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Higher Risk of Mortality for Individuals Diagnosed With Autism Spectrum Disorder or Attention-Deficit/Hyperactivity Disorder Demands a Public Health Prevention Strategy

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In this issue of *JAMA Pediatrics*, Catalá-López et al[1] report the findings of a systematic review and meta-analysis assessing the risk of mortality among persons with autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD) and their first-degree relatives. The take-away message is not subtle nuanced, but clear, direct, and sobering–individuals with ASD or ADHD frequently die of preventable natural causes (eg, cardiac events) and unnatural causes (eg, unintentional injury, suicide). As such, this knowledge demands widespread recognition and the implementation of systematic screening and preventive approaches. Higher mortality rates have been documented in the field of ASD for longer than they have in the field of ADHD, owing to the well-established higher risks for drowning, pedestrian-auto crashes, suicide, seizure disorders, and other medical conditions associated with ASD that can lead to a shorter life expectancy.

Notably, this systematic review and meta-analysis[1] also found higher mortality rates for women with ASD than for men with ASD consistent with a recent study that showed higher rates of both psychiatric and medical comorbidities in female individuals with ASD than male individuals with ASD.[2] Importantly, this systematic review and meta-analysis[1] and the large-scale studies incorporated within the review make it clear that ADHD diagnosis is also associated with markedly higher risk (more than 2-fold) for early mortality in childhood and more than 4-fold increase in risk for mortality by midlife (age 45 years) in adulthood.

Studies of adults with ADHD further show that for each 4-year interval that adults with ADHD go untreated, their risk for early mortality is twice that of typical adults.[3] Clinical researchers have puzzled over the decline in the prevalence of ADHD with age, such that 5% to 8% of children may meet diagnostic criteria for ADHD while that figure falls to 4% to 5% of adults and 2% to 3% of older adults. However, this argument is weakened by recent evidence that with repeated follow-up in adulthood, as has been done in the MTA Cooperative Group study of ADHD,[4] approximately 90% or more of childhood cases will at some point be rediagnosed with ADHD in adulthood, the difference in

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studies owing to variation in symptom severity over time rather than to sustained declines. Thus, the developmental explanation for declining prevalence is far less plausible. Instead, this systematic review and meta-analysis[1] and the studies included within it make plain that another explanation is the greater loss of individuals with these conditions from the population over time owing to heightened mortality compared with typical peers.

This systematic review and meta-analysis[1] (and earlier research) found that the earlier mortality risk in individuals with ASD is driven by both natural causes (ie, cardiac, seizures, etc) and unnatural causes (eg, unintentional injury, suicide), whereas for individuals with ADHD, early deaths were found to arise primarily from unnatural causes, such as behaviors that lead to unintentional yet mortal injuries followed by suicide, and possibly later in adulthood, homicide, as is evident in the population-based studies incorporated into this systematic review and meta-analysis. Even so, some cases of early mortality do arise in patients with ADHD secondary to natural causes. The key message is that, in most cases, whether natural or unnatural, public health screening and prevention strategies could increase the life span and quality of life for individuals with these neurodevelopmental conditions.

Both ADHD and ASD have been associated with factors that would directly or indirectly be expected to contribute to reduced estimated life expectancy (ELE). Specifically, they are associated with various adverse medical conditions, including increased rates of seizure disorders, obesity, eating disorders, substance use, dental trauma and caries, sedentary behavior or low rates of exercise, sleeping problems, migraines, and risk for future coronary heart disease, as well as decreased involvement in preventive health, nutrition, and dental hygiene activities.[5] Given the well-known comorbidity of ADHD with ASD, it is possible that some of the risk for early mortality in individuals with ASD arises from its association with ADHD diagnosis.

Moreover, many of these conditions are well-known correlates of reduced life expectancy and are used in algorithms that predict life expectancy in public health research and in the life insurance industry. While these studies do not specifically compute the cumulative risk of chronically engaging in adverse health and lifestyle activities on ELE, 1 recent longitudinal study of patients with ADHD did so.[6] It found that based on 14 variables related to health, lifestyle, education, demographics, and other factors, by age 27 years, people who had been diagnosed as having ADHD in childhood could be expected to have a 12.7-year reduction in healthy ELE and 11.1-year reduction in total ELE if their disorder persisted to adulthood. Yet, even those who no longer met diagnostic criteria by adulthood were found to have a 9.6-year reduction in healthy ELE and 8.4 years in total ELE regardless of what treatment they received earlier. The magnitude of such reductions in ELE can be appreciated by understanding that such reductions are far greater than those associated with smoking, obesity, alcohol use, high cholesterol, and high blood pressure, either individually or combined. That is because in that study, ADHD diagnosis predisposed people to such risk factors. These included not only demographic risk factors, such as reduced education, lack of high school graduation, and lower annual income, but also the health and lifestyle factors of greater alcohol consumption, poorer overall health, reduced sleep, increased likelihood of smoking and of smoking more than 20 cigarettes per day,

and possibly greater adverse driving consequences that result in license suspensions and revocations.

Behind these first-order or more proximal factors, the background trait of low behavioral disinhibition (and poor self-regulation in general) explained more than 30% of the variance in life expectancy, consistent with numerous earlier findings on the outsized role of the personality trait of low conscientiousness in reducing life span.[7] The association of ADHD with some of these adverse health conditions may also be genetically mediated. A recent genome-wide association study[8] using polygenic risk scores found significant shared genetic relationships between individuals with ADHD and nearly all the first-order risk factors used in the Barkley and Fischer[6] computation of ELE, including educational attainment, obesity, diabetes, smoking, and sleep, among others. This also applied to other factors they did not use, such as level of high-density lipid cholesterol, earlier age at parenthood, and risk for rheumatoid arthritis. Again, the greater association of ADHD diagnosis with ASD diagnosis could well account for some of the early mortality and reduced ELE associated with ASD.

In addition to ADHD diagnosis, ASD diagnosis is also associated with other psychiatric comorbidities that are correlated with increased risk for mortality, including anxiety and affective disorders. In a recent, large study of patients 10 years or older, it was found that individuals with ASD had more than 3-fold higher rates of attempted suicide and suicide compared with the general population and having a psychiatric comorbidity was a significant risk factor.[9] Protective and risk factors associated with suicide risk among individuals with autism were found to be different than those for the general population, underscoring the need for tailored suicide screening and awareness for health care professionals serving individuals on the autism spectrum. Another risk factor associated with increased mortality in general in individuals with ASD is having poorer social and daily living skills.[10] This suggests that early autism detection and intervention designed to improve social engagement and adaptive behavior could play an important role in reducing mortality in individuals with ASD.

These findings in the context of the Catalá-López et al[1] research on increased mortality by midlife argue for individuals with ADHD and individuals with ASD being viewed through a public health lens with screening and prevention strategies offered beginning in early childhood. These findings should also give impetus to efforts to try to reduce the first order risk factors that are predisposing to reduced life expectancy, such as obesity, substance use, poor diet, poor sleep, and limited exercise among children and adults with ASD and ADHD. After all, ELE is malleable–change the adverse health and lifestyle factors affecting it, and one can improve quality of life, as well as life expectancy. A preventive strategy would necessitate primary care physicians becoming more aware of the linkage between both ASD diagnosis and ADHD diagnosis and early mortality as well as their link to reduced ELE. Such professionals are the ones most likely to be evaluating and seeking to improve health and quality of life for patients by reducing adverse health and lifestyle activities of individuals. This approach is imperative for individuals with ADHD and individuals ASD as the higher risk for mortality reported in this review could be reduced by doing so.

Conflict of Interest Disclosures:

Dr Barkley reported other and speaking fees from Takeda Pharmaceutical, Medice Pharmaceutical Co, and AstraZeneca, book royalties from Guilford Publications and American Psychological Association, and course royalties from ContiningEdCourses.net and Premier Educational Seminars, Inc outside the submitted work. Dr Dawson reported grants from The Eunice Kennedy Shriver National Institute of Child Health and Human Development (P50HD093074) and the National Institute of Mental Health (R01MH121329) during the submitted work and personal fees from Apple outside the submitted work. In addition, Dr Dawson had a patent for (15/141,391) licensed to Apple, Inc. Dr Dawson had developed technology and data that have been licensed to Apple, Inc and Dr Dawson and Duke University have benefited financially (63/192,295 pending, 16/678,789 pending, and patent 16/678,789). No other disclosures were reported.

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