**SUPPLEMENTARY MATERIAL**

**A meta-analysis of the prevalence of neuropsychiatric disorders and their association with disease onset in myotonic dystrophy**

**Acta Neuropsychiatrica**

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**Appendix S1**: Search strategy.

**Table S1.** Baseline characteristics of the participants included in the studies.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Country** | **NT** | **Inheritance** | | **Onset** | | | **CTG** | **Age** | **Outcomes** | | | |
| **NM** | **NP** | **NC** | **NJ** | **NA** | **ASD** | **ADHD** | **DEP** | **ANX** |
| **Myotonic dystrophy 1** | | | | | | | | | | | | | |
| Bungener C et al (1998) | France | 15 | - | - | - | - | 15 | 260 to 1000 | 36.8 ± 11.3 | - | - | ✓ | ✓ |
| Caso F et al (2014) | Serbia | 51 | - | - | 0 | 17 | 34 | 750 ± 276 | 42.0 ±10.0 | - | - | ✓ | ✓ |
| Colombo G et al (1992) | Italy | 40 | 12 | 24 | - | - | - | - | 39.9 | - | - | ✓ | ✓ |
| Cuthill J et al (1988) | Canada | 13 | - | - | - | - | - | - | 32.4 (21.0 to 49.0) | - | - | ✓ | ✓ |
| Di Costanzo A et al (2000) | Italy | 10 | - | - | 0 | 0 | 10 | - | 37.7 ± 13.5 | - | - | ✓ | - |
| Douniol M et al (2012) | France | 28 | 17 | 11 | 0 | 28 | 0 | 656 ± 326 | 17.0 ± 3.0 | ✓ | ✓ | ✓ | ✓ |
| Echenne B et al (2008) | France  Canada | 32 | 28 | 4 | 17 | 15 | 0 | 1155 ± 676 | - | ✓ | ✓ | ✓ | ✓ |
| Ekström AB et al (2008) | Sweeden | 57 | 45 | 10 | 37 | 18 | 2 | 550 to 1600 | C1: 9.2  C2: 13.2  J: 14.2  A: 16.4 | ✓ | ✓ | - | - |
| Ekström AB et al (2009) | Sweeden | 55 | 45 | 8 | 37 | 18 | 0 | 930 to 1600 | C1: 10.6  C2:11.9  J: 14.1 | ✓ | - | - | - |
| Fujino H et al (2018) | Japan | 60 | - | - | 0 | 21 | 39 | 1113 ± 1025 | 47.1 ± 10.8 | - | - | ✓ | - |
| Gallais B et al (2015) | France | 38 | - | - | 0 | 0 | 38 | 568 ± 341 | 36.0 ± 10.2 | - | - | ✓ | - |
| Geirdal AO et al (2015) | Norway | 13 | - | - | - | - | - | - | 40.9 ± 14.4 | - | - | ✓ | ✓ |
| Jacobs D et al (2017) | Belgium | 27 | - | - | 0 | 27 | 0 | 1600 ± 775 | 19.5 ± 2.7 | ✓ | ✓ | ✓ | ✓ |
| Johnson N et al (2016) | Canada  Sweden  US | 150 | 37 | 106 | 74 | 69 | 0 | 959.0 | 17.9 ± 10.2 | ✓ | ✓ | - | - |
| Kacem E et al (2021) | Tunisia | 20 | - | - | . | . | 20 | - | 40.0 (28 – 49) | - | - | ✓ | ✓ |
| Kalkman JS et al (2007) | Netherlands | 79 | - | - | 0 | 0 | 79 | - | 41 ± 9.9 | - | - | ✓ | ✓ |
| Kierkegaard M et al (2011) | Sweden | 70 | 24 | 33 | 0 | 12 | 58 | - | 45.0 ± 13.0 | - | - | ✓ | ✓ |
| Krogias C et al (2015) – 1 | Germany | 17 | - | - | - | 7 | 10 | 700 (70 to 1000) | 39.0 ± 15.0 | - | - | ✓ | - |
| Lagrue E et al (2019) | France | 314 | - | - | 155 | 126 | 0 | 846 ± 473 | 11.0 (5.0 – 15.0) | ✓ | - | - | - |
| Meloa G et al (2003) – 1 | Italy | 21 | - | - | 0 | 13 | 8 | 500 to 700 | 44.1 ± 9.5 | - | - | ✓ | ✓ |
| Miller JN et al (2021) | US | 39 | - | - | 0 | 0 | 39 | 146 (81 to 501) | 45.5 ± 9.0 | - | - | ✓ | - |
| Petra A et al (2023) | Norway | 20 | 10 | 5 | 5 | 15 | 0 | To 1600 | - | ✓ | - | - | - |
| Rakocevic Stojanovic V et al (2014) | Serbia | 66 | - | - | - | 22 | 44 | - | - | - | - | ✓ | ✓ |
| Rakocevic Stojanovic V et al (2016) – 1 | Serbia | 42 | - | - | 0 | 0 | 42 | - | 47.3 ± 7.2 | - | - | ✓ | - |
| Rubinsztein JS et al (1998) | UK | 36 | 12 | 20 | 0 | 5 | 30 | 300 to 4600 | 42.3 ± 12.3 | - | - | ✓ | - |
| Schneider-Gold C et al (2015) – 1 | Germany | 12 | - | - | 0 | 3 | 9 | 470.4 ± 238.2 | 45.0 ± 13.0 | - | - | ✓ | - |
| Seijas-Gomez R et al (2015) | Spain | 27 | - | - | 0 | 0 | 27 | - | 38,6 ± 9,2 | - | ✓ | ✓ | ✓ |
| Serra L et al (2015) | Italy | 10 | - | - | 1 | 1 | 8 | 534 ± 539 | 41.8 ± 9.6 | - | - | ✓ | ✓ |
| Steyaert J et al (1997) | Netherlands | 16 | 12 | 4 | 2 | 14 | 0 | 2086 ± 743 | 13.0 ± 3.2 | ✓ | ✓ | ✓ | ✓ |
| Stokes M et al (2019) | US | 74 | - | - | 52 | 22 | 0 | 143 to 2300 | - | ✓ | ✓ | - | - |
| Timman R et al (2010) | Netherlands | 69 | - | - | - | - | - | - | 45.6 | - | - | ✓ | ✓ |
| Urata Y et al (2020) | Japan | 4 | - | - | - | - | - | - | 27.0 ± 3.7 | ✓ | - | - | - |
| Van Heugten C et al (2018) | Netherlands | 66 | - | - | 0 | 0 | 66 | - | 47.0 ± 12.7 | - | - | ✓ | ✓ |
| Van Spaendonck KPM et al (1995) | Netherlands | 26 | 7 | 14 | 0 | - | - | - | 35.5 ± 10.3 | - | - | ✓ | - |
| Winblad S et al (2010) | Sweden | 31 | - | - | 0 | 0 | 31 | 578 ± 401 | 41.8 ± 9.5 | - | - | ✓ | - |
| **Myotonic dystrophy 2** | | | | | | | | | | | | | |
| Krogias C et al (2015) – 2 | Germany | 14 | - | - | - | 1 | 13 | - | 37.0 ± 11.0 | - | - | ✓ | - |
| Meloa G et al (1999) | Italy  US | 20 | - | - | 0 | 9 | 10 | - | - | - | - | ✓ | - |
| Meloa G et al (2003) – 2 | Italy | 19 | - | - | 0 | 0 | 19 | - | 55.7 ± 6.4 | - | - | ✓ | ✓ |
| Montagnese F et al (2020) | Germany | 66 | - | - | - | - | - | - | 54.8 ± 12.4 | - | - | ✓ | - |
| Rakocevic Stojanovic V et al (2016) – 2 | Serbia | 49 | - | - | 0 | 0 | 49 | - | 51.4 ± 10.8 | - | - | ✓ | - |
| Schneider-Gold C et al (2015) – 2 | Germany | 16 | - | - | - | - | 16 | - | 52.0 ± 7.0 | - | - | ✓ | - |
| Suokas KI et al (2012) | Finland | 93 | - | - | 0 | - | - | - | 53.0 (20 to 80) | - | - | ✓ | - |

Abbreviations: NT: Total sample size; NM: Sample size with maternal inheritance; NP: Sample size with paternal inheritance; NC: Sample size with congenital onset; NJ: Sample size with juvenile onset; NA: Sample size with adult onset; CTG: mean (or median if mean is not available) of CTG repeats

**Table S2.** Studies excluded for justified reasons.

|  |  |
| --- | --- |
| **Reference** | **Main reason** |
| D’Alessandro R et al (2021) | Not outcome of interest |
| Gosar D et al (2021) | Not outcome of interest |
| Kim HJ et al (2019) | Not outcome of interest |
| Tanaka H et al (2012) | Not outcome of interest |
| Tuikka RA et al (1993) | Not outcome of interest |
| Woo J et al (2019) | Not outcome of interest |
| Zalonis I et al (2010) | Not population of interest |

Supplementary references

D’alessandro, R., Ragusa, N., Vacchetti, M., Rolle, E., Rossi, F., Brusa, C., *et al.* (2021) Assessing cognitive function in neuromuscular diseases: A pilot study in a sample of children and adolescents, *Journal of Clinical Medicine*, 10 (20). DOI:10.3390/jcm10204777.

Gosar, D., Košmrlj, L., Musek, P. L., Meško, T., Stropnik, S., Krkoč, V., *et al.* (2021) Adaptive skills and mental health in children and adolescents with neuromuscular diseases., *European Journal of Paediatric Neurology : EJPN : Official Journal of the European  Paediatric Neurology Society*, 30, pp. 134–143. DOI:10.1016/j.ejpn.2020.10.008.

Kim, H. J., Na, J.-H. and Lee, Y.-M. (2019) Genotype-phenotype correlations in pediatric patients with myotonic dystrophy type 1, *Korean Journal of Pediatrics*, 62 (2), pp. 55–61. DOI:10.3345/KJP.2018.06919.

Tanaka, H., Arai, M., Harada, M., Hozumi, A. and Hirata, K. (2012) Cognition and event-related potentials in adult-onset non-demented myotonic dystrophy type 1, *Clinical Neurophysiology*, 123 (2), pp. 261–269. DOI:10.1016/j.clinph.2011.06.012.

Tuikka, R. A., Laaksonen, R. K. and Somer, H. V (1993) Cognitive function in myotonic dystrophy: a follow-up study., *European Neurology*, 33 (6), pp. 436–441. DOI:10.1159/000116989.

Woo, J., Lee, H.-W. and Park, J.-S. (2019) Differences in the pattern of cognitive impairments between juvenile and adult onset myotonic dystrophy type 1., *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society  of Australasia*, 68, pp. 92–96. DOI:10.1016/j.jocn.2019.07.029.

Zalonis, I., Bonakis, A., Christidi, F., Vagiakis, E., Papageorgiou, S. G., Kalfakis, N., Manta, P. and Vassilopoulos, D. (2010) Toward understanding cognitive impairment in patients with myotonic dystrophy type 1, *Archives of Clinical Neuropsychology*, 25 (4), pp. 303–313. DOI:10.1093/arclin/acq016.

**Table S3.** Classification of participants by myotonic dystrophy onset.

|  |  |  |  |
| --- | --- | --- | --- |
| **Reference** | **MD form** | **Included onsets** | **Classification** |
| Bungener C et al (1998) | DM1 | The patients had been diagnosed >17 years | Adult (Some cases of juvenile onset cannot be ruled out) |
| Caso F et al (2014) | DM1 | Childhood/Juvenile: <20 years  Adult: ≥20 years | Juvenile + Adult |
| Colombo G et al (1992) | DM1 | Not specified | Not specified |
| Cuthill J et al (1988) | DM1 | Not specified | Not specified |
| Di Costanzo A et al (2000) | DM1 | Adult: ranges of age not specified | Adult |
| Douniol M et al (2012) | DM1 | Onset between 1 and 10 years | Juvenile |
| Echenne B et al (2008) | DM1 | Congenital: at neonatal period  Juvenile: infantile + juvenile | Congenital + Juvenile |
| Ekström AB et al (2008) | DM1 | Congenital: at utero or birth  Childhood: 1-10 years  Classic: At or after adolescence | All |
| Ekström AB et al (2009) | DM1 | Congenital: at utero or birth  Childhood: 1-10 years | Congenital + Juvenile |
| Fujino H et al (2018) | DM1 | Infantile: 1 month to 10 years  Juvenile: 11–20 years  Adult: 21–40 years  Late onset: >40 years | Juvenile + Adult |
| Gallais B et al (2015) | DM1 | Adult or late-onset: the study included participants with 21 to 60 years | Adult |
| Geirdal AO et al (2015) | DM1 | Not specified | Not specified |
| Jacobs D et al (2017) | DM1 | Juvenile: <12 years, but not at birth | Juvenile |
| Johnson N et al (2016) | DM1 | Congenital: <1 year  Childhood: 1-10 years  Juvenile: 11-17 years | Congenital + Juvenile |
| Kacem E et al (2021) | DM1 | Adult onset: reported by authors | Adult |
| Kalkman JS et al (2007) | DM1 | Adult onset | Adult |
| Kierkegaard M et al (2011) | DM1 | Includes childhood and adult onsets, but does not specify the age ranges at the onset | Juvenile + Adult |
| Krogias C et al (2015) | DM1 and DM2 | Juvenile: ≤15 years  Adult: >15 years | Juvenile + Adult |
| Lagrue E et al (2019) | DM1 | Congenital: at birth or during the first month  Infantile: 1–10 years  Juvenile: 10–18 years  Adult  Late-onset | Congenital + Juvenile |
| Meloa G et al (1999) | DM2 | Not classified, but included participants have an onset from the second decade of life. | Juvenile + Adult |
| Meloa G et al (2003) – 1 | DM1 | Not classified, but included participants have an onset from the first decade of life. | Congenital + Juvenile |
| Meloa G et al (2003) – 2 | DM2 | Not classified, but included participants have an onset from the second decade of life. | Adult |
| Miller JN et al (2021) | DM1 | Adult: >18 years | Adult |
| Montagnese F et al (2020) | DM2 | Not specified, presumably adults | Adult |
| Petra A et al (2023) | DM1 | Congenital: < 1 month  Infantile: 1 month to 10 years  Juvenile: 10 to 20 years | Congenital + Juvenile |
| Rakocevic Stojanovic V et al (2014) | DM1 | Juvenile: <20 years (without congenital)  Adult: ≥20 years (without late-onset) | Juvenile + Adult |
| Rakocevic Stojanovic V et al (2016) | DM1 and DM2 | Adult (participants with DM1 are presumably those of Rakocevic Stojanovic V et al (2014)) | Adult |
| Rubinsztein JS et al (1998) | DM1 | Juvenile: 10 to 17 years  Adult: ≥18 years | Juvenile + Adult |
| Schneider-Gold C et al (2015) | DM1 and DM2 | Juvenile: 14 to 20 years  Adult: >20 years | Juvenile + Adult (DM1)  Adult (DM2) |
| Seijas-Gomez R et al (2015) | DM1 | Adult: Not specified age range | Adult |
| Serra L et al (2015) | DM1 | Congenital: Not specified age range  Childhood: Not specified age range  Adult: Not specified age range | All |
| Steyaert J et al (1997) | DM1 | Congenital: at birth  Juvenile: <10 years | Congenital + Juvenile |
| Stokes M et al (2019) | DM1 | Congenital: at birth  Infantile: <10 years  Juvenile: >10 years | Congenital + Juvenile |
| Suokas KI et al (2012) | DM2 | Onset from 6 to 69 years | All |
| Timman R et al (2010) | DM1 | Not specified | Not specified |
| Urata Y et al (2020) | DM1 | Not specified | Not specified |
| Van Heugten C et al (2018) | DM1 | Adult: >18 years | Adult |
| Van Spaendonck KPM et al (1995) | DM1 | Onset between 11 to 40 years | Juvenile + Adult |
| Winblad S et al (2010) | DM1 | Onset between 15 to 50 years | Adult |

**Table S4.** Diagnostic criteria or scales used.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **ASD** | **ADHD** | **Depression disorders** | **Anxiety disorders** |
| Bungener C et al (1998) | - | - | DSM III-R | DSM III-R |
| Caso F et al (2014) | - | - | HDRS (score ≥17) | HARS (score ≥18) |
| Colombo G et al (1992) | - | - | RDC | RDC |
| Cuthill J et al (1988) | - | - | SDS, HDRS (score ≥18) | HARS (score ≥16) |
| Di Costanzo A et al (2000) | - | - | DSM-III-R, HDRS | - |
| Douniol M et al (2012) | DSM-IV, Autism Mental Status Examination, Autism Diagnostic Interview-Revised | DSM-IV, ADHD section of the Diagnostic Interview Schedule for Children IV, Adult ADHD Self-Report Scale | DSM-IV, Children’s Depression Inventory, BDI, HDRS | DSM-IV, STAI |
| Echenne B et al (2008) | DSM-IV | NS | NS | NS |
| Ekström AB et al (2008) | DSM-IV | DSM-IV | - | - |
| Ekström AB et al (2009) | DSM-IV | - | - | - |
| Fujino H et al (2017) | - | - | PHQ-9 | - |
| Gallais B et al (2015) | - | - | MINI | - |
| Geirdal AO et al (2015) | - | - | HADS (score >7) | HADS (score >7) |
| Jacobs D et al (2017) | DSM-IV | DSM-IV | DSM-IV | DSM-IV |
| Johnson N et al (2016) | Self-reported | Self-reported | - | - |
| Kacem E et al (2021) | - | - | HADS | HADS |
| Kalkman JS et al (2007) | - | - | DSM-IV, BDI, SCL-90, GFQ-12 | DSM-IV, SCL-90 |
| Kierkegaard M et al (2011) | - | - | HADS (score >10) | HADS (score >10) |
| Krogias C et al (2015) | - | - | BDI-II (score ≥20) | - |
| Lagrue E et al (2019) | DSM-V | - | - | - |
| Meloa G et al (1999) | - | - | DSM-IV | - |
| Meloa G et al (2003) | - | - | DSM-IV | DSM-IV |
| Miller JN et al (2021) | - | - | BDI-II | - |
| Montagnese F et al (2020) | - | - | BDI-II (score ≥20) | - |
| Petra A et al (2023) | ICD-10 | - | - | - |
| Rakocevic Stojanovic V et al (2014) | - | - | HDRS (score ≥17) | HARS (score ≥18) |
| Rakocevic Stojanovic V et al (2016) | - | - | HDRS (score ≥17) | - |
| Rubinsztein JS et al (1998) | - | - | SADS-L | - |
| Schneider-Gold C et al (2015) | - | - | BDI-II (score ≥20) | - |
| Seijas-Gomez R et al (2015) | - | Conners’ Performance Test II | BDI-II, SCL-90 | HARS |
| Serra L et al (2015) | - | - | BDI (score ≥15) | HARS (score ≥18) |
| Steyaert J et al (1997) | CARS | DSM-III, ADIKA | CDS, BDI | NS |
| Stokes M et al (2019) | Medical records | Medical records | - | - |
| Suokas KI et al (2012) | - | - | RBDI | - |
| Timman R et al (2010) | - | - | HADS (score >7) | HADS (score >7) |
| Urata Y et al (2020) | Medical records | - | - | - |
| Van Heugten C et al (2018) | - | - | HADS (score >7) | HADS (score >7) |
| Van Spaendonck KPM et al (1995) | - | - | ZDS | - |
| Winblad S et al (2010) | - | - | BDI (score ≥10) | - |

**Table S5.** Estimates of the prevalence of neuropsychiatric disorders in the included studies.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Prevalence** | | | |
| **ASD** | **ADHD** | **DEP** | **ANX** |
| **Myotonic dystrophy 1** | | | | |
| Bungener C et al (1998) | - | - | 0.07 (0.01, 0.30) | 0.00 |
| Caso F et al (2014) | - | - | 0.20 (0.11, 0.32) | 0.14 (0.07, 0.26) |
| Colombo G et al (1992) | - | - | 0.20 (0.11, 0.32) | 0.08 (0.03, 0.20) |
| Cuthill J et al (1988) | - | - | 0.23 (0.08, 0.50) | 0.08 (0.01, 0.33) |
| Di Costanzo A et al (2000) | - | - | 0.10 (0.02, 0.40) | - |
| Douniol M et al (2012) | 0.00 | 0.29 (0.15, 0.47) | 0.21 (0.10, 0.40) | 0.43 (0.27, 0.61) |
| Echenne B et al (2008) | 0.03 (0.01, 0.16) | 0.34 (0.20, 0.52) | 0.03 (0.01, 0.16) | 0.09 (0.03, 0.24) |
| Ekström AB et al (2008) | 0.49 (0.37, 0.62) | 0.41 (0.22, 0.64) | - | - |
| Ekström AB et al (2009) | 0.49 (0.37, 0.62) | - | - | - |
| Fujino H et al (2018) | - | - | 0.23 (0.14, 0.35) | - |
| Gallais B et al (2015) | - | - | 0.24 (0.13, 0.39) | - |
| Geirdal AO et al (2015) | - | - | 0.15 (0.04, 0.42) | 0.31 (0.13, 0.58) |
| Jacobs D et al (2017) | 0.15 (0.06, 0.62) | 0.19 (0.08, 0.37) | 0.04 (0.01, 0.18) | 0.00 |
| Johnson N et al (2016) | 0.22 (0.16, 0.29) | 0.18 (0.13, 0.25) | - | - |
| Kacem E et al (2021) | - | - | 0.25 (0.11, 0.47) | 0.25 (0.11, 0.47) |
| Kalkman JS et al (2007) | - | - | 0.22 (0.14, 0.32) | 0.16 (0.10, 0.26) |
| Kierkegaard M et al (2011) | - | - | 0.00 | 0.07 (0.03, 0.16) |
| Krogias C et al (2015) – 1 | - | - | 0.06 (0.01, 0.27) | - |
| Lagrue E et al (2019) | 0.05 (0.02, 0.11) | - | - | - |
| Meloa G et al (2003) – 1 | - | - | 0.00 | 0.00 |
| Miller JN et al (2021) | - | - | 0.10 (0.04, 0.24) | - |
| Petra A et al (2023) | 0.15 (0.05, 0.36) | - | - | - |
| Rakocevic Stojanovic V et al (2014) | - | - | 0.15 (0.08, 0.26) | 0.11 (0.05, 0.20) |
| Rakocevic Stojanovic V et al (2016) – 1 | - | - | 0.24 (0.13, 0.39) | - |
| Rubinsztein JS et al (1998) | - | - | 0.06 (0.02, 0.18) | - |
| Schneider-Gold C et al (2015) – 1 | - | - | 0.08 (0.01, 0.35) | - |
| Seijas-Gomez R et al (2015) | - | 0.04 (0.01, 0.18) | 0.19 (0.08, 0.37) | 0.00 |
| Serra L et al (2015) | - | - | 0.00 | 0.00 |
| Steyaert J et al (1997) | 0.06 (0.01, 0.28) | 0.31 (0.14, 0.56) | 0.13 (0.03, 0.36) | 0.19 (0.07, 0.43) |
| Stokes M et al (2019) | 0.05 (0.02, 0.13) | 0.38 (0.27, 0.49) | - | - |
| Timman R et al (2010) | - | - | 0.14 (0.08, 0.25) | 0.16 (0.09, 0.26) |
| Urata Y et al (2020) | 0.25 (0.05, 0.70) | - | - | - |
| Van Heugten C et al (2018) | - | - | 0.18 (0.11, 0.29) | 0.30 (0.21, 0.42) |
| Van Spaendonck KPM et al (1995) | - | - | 0.00 | - |
| Winblad S et al (2010) | - | - | 0.32 (0.19, 0.50) | - |
| **Myotonic dystrophy 2** | | | | |
| Krogias C et al (2015) – 2 | - | - | 0.21 (0.08, 0.48) | - |
| Meloa G et al (1999) | - | - | 0.10 (0.03, 0.30) | - |
| Meloa G et al (2003) – 2 | - | - | 0.00 | 0.00 |
| Montagnese F et al (2020) | - | - | 0.21 (0.13, 0.33) | - |
| Rakocevic Stojanovic V et al (2016) – 2 | - | - | 0.08 (0.03, 0.19) | - |
| Schneider-Gold C et al (2015) – 2 | - | - | 0.25 (0.10, 0.49) | - |
| Suokas KI et al (2012) | - | - | 0.18 (0.12, 0.27) | - |

**Table S6.** Risk of bias assessment.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** |
| Bungener C et al (1998) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Caso F et al (2014) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Colombo G et al (1992) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cuthill J et al (1988) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Di Costanzo A et al (2000) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Douniol M et al (2012) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Echenne B et al (2008) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ekström AB et al (2008) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ekström AB et al (2009) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fujino H et al (2018) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Gallais B et al (2015) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Geirdal AO et al (2015) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Jacobs D et al (2017) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Johnson N et al (2016) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kacem E et al (2021) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kalkman JS et al (2007) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kierkegaard M et al (2011) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Krogias C et al (2015) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lagrue E et al (2019) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Meloa G et al (1999) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Meloa G et al (2003) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Miller JN et al (2021) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Montagnese F et al (2020) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Petra A et al (2023) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Rakocevic Stojanovic V et al (2014) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Rakocevic Stojanovic V et al (2016) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Rubinsztein JS et al (1998) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Schneider-Gold C et al (2015) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Seijas-Gomez R et al (2015) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serra L et al (2015) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Steyaert J et al (1997) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stokes M et al (2019) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Suokas KI et al (2012) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Timman R et al (2010) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urata Y et al (2020) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Van Heugten C et al (2018) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Van Spaendonck KPM et al (1995) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Winblad S et al (2010) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Assessment of risk of bias for observational studies with 'Study Quality Assessment Tools'. Green: good/low risk; Red: poor/high risk; Yellow: fair/some concerns/not available/not applicable

Items for Study Quality Assessment Tools:

1. Was the research question or objective in this paper clearly stated?

2. Was the study population clearly specified and defined?

3. Was the participation rate of eligible persons at least 50%?

4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

5. Was a sample size justification, power description, or variance and effect estimates provided?

6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?

7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

10. Was the exposure(s) assessed more than once over time?

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

12. Were the outcome assessors blinded to the exposure status of participants?

13. Was loss to follow-up after baseline 20% or less?

14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

15. Overall bias: good, fair, or poor. If poor, it need a justification.

**Table S7.** Quality of evidence assessment.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Certainty assessment | | | | | | | Effect Size | Certainty |
| № of studies | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 1. ASD – Congenital vs. Juvenile | | | | | | | | |
| 5 | Observational studies | Not serious | Not serious | Not serious | Not serious | Large effect | PR = 1.79 (1.12, 2.87) | Moderate |
| 1. ADHD – Congenital vs Juvenile | | | | | | | | |
| 5 | Observational studies | Not serious | Serious | Not serious | Not serious | None | PR = 0.66 (0.43, 1.03) | Very low |
| 1. ASD – Congenital vs. Childhood | | | | | | | | |
| 5 | Observational studies | Not serious | Not serious | Not serious | Serious | None | PR = 1.98 (0.66, 5.94) | Very low |
| 1. ASD – Childhood vs. Juvenile (without Childhood) | | | | | | | | |
| 3 | Observational studies | Not serious | Serious | Not serious | Serious | None | PR = 2.04 (0.16, 25.36) | Very low |
| 1. ADHD – Congenital vs. Childhood | | | | | | | | |
| 5 | Observational studies | Not serious | Serious | Not serious | Not serious | None | PR = 0.69 (0.44, 1.07) | Very low |
| 1. ADHD – Childhood vs. Juvenile (without Childhood) | | | | | | | | |
| 2 | Observational studies | Not serious | Serious | Not serious | Not serious | None | PR = 1.44 (0.44, 4.75) | Very low |

**Table S8.** Sensitivity analyses.

1. Autism spectrum disorders

|  |  |  |
| --- | --- | --- |
| **Study omitted** | **Estimate** | **95% Confidence interval** |
| 1 | -2.0393078 | -2.6801271, -1.3984884 |
| 2 | -1.9351264 | -2.5825708, -1.2876821 |
| 3 | -2.2577462 | -2.8410206, -1.674472 |
| 4 | -2.06493 | -2.7673483, -1.3625119 |
| 5 | -2.1855605 | -3.1019111, -1.26921 |
| 6 | -1.8679143 | -2.4908066, -1.2450221 |
| 7 | -2.0636997 | -2.7594121, -1.3679873 |
| 8 | -1.9861959 | -2.6477346, -1.3246572 |
| 9 | -1.9036084 | -2.5482461, -1.2589706 |
| **Combined** | **-2.0393078** | **-2.6801271, -1.3984884** |

1. Attention deficit hyperactivity disorder

|  |  |  |
| --- | --- | --- |
| **Study omitted** | **Estimate** | **95% Confidence interval** |
| 1 | -1.5355623 | -1.9703227, -1.1008018 |
| 2 | -1.5735401 | -2.0112276, -1.1358527 |
| 3 | -1.3458239 | -1.6816951, -1.0099525 |
| 4 | -1.4639229 | -1.8754354, -1.0524104 |
| 5 | -1.4374459 | -1.8567942, -1.0180974 |
| 6 | -1.4132715 | -1.7713248, -1.0552183 |
| 7 | -1.5362777 | -1.957039, -1.1155163 |
| 8 | -1.5874553 | -1.9874219, -1.1874887 |
| **Combined** | **-1.4815742** | **-1.8574767, -1.1056717** |

1. Depression

|  |  |  |
| --- | --- | --- |
| **Study omitted** | **Estimate** | **95% Confidence interval** |
| **Myotonic dystrophy 1** | | |
| 1 | -1.6842948 | -1.8576325, -1.5109571 |
| 2 | -1.6991044 | -1.8845631, -1.5136456 |
| 3 | -1.707101 | -1.8883747, -1.5258273 |
| 4 | -1.6922839 | -1.8697481, -1.5148195 |
| 5 | -1.7099042 | -1.8941734, -1.525635 |
| 6 | -1.6631293 | -1.822665, -1.5035936 |
| 7 | -1.724934 | -1.9106188, -1.5392493 |
| 8 | -1.7187197 | -1.9024341, -1.5350053 |
| 9 | -1.6969925 | -1.8774601, -1.5165249 |
| 10 | -1.6687375 | -1.832186, -1.5052891 |
| 11 | -1.7130605 | -1.8940398, -1.5320814 |
| 12 | -1.722474 | -1.91312, -1.5318279 |
| 13 | -1.6936167 | -1.8670224, -1.5202112 |
| 14 | -1.6814114 | -1.8530601, -1.5097625 |
| 15 | -1.6936167 | -1.8670224, -1.5202112 |
| 16 | -1.6700374 | -1.842643, -1.4974319 |
| 17 | -1.6828506 | -1.8672476, -1.4984536 |
| 18 | -1.6594683 | -1.8206835, -1.4982531 |
| 19 | -1.6889365 | -1.8647907, -1.5130823 |
| 20 | -1.7022489 | -1.886242, -1.5182557 |
| 21 | -1.6936167 | -1.8670224, -1.5202112 |
| 22 | -1.6913779 | -1.870146, -1.5126096 |
| **Combined** | **-1.6936168** | **-1.8670223, -1.5202112** |
| **Myotonic dystrophy 2** | | |
| 1 | -1.7234367 | -2.0309012, -1.4159721 |
| 2 | -1.6723242 | -1.9439124, -1.400736 |
| 3 | -1.7723911 | -2.1039257, -1.4408566 |
| 4 | -1.6277061 | -1.9050337, -1.3503783 |
| 5 | -1.734743 | -2.0199914, -1.4494945 |
| 6 | -1.724615 | -2.111686, -1.337544 |
| **Combined** | **-1.698117** | **-1.9640899, -1.4321441** |

1. Anxiety

|  |  |  |
| --- | --- | --- |
| **Study omitted** | **Estimate** | **95% Confidence interval** |
| **Myotonic dystrophy 1** | | |
| 1 | -1.8018398 | -2.173867, -1.4298128 |
| 2 | -1.7433599 | -2.118777, -1.3679428 |
| 3 | -1.7783674 | -2.1573472, -1.3993876 |
| 4 | -1.9030588 | -2.2483649, -1.5577527 |
| 5 | -1.7620654 | -2.145226, -1.3789048 |
| 6 | -1.865039 | -2.2635572, -1.4665208 |
| 7 | -1.8018398 | -2.173867, -1.4298128 |
| 8 | -1.7760715 | -2.1601326, -1.3920105 |
| 9 | -1.8158474 | -2.2346413, -1.3970534 |
| 10 | -1.7130085 | -2.0770733, -1.3489438 |
| 11 | -1.8018398 | -2.173867, -1.4298128 |
| 12 | -1.7532958 | -2.1396766, -1.3669149 |
| **Combined** | **-1.8018399** | **-2.173867, -1.4298127** |

**Table S9.** Meta-regressions for the prevalence of neuropsychiatric disorders (in natural logarithm) and mean CTG repeats.

|  |  |  |
| --- | --- | --- |
| **Outcome** | **Slope (95% CI)** | **p-value** |
| Autism spectrum disorders | -0.0002 (-0.0023, 0.0019) | 0.830 |
| Attention deficit hyperactivity disorder | 0.0000 (-0.0009, 0.0011) | 0.894 |
| Depression | -0.0003 (-0.0014, 0.0007) | 0.521 |
| Anxiety | -0.0005 (-0.0124, 0.0114) | 0.696 |

**Figure S1.** Meta-analysis of depression in DM1 and DM2 by onset.

Gráfico

Descripción generada automáticamente

**Figure S2.** Meta-analysis of anxiety in DM1 by onset.

Gráfico

Descripción generada automáticamente

**Figure S3.** Meta-analysis of ASD prevalence-onset association through prevalence ratio considering childhood and juvenile onset.

Gráfico

Descripción generada automáticamente

**Figure S4.** Meta-analysis of ADHD prevalence-onset association through prevalence ratio considering childhood and juvenile onset.

Gráfico, Gráfico de cajas y bigotes

Descripción generada automáticamente

**Figure S5.** Funnel plots of primary outcomes.

1. Funnel plot of ASDs.

Gráfico, Gráfico de dispersión

Descripción generada automáticamente

1. Funnel plot of ADHD.

Gráfico, Gráfico de líneas, Gráfico de dispersión

Descripción generada automáticamente

1. Funnel plot of depression in DM1.

Gráfico, Gráfico de dispersión

Descripción generada automáticamente

1. Funnel plot of depression in DM2.

Gráfico, Gráfico de dispersión

Descripción generada automáticamente

1. Funnel plot of anxiety in DM1.

Gráfico, Gráfico de dispersión

Descripción generada automáticamente

**Appendix S1**: Search strategy.

* Medline, Scopus, Web of Science, Cochrane Library

("myotonic dystrophy" OR "Steinert myotonic dystrophy" OR “myotonic dystrophy type 1” OR “type 1 myotonic dystrophy” OR “myotonic dystrophy type 2” OR “type 2 myotonic dystrophy”) AND (“cognitive profile” OR “cognitive function” OR “psychological profile” OR “mental disorders” OR “mental health” OR “neurodevelopmental” OR “developmental” OR “psychiatric” OR “autism” OR "attention deficit hyperactivity disorder" OR “adhd” OR “depression” OR “anxiety”)

* Grey literature

Not specified.