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1 Later sibling Recurrence of ASD and ADHD: Clinical and Mechanistic Insights

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24

27 Miller and colleagues<sup>1</sup> report on the within- and cross-condition recurrence of later born siblings of  
28 children ('probands') with attention deficit/hyperactivity disorder (ADHD) or autism spectrum  
29 disorder (ASD). The relatively high heritability of both conditions is well established from twin  
30 studies assessing both trait variance<sup>2</sup> and diagnostic recurrence<sup>3</sup>. Two recent large-scale  
31 Scandinavian studies extended this work to show that the two conditions also run together in  
32 families. One population-based study of children with ASD ( $n=3,578$ ) estimated the combined  
33 (older and younger) sibling recurrence of ASD to be 10.5% but also reported that 5.3% had siblings  
34 with a diagnosis of ADHD, giving relative risks of 11.8 and 3.7 compared to matched controls  
35 without ASD<sup>4</sup>. An even larger population registry study with  $n=28,468$  cases of ASD found that  
36 full siblings had a similarly elevated odds ratio of 4.59 of having an ADHD diagnosis compared to  
37 siblings of individuals without an ASD diagnosis<sup>5</sup>. This familial cross-aggregation between the two  
38 conditions highlights the importance both of providing clinically useful estimates of elevated likely  
39 recurrence rates and of studying shared neurodevelopmental paths to the two conditions<sup>6</sup>.

40  
41 Although the US medical records data reported by Miller et al<sup>1</sup> is more modest in scale than these  
42 large Scandinavian population studies it does speak very directly to a question of clinical concern.  
43 When parents are told by clinicians that their child has a diagnosis of a neurodevelopmental  
44 condition such as ASD or ADHD, one important question – often asked by parents themselves – is  
45 “What are the chances that my younger/future children will have ASD or ADHD?”. To answer this  
46 question, we need to know the recurrence rates for *later* born siblings; the question directly  
47 addressed in the current study. Miller and colleagues<sup>1</sup> report that 12.03% of later born siblings of  
48 older probands with ASD also went on to have a diagnosis of ASD themselves (an elevated odds  
49 ratio of 30.38 compared to later born siblings of children without an ASD diagnosis). However,  
50 later born siblings of probands with ASD also had an elevated likelihood of an ADHD diagnosis  
51 (3.80%; odds ratio 3.7). Conversely, for later born siblings of probands with an ADHD diagnosis  
52 the within-condition recurrence rate for ADHD was 12.47% (odds ratio compared to later born

53 siblings of children without an ADHD diagnosis 13.05) and the cross-condition recurrence rate for  
54 ASD was 1.92% (odds ratio 4.35). This is likely if anything to be an underestimate, since children  
55 with a diagnosis of both ASD and ADHD were placed in the ASD group.

56  
57 These within- and cross-condition recurrence figures are of important clinical utility in terms of  
58 informing discussions with parents about the need for enhanced developmental surveillance for  
59 neurodevelopmental conditions such as ASD and ADHD in their younger children. However, there  
60 are some limitations to the clinical utility of the data from this important study. The sample sizes  
61 are modest, comprising  $n=730$  later born children with older probands with an ADHD diagnosis  
62 and  $n=158$  later born children with older probands with an ASD diagnosis. As a result, the  
63 confidence intervals of the elevated odds ratios reported are relatively wide (see Table 2) and this  
64 imprecision should add caution to how this information is conveyed to parents; though it is clear  
65 that the later born siblings are at considerably elevated likelihood of themselves going on to have  
66 ASD and ADHD. Families with an older child who was typically developing but who subsequently  
67 had a child with ASD or ADHD and another younger child were removed from the control group,  
68 perhaps leading to slightly lower estimates of the likelihood of a subsequent diagnosis after a  
69 typically developing child. One useful re-analysis of large population and registry databases<sup>4,5</sup> –  
70 with larger population-representative samples – would be to separate out and report recurrence rates  
71 for later born siblings rather than all siblings (earlier and later born combined) in these studies and  
72 we encourage the authors of these studies to do this.

73  
74 Another set of different clinical issues also arise from these considerations. One question pertains  
75 to when such information should be imparted to parents. Often, parents seeking a diagnosis have  
76 known for some time that something is different about their child, and the developmental and  
77 behavioural difficulties their children are experiencing motivate the clinical consultation. A  
78 diagnosis can help parents to recognise and understand some of the challenges their child is

79 experiencing and should provide a gateway to information and support services that can help  
80 families support their child and anticipate their needs. Proactive monitoring of younger children for  
81 signs of ASD and ADHD could remove significant sources of stress in the process of seeking a  
82 diagnosis. However, we suspect that there is wide variation in clinical practice in how information  
83 about the potential likelihood of another diagnosis in their younger child is presented. It may not be  
84 best to impart this information at the initial feedback from the diagnostic consultation itself but at a  
85 later review meeting when parents have had the opportunity to find out more about ASD or ADHD  
86 and adjust to their new understanding of their child and family. We expect that there is wide  
87 variance in how knowledgeable and confident clinicians feel about imparting information about the  
88 familial nature of neurodevelopmental conditions. Whilst studies such as the present one will help  
89 to provide accessible and clinically translatable estimates of recurrence, more specialist training or  
90 even specialist genetic counselling services might have to be developed to provide this information  
91 to families sensitively and clearly, in the way that is increasingly the case for more monogenic  
92 forms of neurodevelopmental conditions<sup>7</sup>.

93  
94 The increasing recognition of within-child and within-family co-occurrence of neurodevelopmental  
95 conditions such as ASD and ADHD has also spurred developmental studies that aim to help us  
96 understand common and distinct mechanisms that lead to such outcomes. Many studies over the  
97 past 15 years have prospectively studied infants with older siblings with ASD to identify the neural  
98 and developmental changes that fall on the causal path to later autism symptoms<sup>8,9</sup>. Findings  
99 suggest that whilst overt behavioural differences are not consistently found until the second year of  
100 life, various neurodevelopmental differences may be present as early as six months of age that  
101 presage later emergent symptoms and the eventual development of an ASD clinical profile<sup>7,8</sup>.  
102 Similar studies of infants at familial increased likelihood of developing ADHD have been far fewer,  
103 although several are now underway<sup>6,10</sup>. The present study suggests that the rates of an ADHD  
104 diagnosis in an infant with and older sibling with ADHD are similar to the rates of an ASD

105 diagnosis in an infant with an older sibling with ASD, making this design feasible. More recently,  
106 such studies have begun to incorporate the increasing recognition that infants with older siblings  
107 with ASD may also be more likely to develop other neurodevelopmental conditions. In other work,  
108 Miller, Iosif and colleagues<sup>11</sup> have shown not only (consistent with the current paper) that by mid-  
109 childhood rates of ADHD diagnosis are elevated in siblings with an older proband with ASD but  
110 also that in these individuals there is evidence of atypical visual attention from as early as the first  
111 six months of life. We have recently examined infant predictors of mid-childhood ASD and ADHD  
112 traits in our own prospective study of younger siblings with probands with ASD<sup>12</sup> and found that  
113 whilst increased activity levels of poor inhibitory control were associated with later ADHD traits  
114 they were not associated with later ASD traits, suggesting that early developmental pathways to  
115 ADHD might be distinct from ASD. A recent study by Constantino and colleagues<sup>13</sup> has found that  
116 at eighteen months of age traits of early ASD behaviours were both largely independent from those  
117 of early general psychopathology and that the former were highly heritable but the latter largely  
118 environmentally influenced. They suggest that the widely observed co-occurrence of such traits  
119 later in childhood might operate from interactions over time between these independent  
120 susceptibilities. Identification of the underlying mechanisms of co-occurrence between  
121 neurodevelopmental conditions such as ASD and ADHD is important not only to better understand  
122 aetiology but also to guide efforts towards targeted pre-emptive early intervention, examples of  
123 which have begun to emerge<sup>14,15</sup>.

124

125 The current paper<sup>1</sup> should be read by both the clinical and the research readership of the journal. It  
126 utilises a simple and transparent design to report novel data on later born within- and cross-  
127 condition recurrence of ASD and ADHD in a way that is utilisable in the clinic but also motivates  
128 research to understand how and why these conditions so commonly co-occur both within  
129 individuals and within families. Future research should develop and test early, pre-emptive

130 interventions to ameliorate aspects of these neurodevelopmental conditions that can considerably  
131 challenge children and those who care for them.

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