Neurodivergence Linked to Higher Rates of Connective Tissue Disorders

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Key Findings:

- Compared with patients who had no neurodevelopmental diagnosis, patients with autism (ASD), ADHD, or both were more likely to have a connective tissue disorder diagnosis.
- The association was strongest for patients with both ASD and ADHD, who had a 438% higher likelihood of a heritable structural connective tissue disorder and a 340% higher likelihood of a hypermobility spectrum disorder.

The idea that autism (ASD) and ADHD might occur alongside disorders of the body's connective tissue has circulated among clinicians and researchers for years, built largely on small clinical samples and case reports.1,2 Connective tissue disorders are a broad group of conditions affecting the tissues that support and connect the body, and they include:

- Heritable structural disorders such as Ehlers-Danlos syndrome (which affects collagen and can cause fragile skin and unstable joints) and Marfan syndrome (which affects the fibers that support the body's organs and can involve the heart and blood vessels)
- Hypermobility spectrum disorders (in which joints move beyond their normal range)
- Autoimmune conditions such as lupus.

We studied more than 117 million U.S. adults and adolescents aged 15 and older who had an outpatient visit between January 2017 and April 2026. We grouped patients by neurodevelopmental diagnosis into those with ASD but not ADHD, ADHD but not ASD, and co-occurring ASD and ADHD, and matched each of those patients with patients who had no neurodevelopmental diagnosis based on age, sex, and how often they used health care. For each group, we measured the proportion of patients with a connective tissue disorder diagnosis in one of several categories. We also looked at kidney stones, a condition we would not expect to share any biological link with neurodivergence. This helps gauge whether any apparent association simply reflects that neurodivergent patients tend to have more thoroughly documented charts.

Across all three neurodevelopmental groups, connective tissue disorders were consistently more common than in comparison patients and were most likely for patients who were diagnosed with ASD and ADHD. Patients with both ASD and ADHD had a 438% higher likelihood of a heritable structural connective tissue disorder and 340% higher likelihood of a hypermobility spectrum disorder compared with matched patients who had no neurodevelopmental diagnosis. The ASD-only group showed a 311% higher likelihood of heritable structural disorders and a 203% higher likelihood of hypermobility spectrum disorders, while the ADHD-only group showed a 170% and 148% higher likelihood, respectively. Associations were present but smaller for autoimmune and inflammatory connective tissue disorders, ranging from a 41% higher likelihood in the ADHD-only group to a 93% higher likelihood in the co-occurring group.

Connective Tissue Disorder Rates by Neurodevelopmental Group

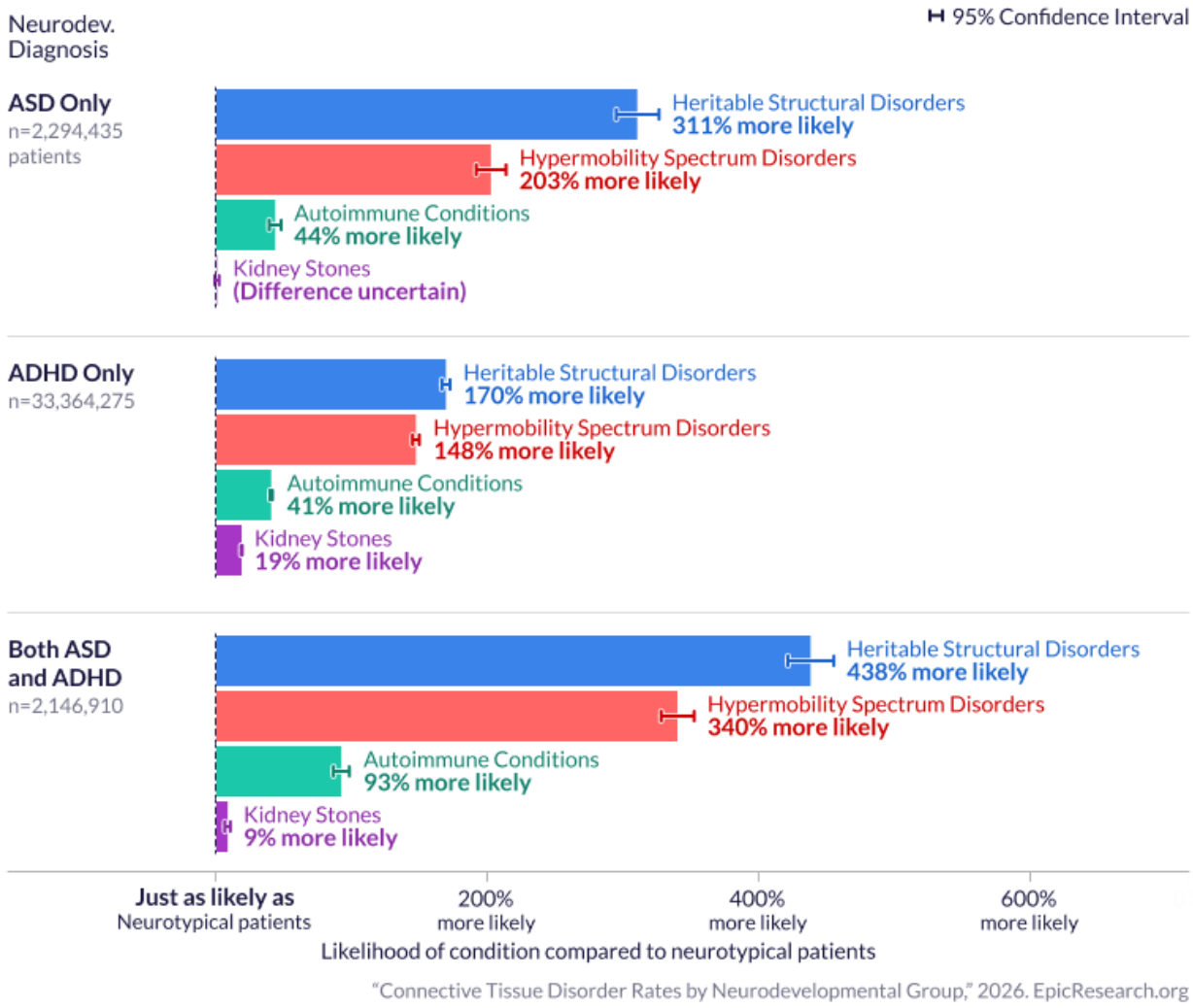

Figure 1a. The relative likelihood of a patient having a connective tissue disorder by the presence of autism spectrum disorder (ASD) only, ADHD only, and co-occurring ASD and ADHD.

Connective Tissue Disorder Rates by Neurodevelopmental Group

Figure 1b. The absolute rate of a patient having a connective tissue disorder by the presence of autism spectrum disorder (ASD) only, ADHD only, and co-occurring ASD and ADHD.

Connective tissue disorders remained rare in absolute terms even where the relative differences were large: heritable structural disorders were documented in roughly 12 per 1,000 ASD-only patients and 21 per 1,000 co-occurring patients, compared with 3 and 4 per 1,000, respectively, among comparison patients.

The negative-control outcome supported this interpretation only partially: kidney stones were no more common among ASD-only patients but were modestly elevated in the ADHD and co-occurring groups (19% and 9% higher likelihood, respectively). Because patients who see clinicians more often tend to accumulate more diagnoses of all kinds, this pattern suggests the connective tissue associations are partly, but not entirely, explained by more thorough documentation rather than a true difference in underlying rates.

These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 300 million patient records from 2,200 hospitals and more than 50,000 clinics from all 50 U.S. states, Canada, Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientist. The two teams came to similar conclusions. Graphics by Brian Olson.

References

1. Csecs JLL, Iodice V, Rae CL, et al. Joint hypermobility links neurodivergence to dysautonomia and pain. *Front Psychiatry*. 2022;12:786916. doi:10.3389/fpsyt.2021.786916
2. Cederlöf M, Larsson H, Lichtenstein P, Almqvist C, Serlachius E, Ludvigsson JF. Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. *BMC Psychiatry*. 2016;16:207. doi:10.1186/s12888-016-0922-6

Data Definitions

Term	Definition
Study period	1/1/2017 to 4/30/2026
Study population: inclusion	Patients meeting all of the following: • have an **index date** in the s**tudy period** • Aged 15+ as of the **index date** • At least one **outpatient face-to-face encounter** at least three years before the **index date** • Any diagnosis (excluding ICD-10-CM code Z*) on chart from problem list, encounter, or billing
Index date	The latest **outpatient face-to-face encounter** in the study period
Exposures	ASD and not ADHD, ADHD and not ASD, co-occurring ASD + ADHD Reference group: patients with no neurodevelopmental exposure diagnosis
Outcomes	Proportion of each exposure group with a connective tissue disorder diagnosis in each category: **heritable structural connective tissue disorders** (classic EDS, vascular EDS, other specified EDS, unspecified EDS, Marfan syndrome), **hypermobility spectrum** (hypermobile EDS, hypermobility syndrome/generalized joint hypermobility), autoimmune/inflammatory (**systemic lupus erythematosus**, **dermatopolymyositis**, **systemic sclerosis**, **Sjögren and other systemic CTD**); and other (**autonomic dysfunction/dysautonomia**, **mast cell activation syndrome**, **fibromyalgia**). Negative-control condition: **kidney stones**
Autism spectrum disorder (ASD)	ICD-10-CM code F84.0* or F84.5* or SNOMED code 35919005
ADHD	ICD-10-CM code F90* or SNOMED code 406506008
Outpatient face-to-face encounter	An encounter with a type of Emergency, Office Visit, Well Child, Follow-up, Telemedicine, Urgent Care, Walk-In, Routine Prenatal, Postpartum Visit, or Fetal Care Consult
Heritable structural connective tissue disorders	Classic EDS: ICD-10-CM code Q79.61; vascular EDS: Q79.63; other specified EDS: Q79.69; unspecified EDS: Q79.60; Marfan syndrome: Q87.4*
Hypermobility spectrum	ICD-10-CM code Q79.62 or M35.7 or SNOMED code 762314000
Autonomic dysfunction / dysautonomia	Idiopathic peripheral autonomic neuropathy: ICD-10-CM code G90.8; unspecified disorder of the autonomic nervous system: G90.9; postural orthostatic tachycardia syndrome (POTS): G90.A (effective Oct 2022;

	earlier years captured under G90.9); SNOMED codes 27822007 and 312080002
Mast cell activation syndrome	ICD-10-CM codes D89.40, D89.41, D89.42, D89.43, D89.49; SNOMED code 783255005
Fibromyalgia	ICD-10-CM code M79.7; SNOMED code 24693007
Systemic lupus erythematosus	ICD-10-CM code M32* (excluding M32.0 drug-induced); SNOMED code 55464009
Dermatopolymyositis	ICD-10-CM code M33*; SNOMED codes 396230008 (dermatomyositis) and 31384009 (polymyositis)
Systemic sclerosis / scleroderma	ICD-10-CM code M34*; SNOMED code 89155008
Sjögren and other systemic CTD	Sjögren syndrome: ICD-10-CM code M35.0*; mixed CTD: M35.1; Behçet's disease: M35.2; diffuse fasciitis: M35.4; multifocal fibrosclerosis: M35.5; relapsing panniculitis: M35.6; other specified systemic CTD involvement: M35.89; unspecified: M35.9; systemic CT disorders in diseases classified elsewhere: M36.8
Kidney stones (negative control)	ICD-10-CM code N20.0; SNOMED code 95570007
Confounders (matching)	Age at index: 15–24, 25–44, 45–64, 65+ Count of **outpatient face-to-face encounters** during the study period: 1–5, 6–15, 16+ Evaluated sex
Model specifications	Descriptive analysis. Patients with a neurodivergent diagnosis were matched 1:4 with patients who did not have a neurodivergence diagnosis.
Limitations	Problem lists are inconsistent and might fail to reflect current clinical status. Older patients who began Epic-based care later in life may have incomplete charts, weakening ascertainment in the oldest age group. Exposure and outcome diagnoses can appear in any order and may predate the study period; this analysis measures correlation in a prevalent population and does not test causation or directionality. Patients had varying amounts of care during the study period. Neurodivergent patients tend to have more health care contact and more complete charts than comparison patients, which can inflate correlations with any chronic condition; matching on health care utilization and the use of negative-control conditions partially address this.

Table 1. Population Characteristics

Type	Subtype	Count	Percent
Total Population	Total Population	117,279,790	100.00
Age	15-24	14,938,190	12.74
	25-44	32,296,606	27.54
	45-64	34,360,506	29.30
	65+	35,684,488	30.43
Sex	Female	65,659,537	55.99
	Male	50,455,483	43.02

	Other	1,164,770	0.99
Healthcare Utilization	1-5	29,674,659	25.30
	16+	52,895,122	45.10
	6-15	34,710,009	29.60
Has Heritable Structural Disorder	0	117,034,890	99.79
	1	244,900	0.21
Has Hypermobility Spectrum Disorder	0	116,993,929	99.76
	1	285,861	0.24
Has Autoimmune CTD	0	115,267,021	98.28
	1	2,012,769	1.72
Has Kidney Stones	0	109,478,103	93.35
	1	7,801,687	6.65
Has ASD Only	0	116,820,903	99.61
	1	458,887	0.39
Has ADHD Only	0	110,390,833	94.13
	1	6,888,957	5.87
Has ASD and ADHD	0	116,850,408	99.63
	1	429,382	0.37

Table 2. Connective Tissue Disorder Rates by Neurodevelopmental Group

Exposure	Outcome	Group	N	Rate (%)
ASD only	Heritable Structural Disorder	Exposure Group	458,887	1.15
		Reference Group	1,835,548	0.28
	Hypermobility Spectrum Disorder	Exposure Group	458,887	1.11
		Reference Group	1,835,548	0.37
	Autoimmune CTD	Exposure Group	458,887	1.20
		Reference Group	1,835,548	0.83
	Kidney Stones	Exposure Group	458,887	4.08

		Reference Group	1,835,548	4.04
ADHD only	Heritable Structural Disorder	Exposure Group	6,672,855	0.77
		Reference Group	26,691,420	0.29
	Hypermobility Spectrum Disorder	Exposure Group	6,672,855	0.93
		Reference Group	26,691,420	0.37
	Autoimmune CTD	Exposure Group	6,672,855	2.02
		Reference Group	26,691,420	1.43
	Kidney Stones	Exposure Group	6,672,855	6.15
		Reference Group	26,691,420	5.16
Both ASD and ADHD	Heritable Structural Disorder	Exposure Group	429,382	2.11
		Reference Group	1,717,528	0.39
	Hypermobility Spectrum Disorder	Exposure Group	429,382	2.42
		Reference Group	1,717,528	0.55
	Autoimmune CTD	Exposure Group	429,382	1.43
		Reference Group	1,717,528	0.74
	Kidney Stones	Exposure Group	429,382	3.25
		Reference Group	1,717,528	2.99