psychologist
**Table 2. Continued**

<table>
<thead>
<tr>
<th>Principal investigator</th>
<th>Sample description</th>
<th>n</th>
<th>Mean age years</th>
<th>Interviewer and diagnostic interview</th>
<th>Major findings regarding comorbid adult mental disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shekikh</td>
<td>Individuals self-referred for treatment of adult ADHD</td>
<td>56</td>
<td>19–65</td>
<td>Interviewer not stated Semistructured interview</td>
<td>1) 34% had Alc &lt;br&gt; 2) 30% had SUD &lt;br&gt; 3) 10% had MDD &lt;br&gt; 4) 25% had dysthymia &lt;br&gt; 5) 25% had cyclothymia &lt;br&gt; 6) 53% had GAD &lt;br&gt; 7) 15% had panic disorder &lt;br&gt; 8) 13% had OCD &lt;br&gt; 9) 8% had phobic disorder &lt;br&gt;No rate was reported for APD</td>
</tr>
<tr>
<td>Torgersen1</td>
<td>Individuals referred to psychiatric clinics and diagnosed with adult ADHD</td>
<td>45</td>
<td>28</td>
<td>Psychiatrist Unstructured interview</td>
<td>The most common comorbid disorders were: &lt;br&gt; 1) MDD (53% lifetime, 9% current) &lt;br&gt; 2) Cannabis abuse (51% lifetime, 36% current) &lt;br&gt; 3) Amphetamine abuse (49% lifetime, 33% current) &lt;br&gt; 4) Alc (47% lifetime, 33% current) &lt;br&gt; 5) APD (44% lifetime, 0% current)</td>
</tr>
</tbody>
</table>

**Studies of individuals with other disorders who were evaluated for adult ADHD**

**Substance use disorders**

<table>
<thead>
<tr>
<th>Clure1</th>
<th>Patients treated at three inpatient substance abuse facilities</th>
<th>136</th>
<th>134</th>
<th>Interviewer not stated Semistructured interview</th>
<th>1) 32% had childhood ADHD &lt;br&gt; 2) 49% of above had ADHD into adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levin8</td>
<td>Cocaine abusers treated at outpatient facilities</td>
<td>281</td>
<td>34</td>
<td>The 2 interviewers had an MA &amp; BA in psychology Semistructured interview</td>
<td>1) 12% had childhood ADHD &lt;br&gt; 2) 15% had full or partial adult ADHD &lt;br&gt; 3) 52% of full ADHD had APD</td>
</tr>
</tbody>
</table>
Another approach to examining the association between ADHD and APD has been to survey groups of incarcerated individuals for the presence of ADHD. Although criminality is not synonymous with APD, the two have considerable overlap. In these groups, rates of ADHD are high. The reliance on retrospective reports from incarcerated individuals is especially problematic, since they may attribute their current legal

![Table 2. Continued](image)

<table>
<thead>
<tr>
<th>Principal investigator</th>
<th>Sample</th>
<th>n</th>
<th>Mean age years</th>
<th>Interviewer and diagnostic interview</th>
<th>Major findings regarding comorbid adult mental disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schubiner</td>
<td>Randomly selected inpatients from two substance abuse treatment facilities</td>
<td>201</td>
<td>35</td>
<td>Psychology graduate students Semistructured interview</td>
<td>1) 24% had adult ADHD 2) Adult ADHD &gt; no adult ADHD- APD 3) Adult ADHD = no adult ADHD- MDD, BD, GAD, So P, PTSD</td>
</tr>
<tr>
<td>Alpert</td>
<td>Patients treated for MDD</td>
<td>116</td>
<td>42</td>
<td>Interviewer not stated Semistructured interview</td>
<td>1) 16% had childhood ADHD 2) 12% had current ADHD</td>
</tr>
<tr>
<td>Hesslinger</td>
<td>Patients from an adult ADHD clinic (P1), and patients from an affective disorders clinic (P2)</td>
<td>P1 - 40</td>
<td>P1 - 33</td>
<td>Psychiatrists Semistructured interview</td>
<td>P1 - 70% had recurrent brief depression P2 - 43% had ADHD</td>
</tr>
<tr>
<td>Adler</td>
<td>Clinic patients with Post-traumatic stress disorder (P) or panic disorder (C)</td>
<td>P - 25</td>
<td>P - 60</td>
<td>Psychiatrists and a psychologist Semistructured interview</td>
<td>1) P&gt;C- childhood ADHD 2) P=C- current ADHD</td>
</tr>
<tr>
<td>Fones</td>
<td>Patients treated for panic disorder</td>
<td>85</td>
<td>36</td>
<td>Interviewer not stated Semistructured interview</td>
<td>1) 24% had full or partial childhood ADHD 2) 65% of above had ADHD into adulthood</td>
</tr>
</tbody>
</table>

P- = ADHD probands, C- = non-ADHD controls; P>C- = probands had significantly higher rates of [X] than controls; P=C- no significant difference in rates.
APD = Antisocial personality disorder, MDD = major depressive disorder, BD = bipolar disorder, AD = anxiety disorders, OCD = obsessive compulsive disorder, GAD = generalized anxiety disorder, So P= social phobia, PTSD = post-traumatic stress disorder, Alc = alcohol abuse or dependence, SUD = substance use disorder other than alcohol.

aBiederman et al. [34]; bBiederman et al. [35]; cMcGough et al. [36]; dMurphy and Barkley [37]; eMurphy et al. [22]; fSecnik et al. [38]; gDowney et al. [19]; hShekim et al. [39]; iTorgersen et al. [20]; jClure et al. [40]; kLevin et al. [41]; lSchubiner et al. [21]; mAlpert et al. [43]; nHesslinger et al. [42]; oAdler et al. [46]; pFones et al. [45].
difficulties to past and current psychopathology. Nevertheless, findings suggest that ADHD is common among incarcerated criminals, probably related to its relationship with APD. However, the methodology in these studies is plagued with difficulties. First, only about half of male prisoners and a fifth of female prisoners have APD [24]. Therefore, drawing conclusions about APD based on prison inmates may be misleading. Second, some investigators (e.g., Abramowitz et al. [25]) report on ‘psychopathy,’ an overlapping but distinct construct, which hinders interpretation of results. Third, most studies have assessed childhood ADHD, but not its persistence into adulthood [25, 26], thus blurring the distinction between diagnostic and prognostic comorbidity. Fourth, diagnosing the childhood disorder is almost invariably based on retrospective self-reports. Fifth, with few exceptions, diagnoses of childhood ADHD and adult APD or psychopathy are based on cut-off scores on questionnaires completed by prisoners, rather than interviews conducted by experienced clinicians. Finally, failure to take into account comorbid conduct disorder in childhood in predicting later APD precludes interpretation of relationships found with ADHD specifically. Three theories have been proposed to explain the relationship between childhood ADHD and criminality: one is that childhood conduct problems mediate the association (i.e., ADHD alone is insufficient), two is that conduct problems and ADHD are independent predictors, and three, that both are needed to confer increased risk for later antisocial outcomes. All three theories have received some support [27–29]. Nevertheless, results consistently have indicated that both retrospectively reported childhood ADHD and adult ADHD are overrepresented among prison populations (41–67% childhood, 45% in adults), probably, as noted, due to its relationship to APD [30, 31].

In sum, there is evidence suggesting that APD is relatively elevated among adults with ADHD. However, clear interpretation of this relationship requires knowledge of the age of onset of each disorder. If the adults with ADHD and APD had conduct disorder in childhood, whereas others did not, it would indicate consistent diagnostic comorbidity. However, if APD developed later than ADHD, it would argue for prognostic comorbidity. The latter issue is reviewed further on.

**Substance Use Disorders**

Interest in the comorbidity of adult ADHD and SUDs can be traced back to the 1980s when Wood et al. [32] reported that 33% of their sample of 27 males with alcohol dependence had attention-deficit disorder, residual type (the DSM-III equivalent of adult ADHD). Since then, numerous studies have been published on the prevalence of adult ADHD among substance abusers, most of which have been reviewed by Wilens [33].

Studies have typically targeted alcohol, cannabis, and/or cocaine, since these are among the commonly abused substances in the general population. There is clearly a strong association between substance abuse and dependence with adult ADHD. As shown in table 2, all controlled studies have reported that alcohol, non-alcohol...
substances, or both are significantly more prevalent among adults with ADHD compared to controls [22, 35–39]. Rates have varied widely (ranging from 20 to 40% for adults with ADHD vs. 5 to 10% for adults without ADHD), depending on the size of the sample, and whether it is abuse or dependence that is reported. Uncontrolled clinical studies have reported that, among adult patients treated for ADHD, one-third have alcohol abuse or dependence, and one-fifth to one-third abuse another substance [19, 20, 39] (see table 2). Finally, both inpatient and outpatient studies of adult substance abusers show relatively high rates of ADHD among these individuals (15–24%) [21, 40, 41] (see table 2). In a study that classified patients by drug of choice (alcohol, cocaine, or both), rates of adult ADHD did not differ [40], leading the authors to conclude that self-medication did not account for the drug use, since the stimulant cocaine was not preferred over alcohol, a central nervous system depressant.

In our prospective follow-up study of children with ADHD, we also found that non-alcohol SUD was significantly more prevalent among those who still had ADHD in adulthood than normal comparisons (53 vs. 29%, p < 0.04). In contrast, alcohol abuse/dependence did not differ between adults with continued ADHD and controls (29% for both groups) [23].

The evidence for comorbidity between ADHD and SUD is considerable. Whether it is mediated by another disorder or other factors is not known.

Mood Disorders
Most studies have reported an association between adult ADHD and depressive disorders (major depression, dysthymia, or depressive disorder NOS). Among the six studies of individuals with adult ADHD shown in table 2, only one [37] did not find a relatively higher prevalence of depressive disorder among ADHD adults. Similarly, uncontrolled studies have reported fairly high rates (25–53%) of depressive disorders among individuals with adult ADHD (table 2). Hesslinger et al. [42] reported that 70% of patients in an adult ADHD clinic had recurrent brief depression, whereas 43% of patients seen at a mood disorders clinic had ADHD. Conversely, in a clinic sample of patients with major depression, 12% of patients were judged to have ongoing ADHD [43].

The few controlled studies of bipolar disorder have reported that ADHD adults have an excess of bipolar disorder. Biederman et al. [35] reported rates of 10 vs. 3% (p < 0.05), McGough et al. [36] reported 5 vs. 0% (p < 0.01), and Secnik et al. [38] reported 4 vs. 1% (p < 0.01). In 56 adult patients in a clinic for bipolar patients, Sachs et al. [44] found a 14% rate of childhood ADHD, but do not indicate whether ADHD had persisted through adulthood. Those judged to have had childhood ADHD had earlier bipolar onsets than the non-ADHD bipolar patients. A prevalence of 14% for childhood ADHD seems high, but it does not exceed some population estimates, and does not reinforce the view that ADHD is highly prevalent in bipolar disorder.

In our prospective follow-up study of children with ADHD [16, 17], we did not find that childhood ADHD predicted mood disorders in adulthood, regardless of
whether specific mood disorders or a conglomerate category was considered. Rates among probands with adult ADHD and non-ADHD comparisons were as follows: major depressive disorder, 29 vs. 24%, ns; bipolar disorder, 0% in both groups; any mood disorder (MDD, dysthymia, etc.), 35 vs. 24%, ns [23]. Notably, our sample was all male, and ADHD probands were free of conduct disorder in childhood. These two features may be relevant since rates of depression and anxiety disorders are lower in males and conduct disorder in childhood contributes to later risk for these conditions. In addition, the number of adults with ADHD was relatively small, and would not provide power to detect an infrequent outcome, such as bipolar disorder.

Anxiety Disorders
In the case of anxiety disorders, findings are inconsistent. Some controlled studies report elevated rates in ADHD in adults [34–36, 38], whereas others do not [22, 37]. Fones et al. [45] reported that 15% of patients with panic disorder had adult ADHD. As with other studies of this kind, the lack of a comparison group is problematic. In addition, the authors do not state who conducted the evaluations, and whether these individuals were blind to study hypotheses. In a small, non-blinded study, the rate of adult ADHD did not differ between patients with panic disorder and those with post-traumatic stress disorder [46]. In our prospective adult follow-up study of boys with ADHD [16, 17], there was no significant preponderance of anxiety disorders in adulthood among probands with adult ADHD compared to non-ADHD controls (18 vs. 8%, ns). In conclusion, a relationship between adult ADHD and anxiety disorders is not established, and requires further systematic study.

Comorbidity in Adults with ADHD in the General Population
All the above studies, whether cross-sectional or of psychiatric disorders longitudinal, have dealt with clinical cases of ADHD. It is well known that comorbidity is higher in clinical than population samples. Only one recent US population study has reported on comorbidity in adults with ADHD [47]. It estimated the prevalence of ADHD to be 4.4% in 18- to 44-year-olds. Comorbidity rates were significantly elevated in this group compared to adults without ADHD. Respective rates were: mood disorders 38 and 11% (p < 0.05); anxiety disorders, 47 and 19% (p < 0.05); SUD, 15 and 6% (p < 0.05), and intermittent explosive disorder, 29 and 6% (p < 0.05). Among the mood and anxiety disorders, all the individual component disorders were significantly elevated in the ADHD adults. Not so in the case of SUDs – only drug dependence was significantly higher in the adults with ADHD (4.4 vs. 0.6%, p < 0.05). There were no significant differences in alcohol abuse, alcohol dependence, and drug abuse. APD was not addressed in the report. Surprisingly, relative comorbidity rates are not appreciably different from those reported in clinical studies. Inevitably, the study suffers from
limitations inherent in retrospective studies that rely on self-reports exclusively, where the positive predictive value of ADHD diagnoses in childhood is likely to be poor.

Factors Influencing Diagnostic Comorbidity

ADHD is more prevalent in men than women, prompting conjecture about possible differences in the disorder and its course between the two sexes. The evidence suggests that men and women have similar comorbidity. The Boston group reported that comorbidity did not differ between men and women [48], and also found no difference in comorbidity between referred and non-referred adults with ADHD [35] (table 2). No other factors have been examined, and little is known about factors that influence diagnostic comorbidity.

Prognostic Comorbidity of Childhood ADHD

Prognostic comorbidity requires two conditions. One, the index disorder (in this case ADHD) must precede the comorbid disorder. Two, the index condition must remain active during the development of the later condition. If the index disorder remits, but predicts other conditions, the index disorder represents a risk factor for subsequent pathology, but strictly speaking, the index and other disorder are not comorbid. This type of information is limited in the case of ADHD. It requires that comprehensive diagnostic information be obtained about all major psychiatric disorders in childhood. In some cases, the absence of comorbidity with childhood ADHD can be taken for granted. SUDs and contact with judicial system (e.g., arrests, convictions and incarcerations) are, for all practical purposes, non-existent in children. However, such is not the case for a host of other conditions. Conduct disorder, for one, has been shown to be highly comorbid with childhood ADHD and strongly predictive of APD [49].

To date, there has been no adult longitudinal follow-up of children with ADHD that can report on the incidence (new onsets) of a variety of psychiatric disorders. This is critical since, as noted, childhood ADHD is highly comorbid with a number of disorders, especially conduct disorder, and anxiety and mood disorders [50]. For example, major depression has been diagnosed in as many as 75% of children, and anxiety disorders in about 30%. Consequently, their comorbid presence in adults with ADHD cannot be attributed unequivocally to the prognostic comorbidity of childhood ADHD. As we note above, substance use and abuse are not features of preadolescents; therefore, outcomes from studies that have followed preadolescents could not have been affected by the presence of these conditions in childhood. The same is not true of longitudinal studies that include adolescents (e.g., the Boston studies).

The Boston group [12] reported a 10-year follow-up of a cohort of 6- to 18-year-olds with ADHD compared to non-ADHD comparisons (mean age 21 at follow-up).
This is the only longitudinal study that controls for initial comorbidity. The report illustrates the potential confound of initial comorbidity in follow-up studies. Initial comorbidity rates were: for major depression, 29%; anxiety disorders, 44%, and conduct disorder, 21%. After controlling for initial comorbidity and relevant baseline characteristics, the study found no difference in 1-year rates of major depression, bipolar disorder, or anxiety disorders between the ADHD and control groups. Only APDs and nicotine dependence were significantly elevated in ADHD probands. Unfortunately, the relationships between initial and outcome comorbidity are not presented. Although the stated goal of the study was to inform on the adult outcome of ADHD, the mean age was just 21, and the sample at follow-up included adolescents. Furthermore, the inclusion of a wide age range confounds interpretation since those diagnosed at 17 are likely to represent a different population of children with ADHD from those identified at age 6. In the latter group, a substantial proportion will no longer have ADHD at age 17. Finally, although 58% of the original ADHD sample no longer met criteria for ADHD at the 10-year mark, the authors do not indicate the distribution of comorbid disorders in the remitted versus persisted ADHD cases, limiting our understanding of the findings.

In the New York follow-up study of children with ADHD, conduct disorder was systematically excluded since the clinical trials then under way required that children have ‘uncomplicated’ ADHD. No other sample of ADHD children provides the opportunity to determine whether ADHD alone predicts the development of antisocial disorder. In two independent samples of children with ADHD, but no conduct disorder (mean age 8 years; range 6–12), we found that the development of antisocial disorder was much more frequent in probands than non-ADHD-matched peers. At mean age 18, APD was ongoing in 37% of probands versus 3% in controls [51, 52]. At average age 25, respective rates were 15 and 2% [16, 17]. In adolescence, the excess of APD was completely accounted for by probands who had retained ADHD. The prevalence of comorbid antisocial disorder among persistent ADHD cases was 48%, as opposed to 17% in probands whose ADHD had remitted, no different from controls (8%). These findings reflect prognostic comorbidity of ADHD for APD in adolescence. In adulthood, we found that probands who retained ADHD beyond age 18 had significantly higher rates of APD than those who remitted before age 18 (47 vs. 23%, p = 0.03). However, unlike adolescence, the excess of APD in the adults was no longer restricted to those who still had ADHD. APD had developed functional autonomy. Of relevance, in this study, in virtually all instances, the age of onset for APD preceded the age at which SUD began [51], thus pointing to a cascading developmental trajectory from ADHD to APD, and then SUD.

Relatedly, we found that criminal behavior was more frequent in ADHD probands at the average age of 22 than in controls [53]. Respective rates were: arrests 39 and 20% (p < 0.02); convictions 28 and 11% (p < 0.01), and incarcerations, 9 and 1% (p < 0.05). These negative judicial outcomes were completely accounted for by the presence of APD. In other words, the rates of criminality did not differ between probands without
APD and controls, even among probands who still had ADHD. Thus, ADHD alone does not predict criminality; the latter requires the development of APD. Similar differences in criminality between probands and controls were found at age 38. Relying on judicial records of probands and controls in New York State, respective rates were: arrests 47 and 24% (p < 0.01); convictions 42 and 14% (p < 0.002); incarcerations, and 15 and 1% (p < 0.02). A history of APD or SUDs was an independent predictor of multiple arrests in probands [23].

Although the New York study excluded ADHD children with conduct disorders, oppositional defiant disorder was allowed. It is therefore possible that the oppositional defiant disorder contributed to the development of APD, rather than ADHD itself. Such was not the case. Oppositional defiant disorder symptoms were not associated with the maintenance of ADHD, or with the development of APD [54]. In sum, childhood ADHD is a precursor of adolescent onset APD, especially in those who retain ADHD, even in the absence of comorbid oppositional defiant disorder or conduct disorder in childhood.

As noted above, SUDs have been found to be relatively more frequent in children with ADHD followed into adulthood. The question here is whether this excess is limited to those who retain ADHD, as in the case of APD. In the New York study, the only report thus far to address this issue, the development of SUDs was not a function of retention of ADHD (53 vs. 45% in persistent and remitted ADHD). Probands who retained ADHD but had not developed APD did not differ from controls with respect to SUDs. Thus, we did not find prognostic comorbidity of ADHD for SUDs. Rather, ADHD represents a risk factor through the mediation of APD. There did not appear to be differential prevalence of anxiety and mood disorders in cases who had retained ADHD into adulthood and those in whom it desisted, but the number of subjects with persistent ADHD is small (rates of mood disorders, 35 vs. 22%, anxiety disorders, 18 vs. 18%, ns).

There would be great merit in understanding factors that influence the prognostic comorbidity of ADHD. To do so requires the identification of characteristics that predict the maintenance of ADHD into adulthood. Efforts in this direction have been disappointing and no consistent evidence points to patterns of predictive value for any feature [55]. One study reports that severity of childhood ADHD and treatment for ADHD predicted persistence into adulthood [56]. However, these reports were retrospectively obtained from adults, and current status may have influenced recall. Neuroimaging work in progress aiming at distinguishing genetic characteristics among ADHD children with good versus poor outcomes may be generating promising results [57].

Summary and Conclusions

Prospective follow-up studies of children with ADHD have provided limited information regarding diagnostic comorbidity among individuals with adult ADHD. Few
studies have reported rates of comorbid disorders among unremitted and remitted cases of ADHD (table 1). Our findings indicate that ADHD leads to the development of APD even in the absence of conduct disorder in childhood. In turn, APD fosters the development of SUDs. Thus, there appears to be no direct relationship between persistent ADHD and SUDs. Despite diverse methodologies across clinical studies of adults with ADHD (tables 1, 2), reports of elevated rates of APD and SUDs are consistent. In contrast, reports of depressive and anxiety disorders are variable. Relative rates may vary with type of clinical sample (inpatient, outpatient), type of assessment (unstructured and semistructured clinical interviews and highly structured inquiry), evaluator (clinician, lay interviewer), and sample characteristics such as socioeconomic status that affect rates of APD.

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