

Neuropsychiatric associations in Duchenne and Becker Muscular Dystrophies: a TriNetX electronic health records study

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Introduction

Becker and Duchenne muscular dystrophies (BMD/DMD) are rare X-linked disorders caused by pathogenic variants in the DMD gene (Xp21.2), which encodes the dystrophin protein.

Dystrophin functions as a “shock absorber”, protecting muscle fibres from contraction-induced damage. Its absence leads to progressive muscle fibre loss, resulting in global motor delays from early childhood, progressive weakness, and loss of ambulation by adolescence. This progresses to cardiomyopathy and respiratory compromise, with life expectancy typically extending only into the third decade for males with DMD. BMD has a milder and more variable natural history than DMD, with life expectancy often approaching that of the general male population, although cardiac involvement remains clinically significant.

Beyond progressive neuromuscular degeneration, adverse neuropsychiatric outcomes are increasingly recognised across the lifespan; however, robust population-level estimates remain limited.

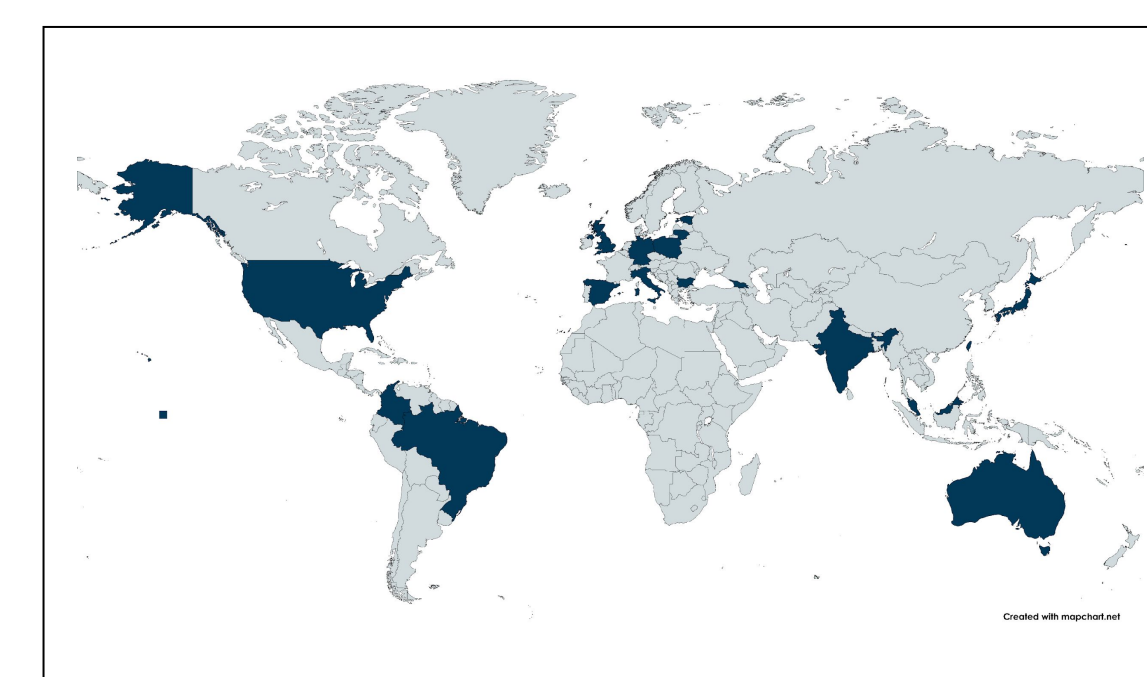
Dystrophin isoforms expressed in the central nervous system contribute to the stabilisation of synaptic GABA_A receptors, influence early brain development, and support astrocytic function. Dystrophinopathies disrupt inhibitory signalling and have been associated with altered emotional reactivity, fear processing, and cognitive function in both clinical and preclinical studies, contributing to increased rates of neuropsychiatric comorbidity. This represents an important unmet clinical need, with significant implications for development and quality of life in individuals with BMD/DMD.

Aim

- To estimate the prevalence of neuropsychiatric diagnoses in a large, real-world cohort of individuals with BMD/DMD.
- To compare neuropsychiatric burden in BMD/DMD with comparator groups, to help distinguish the effects of dystrophin disruption from those of chronic neuromuscular disease more broadly.

Method

- We performed a retrospective cohort study using the TriNetX electronic health records database, leveraging anonymised data from 161 international healthcare organisations



Map of countries in TriNetX network

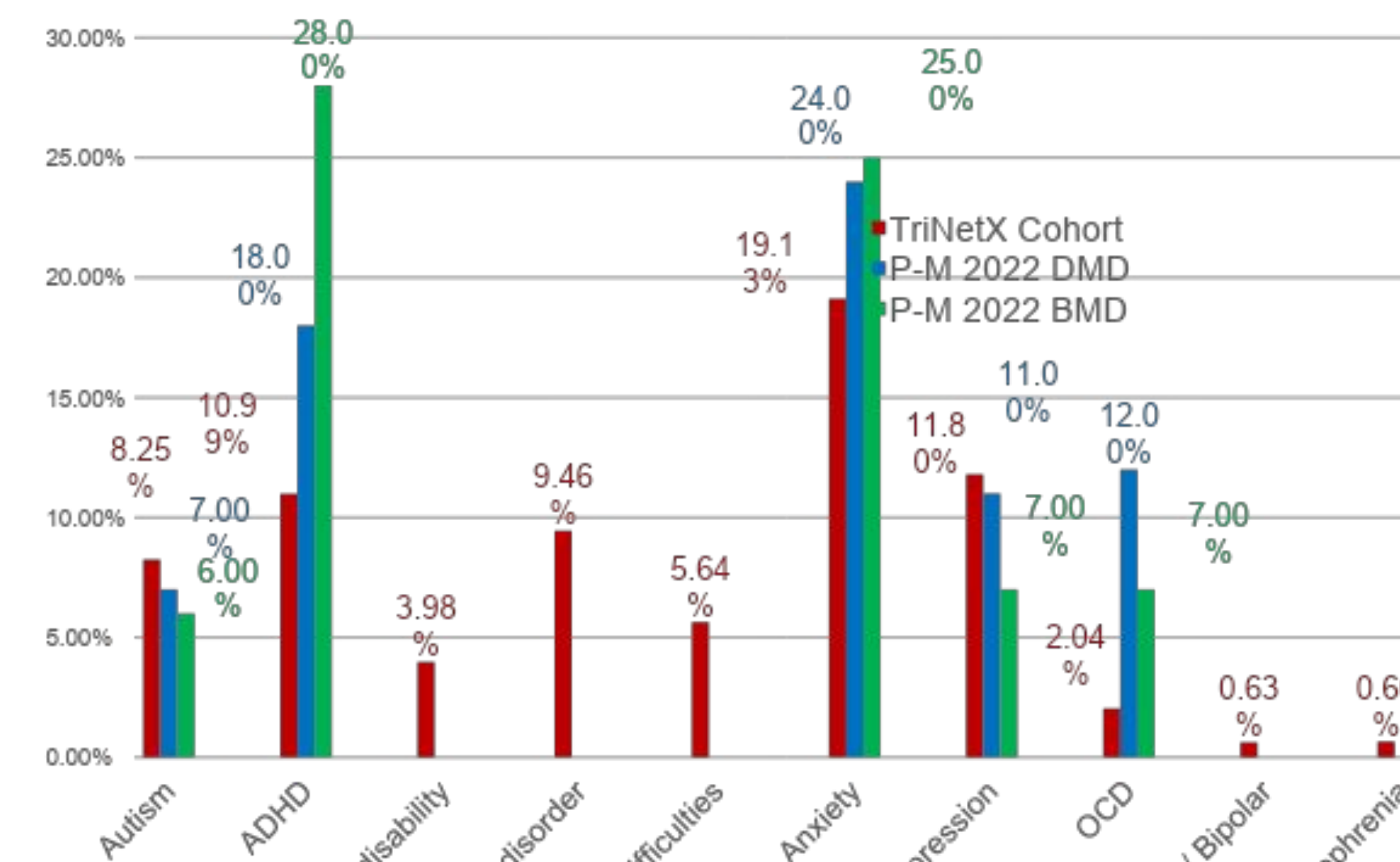
- A total of 7552 individuals with Duchenne or Becker muscular dystrophy were identified using ICD diagnostic codes.
- Comparator groups were:
 - Male healthcare controls with no major pathology coded at the index visit (ICD Z00)
 - Males with Limb Girdle Muscular Dystrophy (LGMD)
 - Female carriers of the DMD geneFurther analyses compared
 - LGMD males to healthcare controls
 - Female DMD carriers to healthcare controls
- Cohorts were propensity-score matched on age, sex, race, and socio-economic status
- Neuropsychiatric outcomes were extracted using ICD codes:

- Autism F84.0 + F84.5
- ADHD F90
- Intellectual disability F70-F79
- Language disorder F80
- Learning difficulties F81

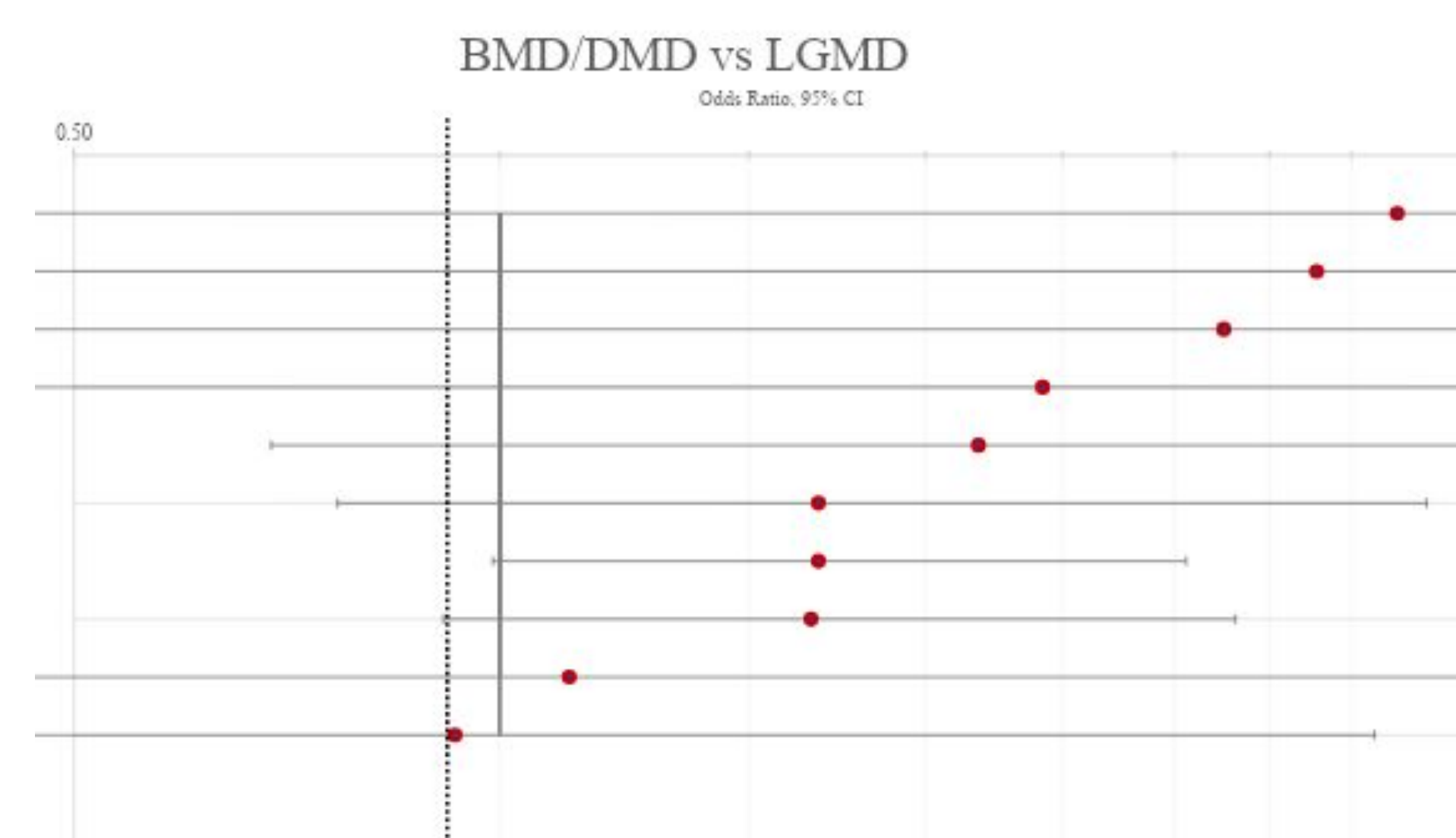
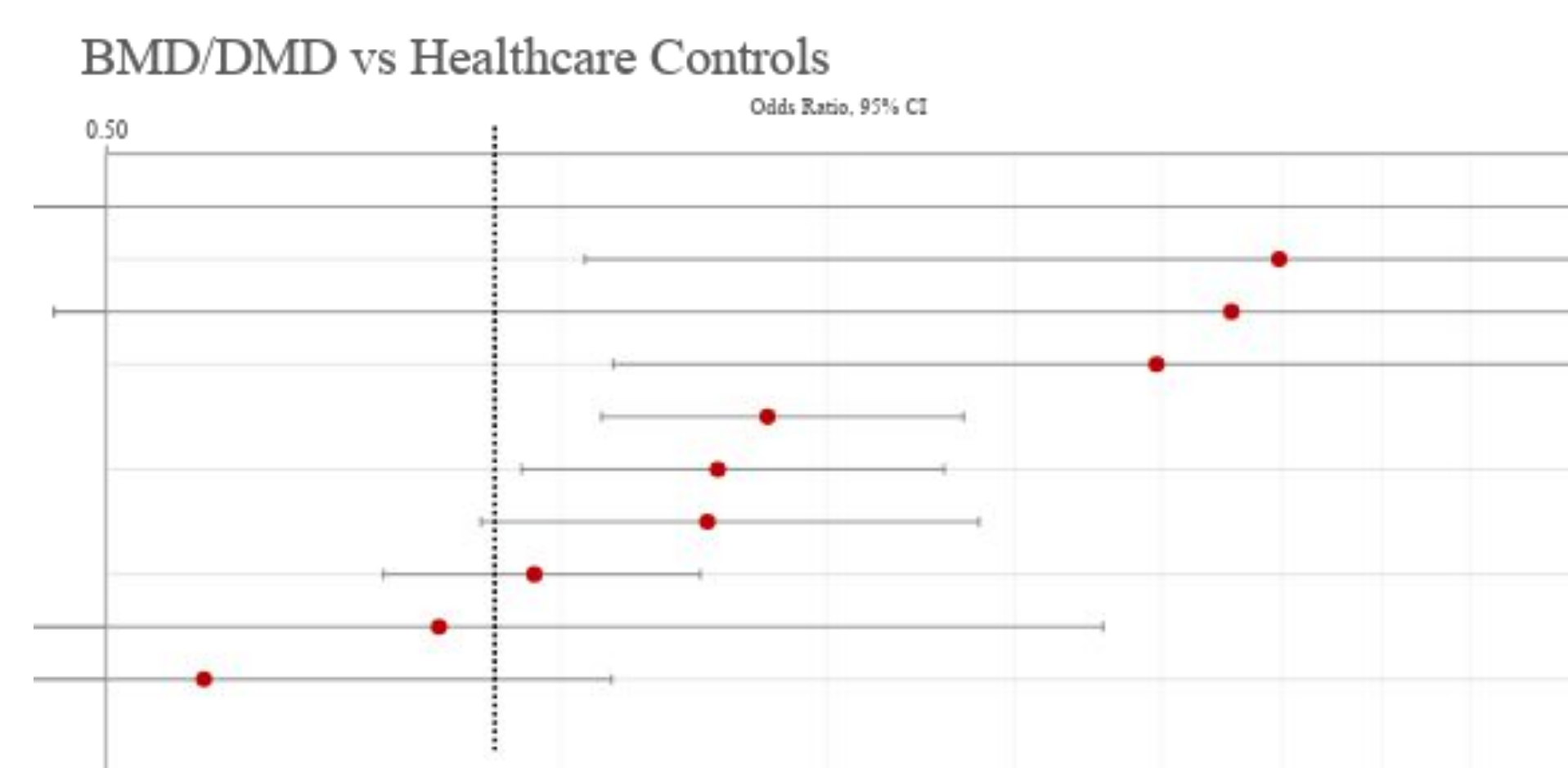
- Prevalence rates were calculated within each cohort, and odds ratios with 95% confidence intervals were derived for BMD/DMD versus each comparator group.
 - Depression F32, F33, F34
 - OCD F42
 - Mania/ Bipolar F30/F31
 - Schizophrenia F20-F29

Results

Prevalence rates for psychiatric comorbidities in individuals with BMD/DMD were: autism spectrum disorder (ASD) 8.25%; ADHD 10.99%; intellectual disability 3.98%; language disorder 9.46%; learning difficulties 5.64%; anxiety 19.13%; and depression 11.80%.



TriNetX cohort prevalence rates compared to rates of neuropsychiatric outcomes in DMD (blue) and BMD (green) in the largest published systematic review and meta-analysis to date (Pascual-Morena et al. 2022).



BMD/DMD showed strong enrichment for autism, intellectual disability, language disorder, learning difficulties, anxiety, depression and OCD compared to healthcare controls and LGMD. Surprisingly, odds of ADHD diagnosis were not elevated compared to healthcare controls but were increased relative to LGMD (OR 1.68) and female carriers (OR 1.64), suggesting that the signal is present but obscured by high background ADHD rates and ascertainment differences in the healthcare control group.

Compared with female carriers, individuals with BMD/DMD had higher odds of autism (OR 2.03), learning difficulties (OR 2.24) and OCD (OR 2.24), and lower odds of anxiety (0.83), depression (0.78) and bipolar disorder (0.31).

Female carriers showed increased odds of ASD (OR 1.48) and language disorder (OR 1.41) versus female healthcare controls.

LGMD males did not show increased neuropsychiatric risk compared to healthcare controls.

Conclusion

Neuropsychiatric disorders are substantially over-represented in Becker and Duchenne dystrophinopathies, with a distinct profile characterised by elevated rates of autism, intellectual disability, learning difficulties, ADHD and mood disorders.

Diagnostic overshadowing, ascertainment bias and reliance on ICD coding mean these electronic healthcare estimates likely underestimate true burden, underscoring the need to embed systematic neuropsychiatric screening and intervention into BMD/DMD standards of care to improve patient outcomes and quality of life.

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