



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


Review Article

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Abstract

There is a high prevalence of neuropsychiatric disorders in myotonic dystrophy types 1 and 2 (DM1 and DM2), including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) in DM1, and depression and anxiety in both DMs. The aim of this systematic review and meta-analysis was to estimate the prevalence of ASD, ADHD, depression and anxiety in the population with DM, and their association with disease onset. A systematic search of Medline, Scopus, Web of Science, and the Cochrane Library was conducted from inception to November 2023. Observational studies estimating the prevalence of these disorders in DM1 or DM2 were included. A meta-analysis of the prevalence of these disorders and an association study with disease onset by prevalence ratio meta-analysis were performed. Thirty-eight studies were included. In DM1, the prevalence of ASD was 14%, with congenital onset being 79% more common than juvenile onset, while the prevalence of ADHD was 21%, with no difference between congenital and juvenile onset, and the prevalence of depression and anxiety were 14% and 16%. Depression was more common in the adult onset. Finally, the prevalence of depression in DM2 was 16%. A higher prevalence of neuropsychiatric disorders is observed in individuals with DM1 and DM2 than in the general population. Therefore, actively screening for congenital and juvenile neurodevelopmental disorders in DM1 and emotional disorders in DM1 and DM2 may improve the quality of life of those affected.

Summations

- Neurodevelopmental disorders were common in both congenital and juvenile-onset myotonic dystrophy type 1.
- The risk of autism spectrum disorders is higher in congenital onset myotonic dystrophy type 1 than in juvenile onset.
- Emotional disorders are common in both myotonic dystrophy types 1 and 2 and are also more common in adult-onset myotonic dystrophy type 1.

Considerations

- The number of studies and sample sizes limit some estimates, such as the association between disease onset and prevalence of attention deficit hyperactivity disorder.
- The classification of disease onset varies between authors and/or time periods, which may slightly affect the estimates from the meta-analyses.

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Introduction

Myotonic dystrophies (DMs) are genetic, dominant, and progressive diseases, with a prevalence of 10 cases per 100,000 inhabitants (Machuca-Tzili *et al.*, 2005; Liao *et al.*, 2022). There are two types of DMs, type 1 or Steinert DM (DM1), caused by pathological CTG triplet expansions in the 3' untranslated region of the 'myotonic dystrophy protein kinase' (*DMPK*) gene and type

2 DM (DM2), with CCTG tetranucleotide expansions in intron 1 of the 'zinc finger protein 9' (*ZNF9*) gene (Machuca-Tzili *et al.*, 2005; Kumar *et al.*, 2013). The mRNA of these genes ultimately affects the expression, translation, and function of other proteins (Kumar *et al.*, 2013). Both dystrophies present with progressive muscular dystrophy and weakness, myotonia, cataracts, and cardiac involvement. However, the symptoms of DM1 are more severe, with the phenomenon of 'anticipation' in maternal inheritance, whereas DM2 has predominantly proximal muscle involvement and no well-established 'anticipation' (Day *et al.*, 2003; Kumar *et al.*, 2013; Russo *et al.*, 2020; Wahbi and Furling, 2020; Rautemaa *et al.*, 2021). These patients need to be followed up by a multidisciplinary team to determine the necessary interventions, such as treatment for apnoea, cardiac problems or genetic counselling, among others (Smith and Gutmann, 2016; Rautemaa *et al.*, 2021).

In addition to neuromuscular disease, DM, especially DM1, is associated with several cognitive, personality, and neuropsychiatric disorders, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), depressive disorders and anxiety. These disorders have been linked to CTG triplet expansion, which ultimately leads to changes in gene expression, neuroplasticity, and brain areas and circuits involved in social communication, behaviour, attention, and motor activity (Peric *et al.*, 2017; Wenninger *et al.*, 2018; Gutiérrez Gutiérrez *et al.*, 2020; Leddy *et al.*, 2021). However, these disorders, especially ASD and ADHD, are more common in early-onset DM1, partly related to the genotype of the patients and anticipatory phenomena, among others. Thus, DM1 is currently classified as congenital (onset <1 year), infantile (onset between 1 and 10 years), juvenile (onset between 10 and 20 years), adult (onset between 20 and 40 years), and late-onset (onset >40 years). However, this classification varies between authors and time periods and can be simplified into congenital, juvenile (infantile + juvenile), and adult (adult + late-onset). Regardless, congenital onset is considered to be highly associated with ASD and ADHD (De Antonio *et al.*, 2016; Yum *et al.*, 2017; Wenninger *et al.*, 2018).

Depression and anxiety are known to be common in DM1 (van der Velden *et al.*, 2019). However, the prevalence of these emotional disorders in DM2 is unknown. In addition, the prevalence of neurodevelopmental disorders in DM1 and their association with disease onset is not well understood. Therefore, the aim of this systematic review and meta-analysis was to estimate the prevalence of neurodevelopmental disorders (i.e. ASD and ADHD) and emotional disorders (i.e. depression and anxiety) in participants with DM1 and DM2 and their association with disease onset.

Methods

This systematic review and meta-analysis was conducted according to the Cochrane Collaboration Handbook, the Meta-analyses of Observational Studies in Epidemiology (MOOSE), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Stroup *et al.*, 2000; Higgins and Green, 2008; Moher *et al.*, 2009), and it was previously registered in PROSPERO (CRD42023401308).

Search strategy

A systematic search was conducted in Medline (via PubMed), Scopus, Web of Science, and the Cochrane Library from inception

to November 2023. An open search of grey literature, including Theseo, Networked Digital Library of Theses and Dissertations, Google Scholar, and OpenGrey, was also carried out, and references of previously published reviews were checked and, if necessary, attempts were made to contact the authors of manuscripts without full text. Search terms included *myotonic dystrophy*, *Steinert myotonic dystrophy*, *myotonic dystrophy type 1*, *type 1 myotonic dystrophy*, *myotonic dystrophy type 2*, *type 2 myotonic dystrophy*, *cognitive profile*, *cognitive function*, *psychological profile*, *mental disorders*, *mental health*, *neurodevelopmental*, *developmental*, *psychiatric*, *autism*, *attention deficit hyperactivity disorder*, *adhd*, *depression*, and *anxiety*. The complete search strategy is detailed in Appendix S1.

The literature search was performed independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or by a third reviewer (VM-V).

Inclusion/exclusion criteria

Inclusion criteria were as follows: (1) participants: population with DM1 or DM2, without age restriction; (2) design: observational studies, including cross-sectional, retrospective, prospective, and case series studies; (3) outcomes: i) prevalence of ASD, ADHD, depressive disorders, and anxiety disorders; ii) association of the prevalence of ASD and ADHD with the onset of DM1. In addition to formal diagnoses using the Diagnostic and Statistical Manual of Mental Disorders (DSM), studies using validated scales, clinical records, and self-reports were included. Congenital, juvenile (childhood/infantile + juvenile) and adult (adult + late onset) onset were also included. There were no language restrictions.

Exclusion criteria were as follows: (1) participants: studies that included participants with other dystrophies, without being able to determine the estimates for participants with DM1 or DM2. We also excluded if participants with DM1 and DM2 were included without being able to separate estimates for each population; (2) design: single case studies; and (3) outcome: studies with populations with neuropsychiatric disorders only.

Study selection was performed independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or by a third reviewer (VM-V).

Data extraction

An *ad hoc* table was created with the data extracted from the studies included in the systematic review, including: (1) reference (author and year of publication); (2) country/ies where the study was conducted; (3) type of dystrophy (DM1 and/or DM2); (4) sample size; (5) participants with maternal and paternal inheritance; (6) disease onset (congenital, juvenile, adult); (7) mean CTG repeats; (8) mean age; and (9) outcomes (ASD, ADHD, depression, and anxiety).

Risk of bias assessment

Risk of bias was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the United States National Institutes of Health National Heart, Lung, and Blood Institute (Study Quality Assessment Tools | NHLBI, NIH, no date, 2023). This tool includes 14 items that assess methodological and statistical issues. The overall risk of bias was good if there was ≤ 1 item at risk of bias, fair if there were 2 items at risk of bias, and poor if there were ≥ 2 items at risk of bias.

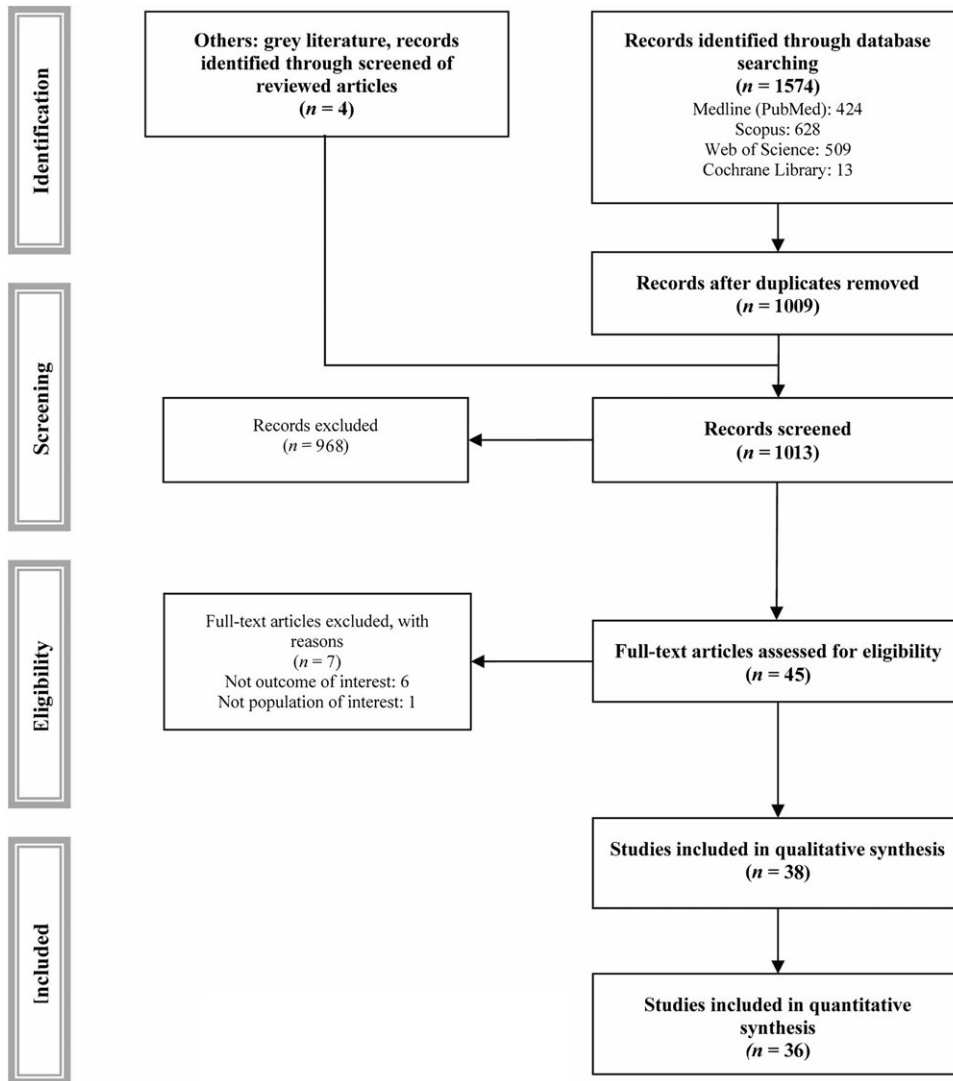


Figure 1. PRISMA flowchart of study selection.

Risk of bias was assessed independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or by a third reviewer (VM-V).

Grading the quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used to assess the quality of the evidence (Atkins *et al.*, 2004; Neumann *et al.*, 2014). This tool rates each outcome from high to very low, taking into account factors such as study design, risk of bias, inconsistency and imprecision of results, and effect size.

Data synthesis

A narrative synthesis of the results from each study was performed. Overall prevalence and prevalence by onset were estimated from 0.00 to 1.00, with a 95% confidence interval (95% CI), while the association between prevalence and onset was estimated using prevalence ratios (PRs) and their 95% CIs.

Random-effects meta-analyses were performed when there were more than 10 studies and/or the heterogeneity was

statistically significant, while fixed-effects meta-analyses were performed when there were fewer than 10 studies and the heterogeneity was not statistically significant (DerSimonian and Laird, 1986; Tufanaru *et al.*, 2015). Furthermore, in meta-analyses that assessed the same outcome but in different subgroups of participants, the same meta-analysis model was used, as long as the statistical significance was similar in these subgroups. If this was not the case, or if heterogeneity was not available, random-effects models were preferred. Heterogeneity was assessed using the I^2 statistic and classified as not important ($I^2 < 30\%$), moderate ($I^2 = 30\text{--}50\%$), substantial ($I^2 = 50\text{--}75\%$) and considerable ($I^2 > 75\%$), and it was considered statistically significant when $p < 0.05$ (Higgins and Green, 2008). Although potentially duplicate studies were included in the systematic review, their inclusion in the meta-analyses was avoided. Finally, the publication bias was assessed visually and using Egger's test and was statistically significant when $p < 0.10$ (Egger *et al.*, 1997).

Sensitivity and meta-regression analyses

A sensitivity analysis for the prevalence of ASD, ADHD, depressive and anxiety disorders was performed with study-by-study

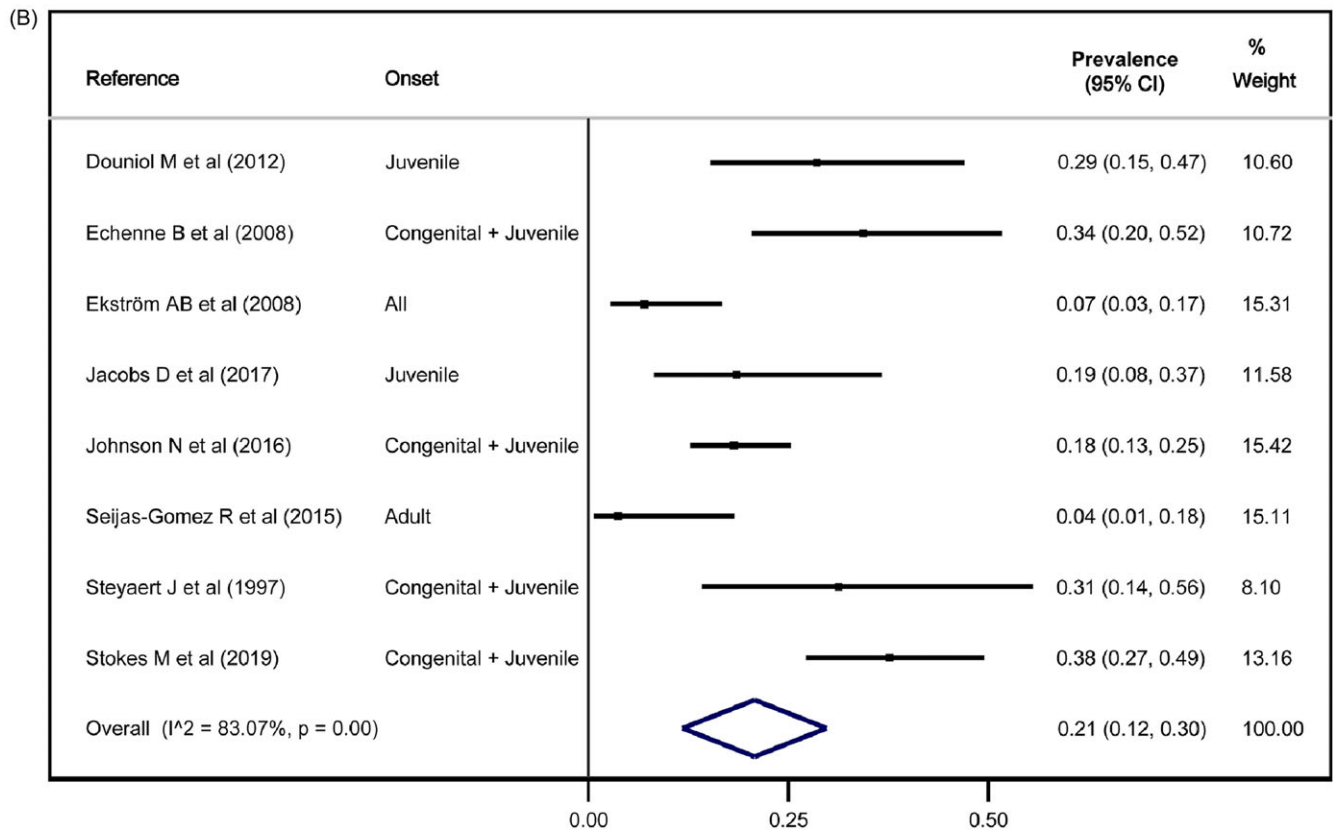
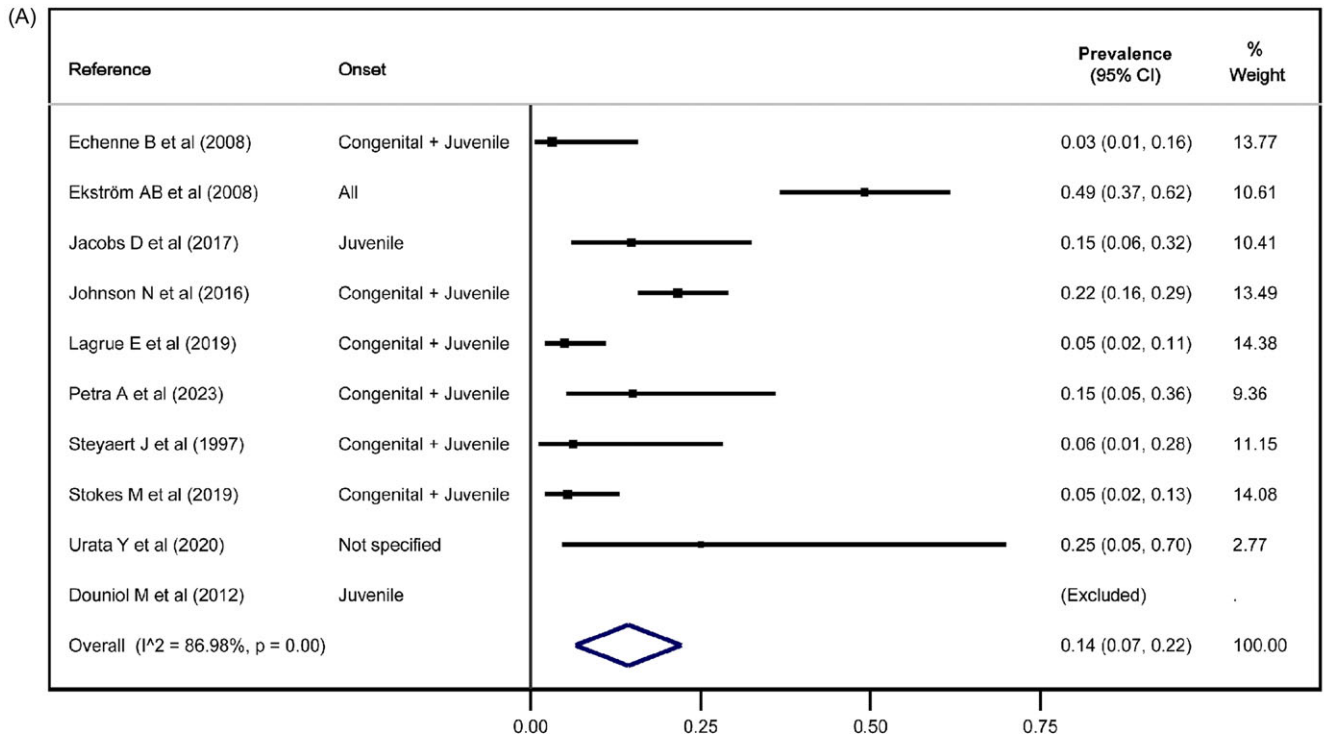


Figure 2. Meta-analyses of the prevalence of autism spectrum disorders (A) and attention deficit hyperactivity disorder (B) in myotonic dystrophy type 1.

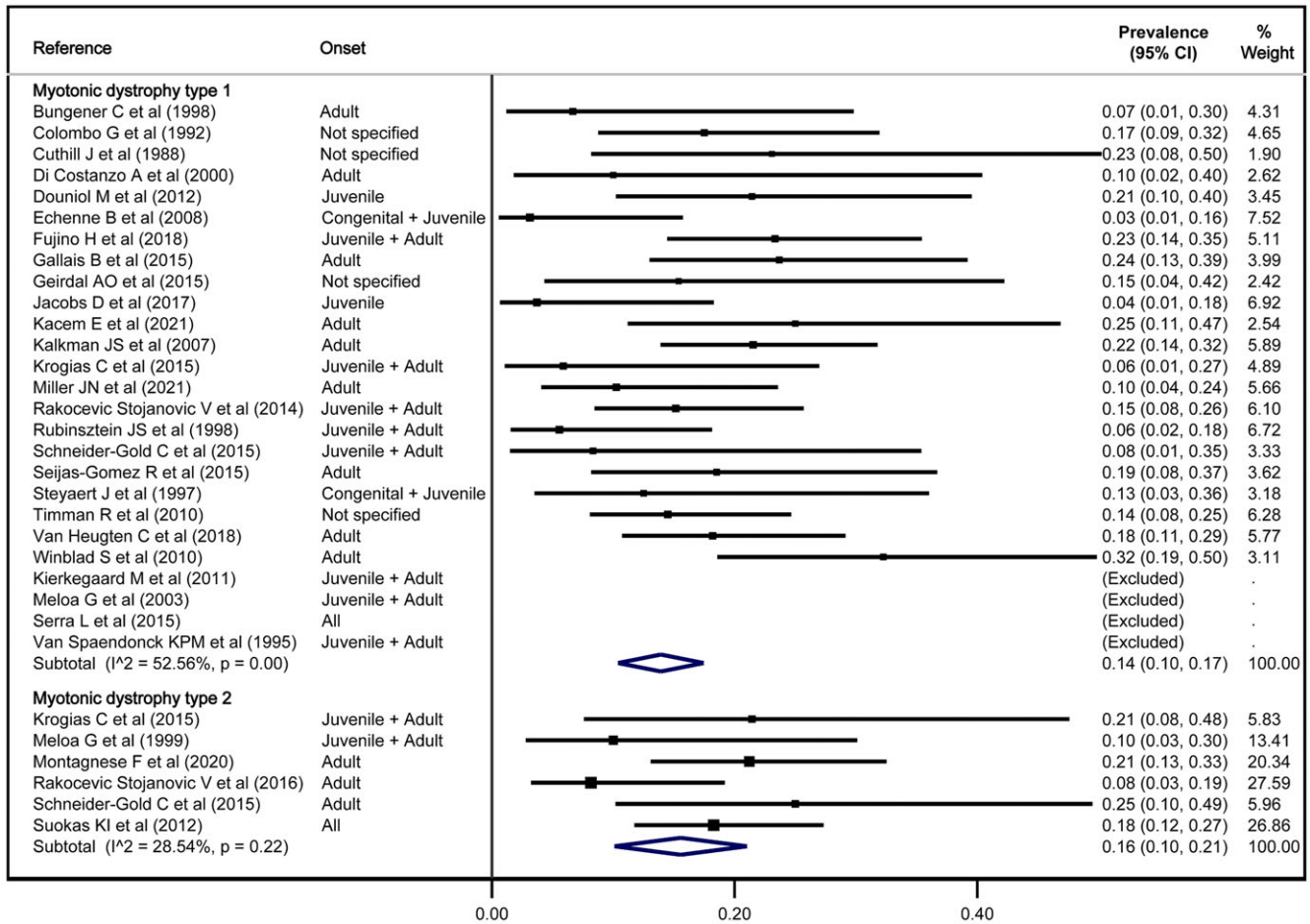


Figure 3. Meta-analyses of the prevalence of depression in myotonic dystrophy type 1 and type 2.

exclusion to determine the possible influence of a single study as a potential source of heterogeneity that would substantially affect the estimates from the meta-analyses. Meta-regressions were also performed on the prevalence of ASD and ADHD in natural logarithmic form, using mean CTG repeats as a covariate.

All statistical analyses were performed using Stata v15 (StataCorp, College Station, TX, US).

Modifications of the initial protocol PROSPERO

Initially, a meta-analysis of the association of ASD/ADHD-DM1 onset prevalence was established including the Congenital versus Juvenile (Childhood + Juvenile) comparison. However, due to the presumed similarity of congenital and childhood and juvenile and adult-onset CNS alterations, it was decided to add the congenital versus childhood and childhood versus juvenile comparisons to improve the interpretability of the results. Furthermore, although the protocol established a meta-analysis of the prevalence-genotype association, it was not possible due to a lack of studies.

Results

Of the 1578 studies identified, 38 met the inclusion and exclusion criteria and were included in the systematic review (Cuthill et al., 1988; Colombo et al., 1992; Van Spaendonck et al., 1995; Steyaert

et al., 1997; Bungener et al., 1998; Rubinsztein et al., 1998; Melo et al., 1999; Di Costanzo et al., 2000; Kalkman et al., 2007; Echenne et al., 2008; Ekström et al., 2009; Timman et al., 2010; Winblad et al., 2010; Kierkegaard et al., 2011; Douniol et al., 2012; Suokas et al., 2012; Caso et al., 2014; Rakocevic-Stojanovic et al., 2014; Gallais et al., 2015; Geirdal et al., 2015; Krogias et al., 2015; Seijas-Gómez et al., 2015; Serra et al., 2015; Johnson et al., 2016; Rakocevic Stojanovic et al., 2016; Jacobs et al., 2017; Fujino et al., 2018; Van Heugten et al., 2018; Lagrue et al., 2019; Melo et al., 2003; Stokes et al., 2019; Montagnese et al., 2020; Urata et al., 2020; Kacem et al., 2021; Miller et al., 2021; Aden et al., 2023; Van Spaendonck et al., 1995; Winblad et al., 2010), and 36 of these were included in the meta-analyses (Figure 1, Supplementary Table S1). Seven studies were excluded for justified reasons (Supplementary Table S2).

Thirty-five studies were on DM1, including 1500 participants, and 7 studies were on DM2, including 277 participants, and were conducted in Africa, the Americas, Asia, and Europe. In DM1, 204 participants had maternal inheritance and 231 had paternal inheritance, while 343 had congenital onset, 418 had juvenile onset and 533 had adult onset. In DM2, however, adult onset predominated. In DM1, CTG repeats ranged from 143 to 4600 and age ranged from 9.2 to 47.3 years, and in DM2 ranged from 37.0 to 55.7 years. Finally, ASD and ADHD were identified only in DM1, whereas depressive disorders were estimated in DM1 and

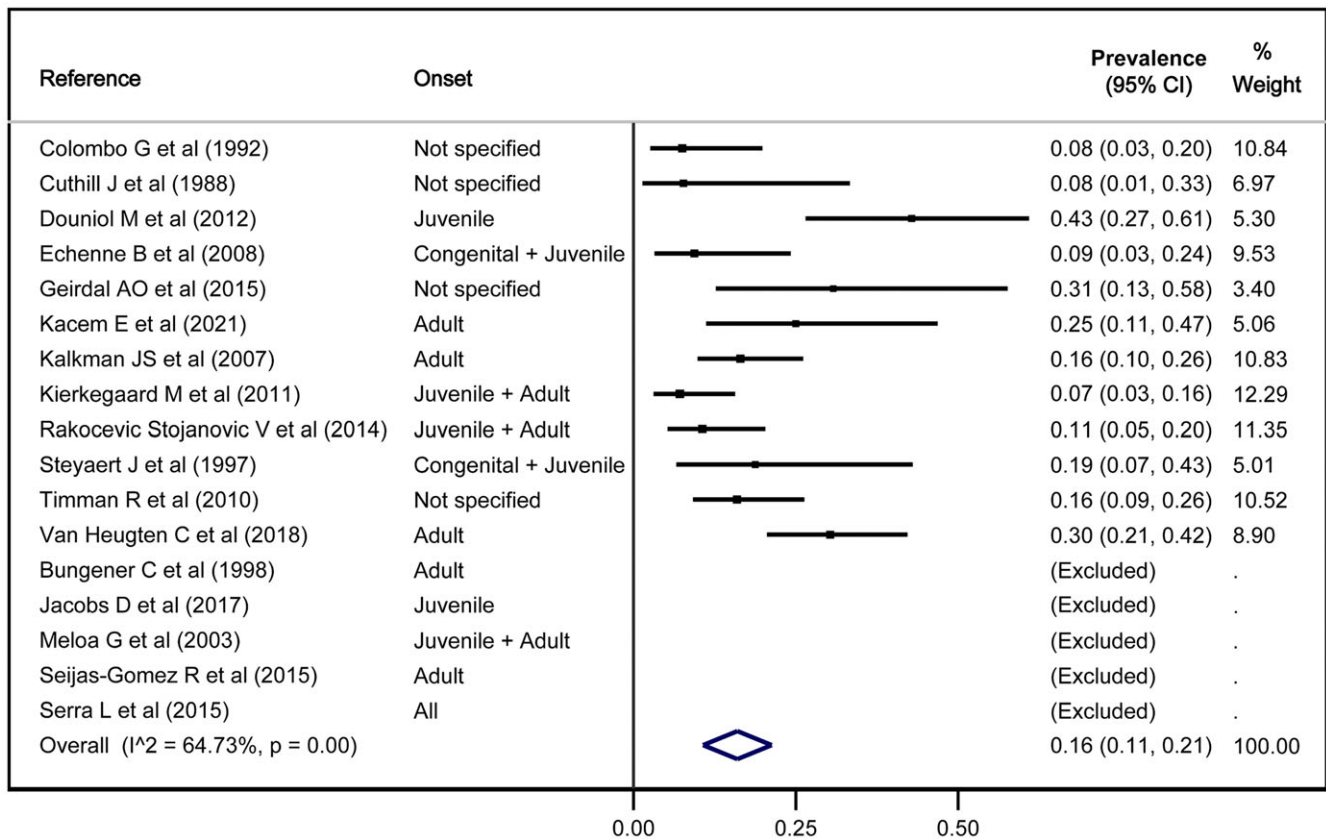


Figure 4. Meta-analyses of the prevalence of anxiety in myotonic dystrophy type 1.

DM2. The classification of DM onset is available in Supplementary Table S3, while the diagnostic criteria for neuropsychiatric disorders are available in Supplementary Table S4.

Systematic review

Supplementary Table S5 shows the overall estimates of the prevalence of neuropsychiatric disorders for each study.

In DM1, the prevalence of ASD ranged from 0.00 to 0.49 (95% CI: 0.37, 0.62), while the prevalence of ADHD ranged from 0.04 (95% CI: 0.01, 0.18) to 0.41 (95% CI: 0.22, 0.64). With the exception of one participant with adult-onset ADHD, all other participants with ASD or ADHD had congenital or juvenile onset. Regarding emotional problems, the prevalence of depressive disorders ranged from 0.00 to 0.32 (95% CI: 0.19, 0.50), while the prevalence of anxiety disorders ranged from 0.00 to 0.43 (95% CI: 0.27, 0.61). For both depressive and anxiety disorders, participants with congenital, juvenile, and adult onset were included. In DM2, the prevalence of depressive disorders (or risk of depressive disorders) ranged from 0.00 to 0.25 (95% CI: 0.10, 0.49), while the prevalence of anxiety disorders was found to be 0.00 in only one study.

Risk of bias assessment

According to the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the United States National Institutes of Health National Heart, Lung, and Blood Institute, overall bias was scored as good in 33 out of 38 studies (86.8%), while 5 studies (13.2%) were scored as fair. The main concern in these studies was the lack of categorisation of participants according to DM1 onset, which was likely to affect estimates of

neurodevelopmental disorders. Risk of bias is shown in Supplementary Table S6.

Quality of evidence assessment

According to the GRADE tool, the only outcome with moderate certainty was the association between ASD and congenital versus juvenile, while all other comparisons had very low certainty (Supplementary Table S7).

Meta-analysis

In DM1, the prevalence of ASD was 0.14 (95% CI: 0.07, 0.22), and the prevalence of ADHD was 0.21 (95% CI: 0.12, 0.30) (Figure 2), while the prevalence of depression was 0.14 (95% CI: 0.10, 0.17) and the prevalence of anxiety was 0.16 (95% CI: 0.11, 0.21). In addition, the prevalence of depression in DM2 was 0.16 (95% CI: 0.10, 0.21) (Figures 2–4).

Congenital DM1 had a prevalence of ASD of 0.25 (95% CI: 0.05, 0.45) and juvenile DM1 of 0.16 (95% CI: 0.10, 0.22), while congenital DM1 had a prevalence of ADHD of 0.24 (95% CI: 0.09, 0.39) and juvenile DM1 of 0.22 (95% CI: 0.16, 0.28) (Figures 5 and 6). However, the prevalence of depression was 0.07 (95% CI: 0.02, 0.11) in juvenile DM1 and 0.18 (95% CI: 0.14, 0.23) in adult DM1, with statistically significant differences between the two onsets (Figure S1). Finally, the prevalence of anxiety ranged from 0.14 (95% CI: -0.01, 0.29) to 0.21 (95% CI: 0.14, 0.28) for congenital and adult onset, respectively (Figure S2).

Meta-analyses of the association of ASD onset for the comparison 'Congenital versus Juvenile' showed a PR = 1.79 (95% CI: 1.12, 2.87) (Figure 7), an association that lost statistical

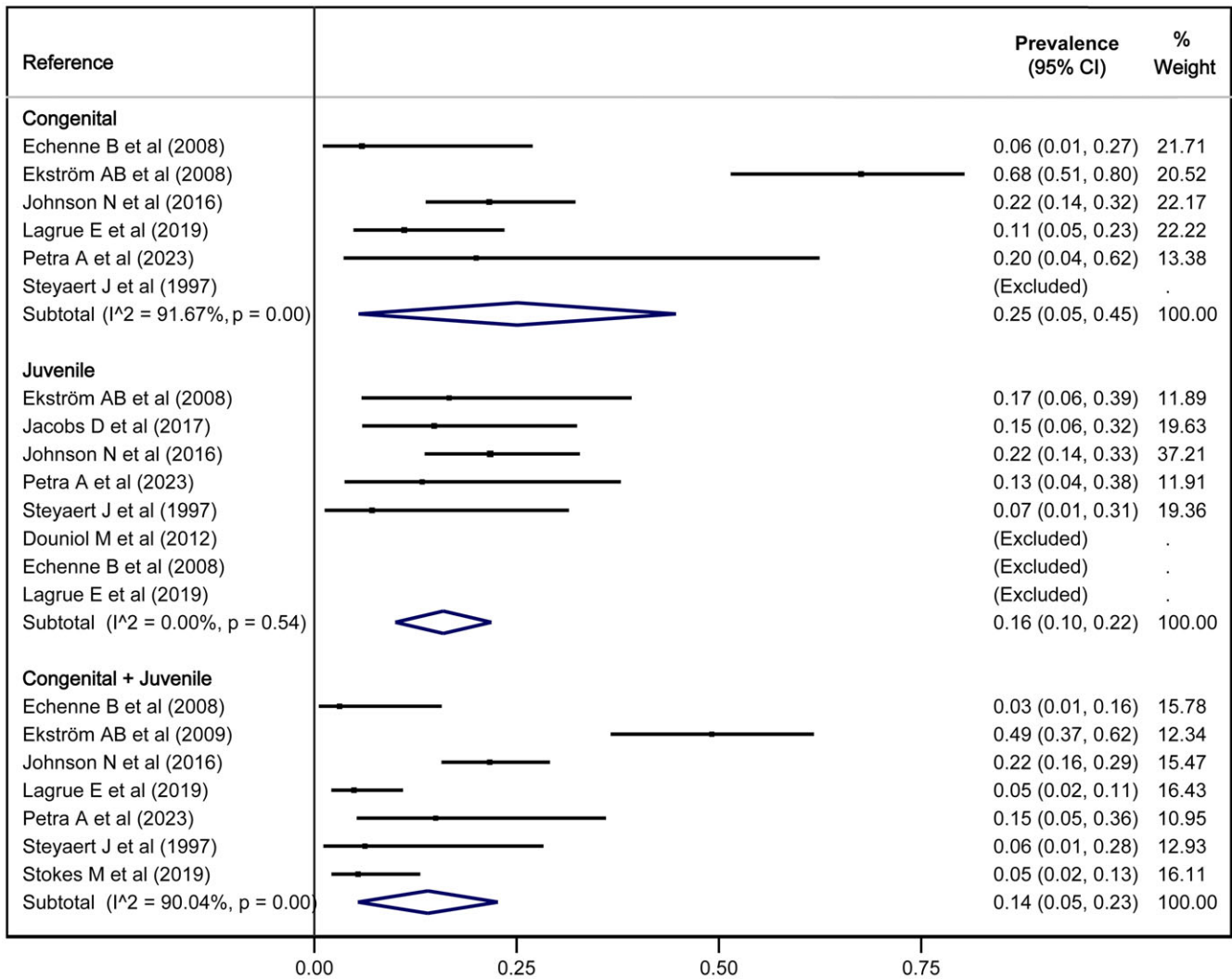


Figure 5. Meta-analysis of prevalence of autism spectrum disorders in myotonic dystrophy type 1 by disease onset.

significance when Juvenile onset was subdivided into Childhood and Juvenile (Figure S3). However, no association of ADHD was observed for ‘Congenital versus Juvenile’ or when Juvenile was subdivided into Childhood and Juvenile (Figure 7, Figure S4).

With few exceptions, heterogeneity was moderate to considerable. In addition, publication bias was found for the prevalence of ASD, depressive disorders in DM1, and anxiety (Figure S5).

Sensitivity and meta-regression analyses

Sensitivity analyses with study-by-study exclusion did not show that excluding any study significantly affected the final estimates (Supplementary Table S8). Finally, meta-regressions of the prevalence of the studied disorders using the mean number of CTG repetitions as a covariate showed no statistically significant association (Supplementary Table S9).

Discussion

Main findings

This systematic review and meta-analysis estimated the overall prevalence of the main neuropsychiatric disorders in DM. In DM1,

the prevalence of ASD was 14%, with a clear association with congenital onset, while the prevalence of ADHD was 21%, associated with both congenital and juvenile onset. In addition, depression was 14%, higher in adult onset than in juvenile onset, and anxiety was 16%. Finally, the prevalence of depressive disorders was 16% in DM2, with no statistically significant differences compared with DM1.

Interpretation

The overall onset prevalence of ASD was 14%, similar to the prevalence in juvenile onset, but twice that of congenital onset. This prevalence contrasts with the 0.76% found in the general population (AJ et al., 2015). Some of this variability is explained by limited sample sizes, possible underdiagnosis of ASD if not actively sought (Stokes et al., 2019), the possible relationship between IQ and ASD prevalence, and the different proportions of participants with congenital versus juvenile onset (Echenne et al., 2008; Ekström et al., 2008; Douniol et al., 2012). Although the specific mechanism of ASD in congenital or juvenile onset DM1 is unknown, some hypotheses have been proposed. These include cerebellar cortical heterotopia, white matter alterations, ventricular dilatation, corpus callosum hypoplasia and periventricular

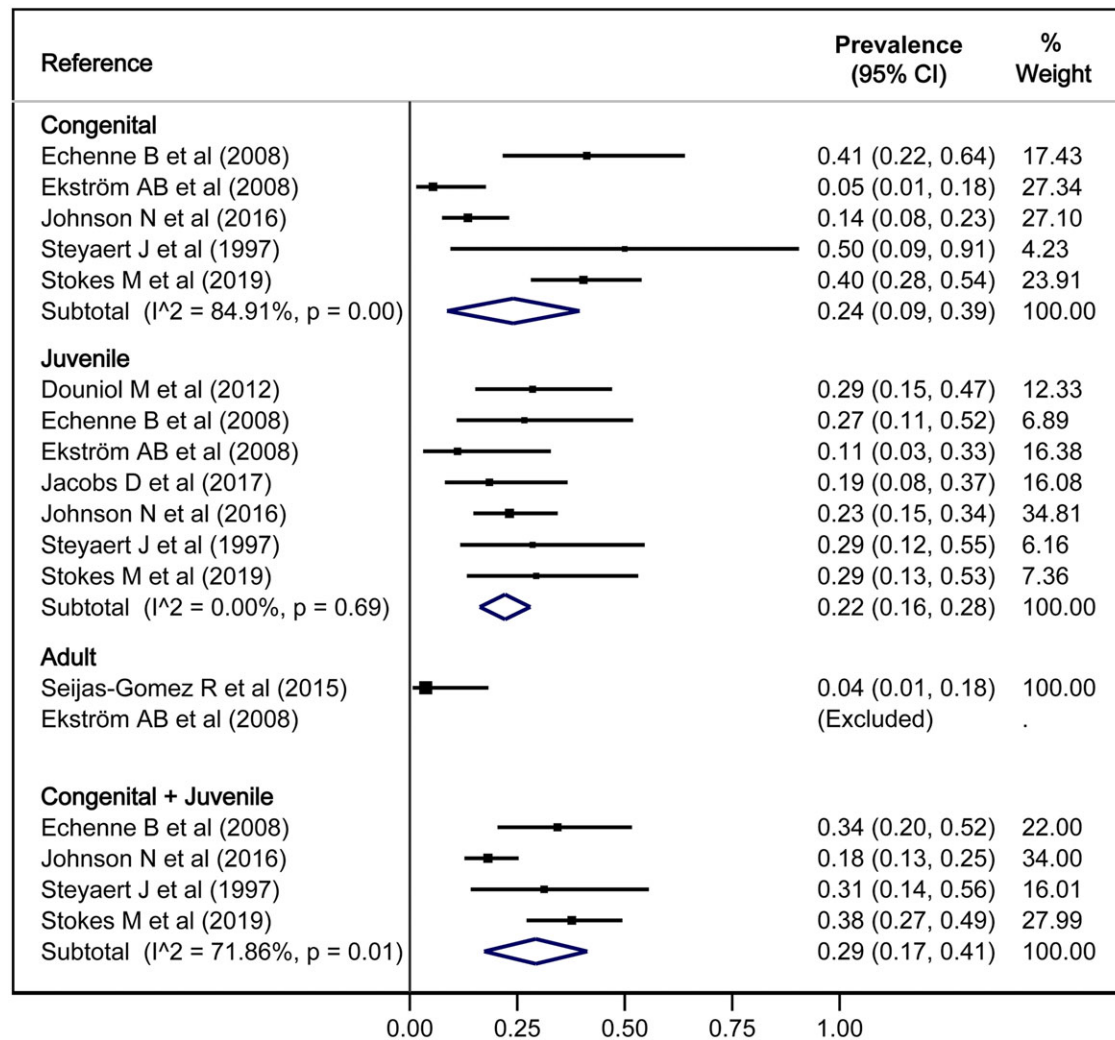


Figure 6. Meta-analysis of prevalence of attention deficit hyperactivity disorder in myotonic dystrophy type 1 by disease onset.

leukomalacia, among others (Garcia-Alix *et al.*, 1991; Bachmann *et al.*, 1996; Martinello *et al.*, 1999; Endo *et al.*, 2000; Angeard *et al.*, 2018).

ADHD was present in 21% of the total sample, with a priori no statistically significant differences between congenital and juvenile onset, and with one testimonial case in an adult-onset participant. These estimates are significantly higher than those found in healthy children and adolescents, estimated at 3.4% (Polanczyk *et al.*, 2015). Some of the observed variability may be explained by sample size. In addition, the different proportions of participants with different onsets should affect the final estimates, with very low proportions for adult onset (Seijas-Gómez *et al.*, 2015). Interestingly, the association study showed a non-statistically adverse trend for juvenile (childhood) onset, an estimate that should be considered with caution due to sample size, number of included studies, and other limitations. The mechanisms that may explain ADHD in DM1 are not well understood, but may be due to neurodevelopmental abnormalities, neuroplasticity, and other brain and cerebellar alterations (Garcia-Alix *et al.*, 1991; Bachmann *et al.*, 1996; Martinello *et al.*, 1999; Endo *et al.*, 2000; Angeard *et al.*, 2018).

Regarding emotional disorders, depression was estimated at around 15% in DM1 and DM2, and anxiety at around 15% in DM1.

These estimates are higher than those in the general population, particularly in children and adolescents, with an estimated 2.6% depression and 6.5% anxiety (Polanczyk *et al.*, 2015). Furthermore, although the prevalence of depression in adult onset was higher than in juvenile onset, an association study could not be performed due to a lack of studies, and furthermore, two studies in adult onset were excluded from the analysis because they did not present cases of depression. There are two hypotheses about the causes of emotional disorders in DM1 and DM2. In DM1, there are alterations in the prefrontal, frontal and parietotemporal cortex and thalamus, whereas in DM2 there are changes in the pons and cerebellar peduncles, as well as white matter lesions that occur in both DM1 and DM2. The latter reinforces the hypothesis of a reactive-adaptive disorder, since it has been observed that in DM1, depression seems to decrease as the disease progresses and white matter lesions increase; in DM2, however, the opposite is true, with depression increasing as white matter lesions progress (Minnerop *et al.*, 2011; Peric *et al.*, 2021).

Although the exact pathophysiological mechanism of these disorders in DM1, particularly ASD and ADHD, is not known, they may be partly explained by the genetics of the disease itself. The pathological CTG repeat in the 3'-UTR of the DMPK gene in DM1 leads to the accumulation of toxic RNA in the nucleus,

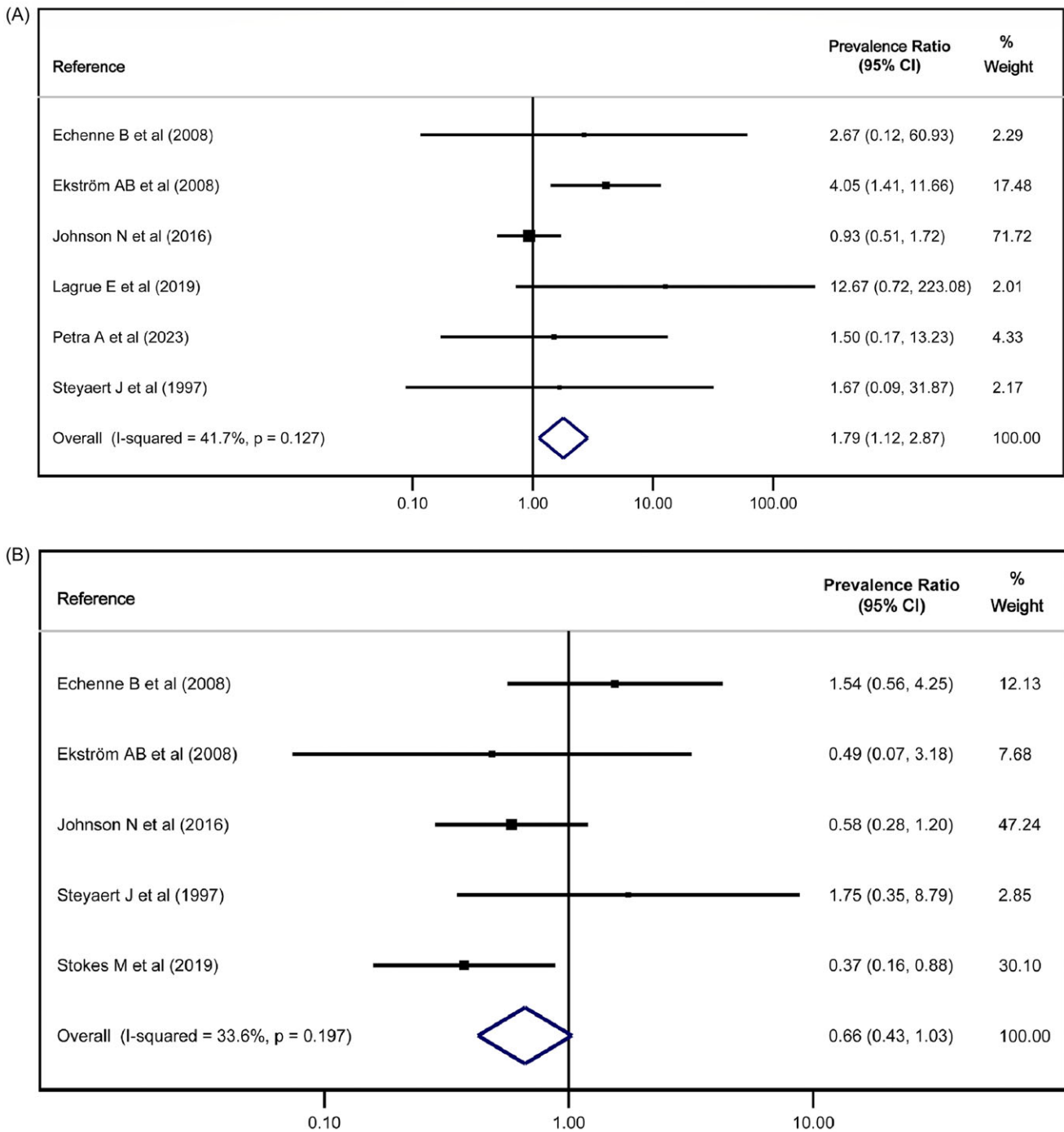


Figure 7. Meta-analyses of prevalence ratios comparing congenital versus juvenile onset for autism spectrum disorder (A) and attention deficit hyperactivity disorder (B).

forming ‘nuclear foci’. These foci sequester RNA-binding proteins of the MBNL family, in particular MBNL1, and upregulate CELF proteins such as CELF1 and CELF2. MBNL1 deficiency and elevated CELF1/CELF2 affect alternative splicing of several genes, including those critical for brain function. In animal models, loss of MBNL1 function has been associated with cognitive and behavioural abnormalities, while MBNL2 is associated with deficits in memory and synaptic plasticity. In addition, regulation of specific exons of tau and NMDAR1 by CELF1 and CELF2 may contribute to neuronal signalling defects and synaptic plasticity (Liu *et al.*, 2021).

Our study has some implications that should be highlighted. First, rehabilitation, physiotherapy and orthopaedic adjustments are essential in the management of DM (Turner and Hilton-Jones, 2014). However, these patients may have reduced disease awareness (Baldanzi *et al.*, 2016), particularly those with ASD or ADHD, which is associated with early onset of the disease, reducing adherence to these interventions. Greater follow-up is therefore needed, as well as the involvement of family members and carers. Second, there is a high prevalence of neurodevelopmental disorders in congenital and juvenile DM1, highlighting the importance of actively screening for these disorders in this

population, which is not always done (Stokes *et al.*, 2019). There is also a high prevalence of emotional disorders, particularly depression, in adults with DM1. Identifying these disorders would greatly improve the quality of life for these people. Third, although the current classification of the DM1 phenotype according to onset is probably the most appropriate and practical (i.e. congenital, childhood, juvenile, adult and late onset), it actually implies a continuous spectrum, with a gradual reduction of neurodevelopmental disorders, especially ASD, as the age of onset increases, which means that some cases of juvenile and adult onset cannot be excluded. Fourth, with regard to the latter, future studies are needed to analyse the association between neurodevelopmental disorders and CTG repeats in large cohorts of participants with DM1. An association is suspected, but meta-analysis was not possible and it is not known whether this possible association correlates better with these disorders than with onset.

Limitations

Some limitations of our study should be considered. First, the sample sizes were sometimes limited, so any small variation in cases could affect the final estimate. Second, few studies could be included in the meta-analyses of association by disease onset, which limits the interpretability of the estimates. Third, a meta-analysis of the association by disease onset for emotional disorders could not be performed due to a lack of studies. Fourth, publication bias was observed in some studies. Fifth, selection or recall bias cannot be ruled out, depending on the characteristics of the sample and the method of data collection. Sixth, different tools and scales were used to diagnose or screen cases. However, a formal diagnosis must be made using the DSM, which is rarely used (at least explicitly). Formal diagnosis using the DSM would give greater validity to the estimates obtained.

Conclusions

Neurodevelopmental and emotional disorders are highly prevalent in DM1, with ASD and ADHD being particularly common in congenital and juvenile onset. In DM2, emotional disorders also have a relatively high prevalence, comparable to DM1. However, classification by onset does not fully explain the findings, perhaps because it is a continuous spectrum, with congenital onset having a higher likelihood of ASD and ADHD, decreasing progressively with increasing age of onset. In addition, although meta-regression of ASD and ADHD using CTG repeats as a covariate showed no association, a more appropriate meta-analysis of association by subgroups based on CTG repeats could not be performed. Finally, these findings highlight the importance of active and early diagnosis to improve quality of life and suggest the need for studies with larger sample sizes.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/neu.2024.27>.

Data statement. The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author/s.

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Authors contributions. Conceptualisation: CP-M; methodology: CP-M and VM-V; data curation and investigation: CP-M and IC-R; formal analysis: CP-M, AS-L, CA-B, and IM-G; validation and visualisation: ML-L-T, CA-B, and IM-G; writing – original draft preparation: CP-M, IC-R, and VM-V; writing –

review and editing: all authors; supervision: IC-R and VM-V; funding acquisition: VM-V; project administration: VM-V. All authors have read and agreed to the published version of the manuscript.

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Competing interests. The authors declare that they have no conflict of interest.

Ethical standards. Prior approval from an ethics committee was not required due to the design of our study. The studies included in this systematic review adhered to the Declaration of Helsinki and the required ethical standards.

References

- Aden P, Skarbø A-B, Wallace S, Ørstavik K and Rasmussen M (2023) Cognitive function, behaviour and quality of life in children with myotonic dystrophy type 1 in South - Eastern Norway. *European Journal of Paediatric Neurology : EJPN : Official Journal of the European Paediatric Neurology Society* 45, 1–6. DOI: [10.1016/j.ejpn.2023.05.004](https://doi.org/10.1016/j.ejpn.2023.05.004).
- Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T and Scott JG (2015) The epidemiology and global burden of autism spectrum disorders. *Psychological Medicine* 45, 601–613. DOI: [10.1017/S003329171400172X](https://doi.org/10.1017/S003329171400172X).
- Angeard N, Huerta E, Jacquette A, Cohen D, Xavier J, Gargiulo M, Servais L, Eymard B and Héron D (2018) Childhood-onset form of myotonic dystrophy type 1 and autism spectrum disorder: is there comorbidity? *Neuromuscular Disorders : NMD* 28, 216–221. DOI: [10.1016/j.nmd.2017.12.006](https://doi.org/10.1016/j.nmd.2017.12.006).
- Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, *et al.* (2004) Grading quality of evidence and strength of recommendations. *BMJ (Clinical Research Ed.)* 328, 1490. DOI: [10.1136/bmj.328.7454.1490](https://doi.org/10.1136/bmj.328.7454.1490).
- Bachmann G, Damian MS, Koch M, Schilling G, Fach B and Stöppler S (1996) The clinical and genetic correlates of MRI findings in myotonic dystrophy. *Neuroradiology* 38, 629–635. DOI: [10.1007/s002340050322](https://doi.org/10.1007/s002340050322).
- Baldanzi S, Bevilacqua F, Lorio R, Volpi L, Simoncini C, Petrucci A *et al.* (2016) Disease awareness in myotonic dystrophy type 1: an observational cross-sectional study. *Orphanet Journal of Rare Diseases* 11, 34. DOI: [10.1186/s13023-016-0417-z](https://doi.org/10.1186/s13023-016-0417-z).
- Bungener C, Jouvent R and Delaporte C (1998) Psychopathological and emotional deficits in myotonic dystrophy. *Journal of Neurology, Neurosurgery, and Psychiatry* 65, 353–356. DOI: [10.1136/jnnp.65.3.353](https://doi.org/10.1136/jnnp.65.3.353).
- Caso F, Agosta F, Peric S, Rakočević-Stojanović V, Copetti M, Kostic VS and Filippi M (2014) Cognitive impairment in myotonic dystrophy type 1 is associated with white matter damage. *PLoS One* 9, e104697. DOI: [10.1371/journal.pone.0104697](https://doi.org/10.1371/journal.pone.0104697).
- Colombo G, Perini GI, Miotti MV, Armani M and Angelini C (1992) Cognitive and psychiatric evaluation of 40 patients with myotonic dystrophy. *Italian Journal of Neurological Sciences* 13, 53–58. DOI: [10.1007/BF02222889](https://doi.org/10.1007/BF02222889).
- Cuthill J, Gattreau A and Vigiú F (1988) Myotonic dystrophy of steinert: are anxiety and depression necessarily concomitants? *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie* 33, 203–206. DOI: [10.1177/070674378803300308](https://doi.org/10.1177/070674378803300308).
- Day JW, Ricker K, Jacobsen JF, Rasmussen LJ, Dick KA, Kress W *et al.* (2003) Myotonic dystrophy type 2 - molecular, diagnostic and clinical spectrum. *Neurology* 60, 657–664. DOI: [10.1212/01.WNL.0000054481.84978.F9](https://doi.org/10.1212/01.WNL.0000054481.84978.F9).
- De Antonio M, Dogan C, Hamroun D, Mati M, Zerrouki S, Eymard B, Katsahian S and Bassez G (2016) Unravelling the myotonic dystrophy type 1 clinical spectrum: a systematic registry-based study with implications for disease classification. *Revue Neurologique* 172, 572–580. DOI: [10.1016/j.neurol.2016.08.003](https://doi.org/10.1016/j.neurol.2016.08.003).
- DerSimonian R and Laird N (1986) Meta-analysis in clinical trials. *Controlled Clinical Trials* 7, 177–188. DOI: [10.1016/0197-2456\(86\)90046-2](https://doi.org/10.1016/0197-2456(86)90046-2).
- Di Costanzo A, Mottola A, Toriello A, Di Iorio G, Tedeschi G and Bonavita V (2000) Does abnormal neuronal excitability exist in myotonic dystrophy? II Effects of the antiarrhythmic drug hydroquinidine on

- apathy and hypersomnia. *Neurological Sciences* 21, 81–86. DOI: [10.1007/s100720070100](https://doi.org/10.1007/s100720070100).
- Douniol M, Jacquette A, Cohen D, Bodeau N, Rachidi L, Angeard N et al (2012) Psychiatric and cognitive phenotype of childhood myotonic dystrophy type 1. *Developmental Medicine & Child Neurology* 54, 905–911. DOI: [10.1111/j.1469-8749.2012.04379.x](https://doi.org/10.1111/j.1469-8749.2012.04379.x).
- Echenne B, Rideau A, Roubertie A, Sébire G, Rivier F and Lemieux B (2008) Myotonic dystrophy type I in childhood. Long-term evolution in patients surviving the neonatal period. *European Journal of Paediatric Neurology* 12, 210–223. DOI: [10.1016/j.ejpn.2007.07.014](https://doi.org/10.1016/j.ejpn.2007.07.014).
- Egger M, Smith GD, Schneider M and Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *Bmj* 315, 629–634. DOI: [10.1136/bmj.315.7109.629](https://doi.org/10.1136/bmj.315.7109.629).
- Ekström A-B, Hakenäs-Plate L, Samuelsson L, Tulinius M and Wentz E (2008) Autism spectrum conditions in myotonic dystrophy type 1: a study on 57 individuals with congenital and childhood forms. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics* 147B, 918–926. DOI: [10.1002/ajmg.b.30698](https://doi.org/10.1002/ajmg.b.30698).
- Ekström A-B, Hakenäs-Plate L, Tulinius M and Wentz E (2009) Cognition and adaptive skills in myotonic dystrophy type 1: a study of 55 individuals with congenital and childhood forms. *Developmental Medicine and Child Neurology* 51, 982–990. DOI: [10.1111/j.1469-8749.2009.03300.x](https://doi.org/10.1111/j.1469-8749.2009.03300.x).
- Endo A, Motonaga K, Arahata K, Harada K, Yamada T and Takashima S (2000) Developmental expression of myotonic dystrophy protein kinase in brain and its relevance to clinical phenotype. *Acta Neuropathologica* 100, 513–520. DOI: [10.1007/s004010000216](https://doi.org/10.1007/s004010000216).
- Fujino H, Shingaki H, Suwazono S, Ueda Y, Wada C, Nakayama T, Takahashi MP, Imura O and Matsumura T (2018) Cognitive impairment and quality of life in patients with myotonic dystrophy type 1. *Muscle & Nerve* 57, 742–748. DOI: [10.1002/mus.26022](https://doi.org/10.1002/mus.26022).
- Gallais B, Montreuil M, Gargiulo M, Eymard B, Gagnon C and Laberge L (2015) Prevalence and correlates of apathy in myotonic dystrophy type 1. *BMC Neurology* 15, 148. DOI: [10.1186/s12883-015-0401-6](https://doi.org/10.1186/s12883-015-0401-6).
- García-Alix A, Cabañas F, Morales C, Pellicer A, Echevarria J, Paisan L and Quero J (1991) Cerebral abnormalities in congenital myotonic dystrophy. *Pediatric Neurology* 7, 28–32. DOI: [10.1016/0887-8994\(91\)90102-q](https://doi.org/10.1016/0887-8994(91)90102-q).
- Geirdal AØ, Lund-Petersen I and Heiberg A (2015) Understanding the experience of myotonic dystrophy. Mixed method study. *Journal of Genetic Counseling* 24, 169–178. DOI: [10.1007/s10897-014-9752-1](https://doi.org/10.1007/s10897-014-9752-1).
- Gutiérrez Gutiérrez G, Díaz-Manera J, Almendrote M, Azriel S, Eulalio Bárcena J, Cabezudo García P et al (2020) Clinical guide for the diagnosis and follow-up of myotonic dystrophy type 1, MD1 or Steinert's disease. *Neurologia* 35, 185–206. DOI: [10.1016/j.nrl.2019.01.001](https://doi.org/10.1016/j.nrl.2019.01.001).
- Higgins JP and Green S (2008) *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series, Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*. Hoboken, New Jersey: John Wiley and Sons, [10.1002/9780470712184](https://doi.org/10.1002/9780470712184).
- Jacobs D, Willekens D, de Die-Smulders C, Frijns J-P and Steyaert J (2017) Delusional and psychotic disorders in juvenile myotonic dystrophy type-1. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics* 174, 359–366. DOI: [10.1002/ajmg.b](https://doi.org/10.1002/ajmg.b).
- Johnson NE, Ekstrom A-B, Campbell C, Hung M, Adams HR, Chen W et al (2016) Parent-reported multi-national study of the impact of congenital and childhood onset myotonic dystrophy. *Developmental Medicine and Child Neurology* 58, 698–705. DOI: [10.1111/dmcn](https://doi.org/10.1111/dmcn).
- Kacem E, Sakka S, Mguidich T, Fray S, Bouattour N, Moalla KS et al (2021) Depression and anxiety in adults with myotonic dystrophy type 1 in Tunisian population. *Journal of the Neurological Sciences* 429, 1–18418. DOI: [10.1016/j.jns.2021](https://doi.org/10.1016/j.jns.2021).
- Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BGM and Bleijenberg G (2007) Psychiatric disorders appear equally in patients with myotonic dystrophy, facioscapulohumeral dystrophy, and hereditary motor and sensory neuropathy type I. *Acta Neurologica Scandinavica* 115, 265–270. DOI: [10.1111/j.1600-0404.2006.00737.x](https://doi.org/10.1111/j.1600-0404.2006.00737.x).
- Kierkegaard M, Harms-Ringdahl K, Holmqvist LW and Tollback A (2011) Functioning and disability in adults with myotonic dystrophy type 1. *Disability and Rehabilitation* 33, 1826–1836. DOI: [10.3109/09638288.2010.549287](https://doi.org/10.3109/09638288.2010.549287).
- Krogias C, Bellenberg B, Prehn C, Schneider R, Meves SH, Gold R, Lukas C and Schneider-Gold C (2015) Evaluation of CNS involvement in myotonic dystrophy type 1 and type 2 by transcranial sonography. *Journal of Neurology* 262, 365–374. DOI: [10.1007/s00415-014-7566-6](https://doi.org/10.1007/s00415-014-7566-6).
- Kumar A, Agarwal S, Agarwal D and Phadke SR (2013) Myotonic dystrophy type 1 (DM1): a triplet repeat expansion disorder. *Gene* 522, 226–230. DOI: [10.1016/j.gene.2013.03.059](https://doi.org/10.1016/j.gene.2013.03.059).
- Laguerre E, Dogan C, De Antonio M, Audic F, Bach N, Barnerias C et al (2019) A large multicenter study of pediatric myotonic dystrophy type 1 for evidence-based management. *Neurology* 92, e852–e865. DOI: [10.1212/WNL.0000000000006948](https://doi.org/10.1212/WNL.0000000000006948).
- Leddy S, Cercignani M, Serra L and Bozzali M (2021) Social cognition in type 1 myotonic dystrophy - a mini review. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 142, 389–399. DOI: [10.1016/j.cortex.2021.05.004](https://doi.org/10.1016/j.cortex.2021.05.004).
- Liao Q, Zhang Y, He J and Huang K (2022) Global prevalence of myotonic dystrophy: an updated systematic review and meta-analysis. *Neuroepidemiology* 56, 163–173. DOI: [10.1159/000524734](https://doi.org/10.1159/000524734).
- Liu J, Guo Z-N, Yan X-L, Yang Y and Huang S (2021) Brain pathogenesis and potential therapeutic strategies in myotonic dystrophy type 1. *Frontiers in Aging Neuroscience* 13, 755392. DOI: [10.3389/fnagi.2021.755392](https://doi.org/10.3389/fnagi.2021.755392).
- Machuca-Tzili L, Brook D and Hilton-Jones D (2005) Clinical and molecular aspects of the myotonic dystrophies: a review. *Muscle & Nerve* 32, 1–18. DOI: [10.1002/mus.20301](https://doi.org/10.1002/mus.20301).
- Martinello F, Piazza A, Pastorello E, Angelini C and Trevisan CP (1999) Clinical and neuroimaging study of central nervous system in congenital myotonic dystrophy. *Journal of Neurology* 246, 186–192. DOI: [10.1007/s004150050332](https://doi.org/10.1007/s004150050332).
- Meola G, Sansone V, Perani D, Colleluori A, Cappa S, Cotelli M, Fazio F, Thornton CA and Moxley RT (1999) Reduced cerebral blood flow and impaired visual-spatial function in proximal myotonic myopathy. *Neurology* 53, 1042–1050. DOI: [10.1212/wnl.53.5.1042](https://doi.org/10.1212/wnl.53.5.1042).
- Meola G, Sansone V, Perani D, Scarone S, Cappa S, Dragoni C et al (2003) Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myotonic myopathy (PROMM/DM-2), neuromuscular disorders. *NMD* 13, 813–821. DOI: [10.1016/s0960-8966\(03\)00137-8](https://doi.org/10.1016/s0960-8966(03)00137-8).
- Miller JN, Kruger A, Moser DJ, Gutmann L, van der Plas E, Kosciak TR, Cumming SA, Monckton DG and Nopoulos PC (2021) Cognitive deficits, apathy, and hypersomnolence represent the core brain symptoms of adult-onset myotonic dystrophy type 1. *Frontiers in Neurology* 12, 700796. DOI: [10.3389/fneur.2021.700796](https://doi.org/10.3389/fneur.2021.700796).
- Minnerop M, Weber B, Schoene-Bake J-C, Roeske S, Mirbach S, Anspach C, et al. (2011) The brain in myotonic dystrophy 1 and 2: evidence for a predominant white matter disease. *Brain* 134, 3530–3546. DOI: [10.1093/brain/awr299](https://doi.org/10.1093/brain/awr299).
- Moher D, Liberati A, Tetzlaff J, Altman DG, Antes G et al (2009, July) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 6, e1000097. DOI: [10.1371/journal.pmed.1000097](https://doi.org/10.1371/journal.pmed.1000097).
- Montagnese F, Rastelli E, Stahl K, Massa R and Schoser B (2020) How to capture activities of daily living in myotonic dystrophy type 2?, neuromuscular disorders. *NMD* 30, 796–806. DOI: [10.1016/j.nmd.2020.07.011](https://doi.org/10.1016/j.nmd.2020.07.011).
- Neumann I, Pantoja T, Peñaloza B, Cifuentes L and Rada G (2014) El sistema GRADE: Un cambio en la forma de evaluar la calidad de la evidencia y la fuerza de recomendaciones. *Revista Médica de Chile* 142, 630–635. DOI: [10.4067/S0034-98872014000500012](https://doi.org/10.4067/S0034-98872014000500012).
- Peric S, Rakocevic Stojanovic V, Mandic Stojmenovic G, Ilic V, Kovacevic M, Parojcic A, Pesovic J, Mijajlovic M, Savic-Pavicevic D and Meola G (2017) Clusters of cognitive impairment among different phenotypes of myotonic dystrophy type 1 and type 2. *Neurological Sciences* 38, 415–423. DOI: [10.1007/s10072-016-2778-4](https://doi.org/10.1007/s10072-016-2778-4).
- Peric S, Rakocevic Stojanovic V and Meola G (2021) Cerebral involvement and related aspects in myotonic dystrophy type 2. *Neuromuscular Disorders* 31, 681–694. DOI: [10.1016/j.nmd.2021.06.002](https://doi.org/10.1016/j.nmd.2021.06.002).

- Polaczyk GV, Salum GA, Sugaya LS, Caye A and Rohde LA (2015) Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of Child Psychology and Psychiatry and Allied Disciplines* **56**, 345–365. DOI: [10.1111/JCPP](https://doi.org/10.1111/JCPP).
- Rakocevic Stojanovic V, Peric S, Paunic T, Pesovic J, Vujnic M, Peric M, Nikolic A, Lavrnic D and Savic Pavicevic D (2016) Quality of life in patients with myotonic dystrophy type 2. *Journal of the Neurological Sciences* **365**, 158–161. DOI: [10.1016/j.jns.2016.04.018](https://doi.org/10.1016/j.jns.2016.04.018).
- Rakocevic-Stojanovic V, Peric S, Madzarevic R, Dobricic V, Ralic V, Ilic V, Basta I, Nikolic A and Stefanova E (2014) Significant impact of behavioral and cognitive impairment on quality of life in patients with myotonic dystrophy type 1. *Clinical Neurology and Neurosurgery* **126**, 76–81. DOI: [10.1016/j.clineuro.2014.08.021](https://doi.org/10.1016/j.clineuro.2014.08.021).
- Rautemaa V, Roberts ME, Bentley A and Felton TW (2021) The role of noninvasive ventilation in the management of type II respiratory failure in patients with myotonic dystrophy. *ERJ Open Research* **7**, 00192–2020. DOI: [10.1183/23120541.00192-2020](https://doi.org/10.1183/23120541.00192-2020).
- Rubinsztein JS, Rubinsztein DC, Goodburn S and Holland AJ (1998) Apathy and hypersomnia are common features of myotonic dystrophy. *Journal of Neurology, Neurosurgery, and Psychiatry* **64**, 510–515. DOI: [10.1136/jnnp.64.4.510](https://doi.org/10.1136/jnnp.64.4.510).
- Russo V, Sperlongano S, Gallinoro E, Rago A, Papa AA, Golino P, Politano L, Nazarian S and Nigro G (2020) Prevalence of left ventricular systolic dysfunction in myotonic dystrophy type 1: A. *Systematic Review*. *Journal of Cardiac Failure* **26**, 849–856. DOI: [10.1016/j.cardfail.2019.07.548](https://doi.org/10.1016/j.cardfail.2019.07.548).
- Seijas-Gómez R, Basterra-Jiménez I, Luna-Lario P, Tirapu-Ustárroz J, Cabada-Giadás T, Iridoy-Zulet M, Jericó-Pascual I, Gargallo-Vaamonde Á and López-Goñi JJ (2015) A descriptive study of the neuropsychological and psychopathological profile in patients with type 1 myotonic dystrophy [Estudio descriptivo del perfil neuropsicológico y psicopatológico en pacientes con distrofia miotónica tipo]. *Revista de Neurología* **61**, 529–535. DOI: [10.33588/rn.6112](https://doi.org/10.33588/rn.6112).
- Serra L, Petrucci A, Spanò B, Torso M, Olivito G, Lispi L et al (2015) How genetics affects the brain to produce higher-level dysfunctions in myotonic dystrophy type 1. *Functional Neurology* **30**, 21–31. DOI: [10.1138/FNur/2015.30.1.021](https://doi.org/10.1138/FNur/2015.30.1.021).
- Smith CA and Gutmann L (2016) Myotonic dystrophy type 1 Management and therapeutics. *Current Treatment Options in Neurology* **18**, 52. DOI: [10.1007/s11940-016-0434-1](https://doi.org/10.1007/s11940-016-0434-1).
- Steyaert J, Umans S, Willekens D, Legius E, Pijkels E, de Die-Smulders C, Van den Berghe H and Fryns JP (1997) A study of the cognitive and psychological profile in 16 children with congenital or juvenile myotonic dystrophy. *Clinical Genetics* **52**, 135–141. DOI: [10.1111/j.1399-0004.1997](https://doi.org/10.1111/j.1399-0004.1997).
- Stokes M, Varughese N, Iannaccone S and Castro D (2019) Clinical and genetic characteristics of childhood-onset myotonic dystrophy. *Muscle & Nerve* **60**, 732–738. DOI: [10.1002/mus.26716](https://doi.org/10.1002/mus.26716).
- Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA and Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Journal of the American Medical Association* **283**, 2008–2012. DOI: [10.1001/jama.283.15.2008](https://doi.org/10.1001/jama.283.15.2008).
- Study Quality Assessment Tools | NHLBI, NIH [no date]. (2023) Available from: <https://www.nlm.nih.gov/health-topics/study-quality-assessment-tools> Accessed.
- Suokas KI, Haanpää M, Kautiainen H, Udd B and Hietaharju AJ (2012) Pain in patients with myotonic dystrophy type 2: a postal survey in Finland. *Muscle & Nerve* **45**, 70–74. DOI: [10.1002/mus](https://doi.org/10.1002/mus).
- Timman R, Tibben A and Wintzen AR (2010) Myotonic dystrophy: the burden for patients and their partners. *Journal of Rehabilitation Medicine* **42**, 823–830. DOI: [10.2340/16501977-0598](https://doi.org/10.2340/16501977-0598).
- Tufanaru C, Munn Z, Stephenson M and Aromataris E (2015) Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *International Journal of Evidence-Based Healthcare* **13**, 196–207. DOI: [10.1097/XEB.0000000000000065](https://doi.org/10.1097/XEB.0000000000000065).
- Turner C and Hilton-Jones D (2014) Myotonic dystrophy: diagnosis, management and new therapies. *Current Opinion in Neurology* **27**, 599–606. DOI: [10.1097/WCO.0000000000000128](https://doi.org/10.1097/WCO.0000000000000128).
- Urata Y, Nakamura M, Shiokawa N, Yasuniwa A, Takamori N, Imamura K et al (2020) Sleep disorders in four patients with myotonic dystrophy type 1. *Frontiers in Neurology*, **11**, 12. DOI: [10.3389/fneur.2020.00012](https://doi.org/10.3389/fneur.2020.00012).
- van der Velden BG, Okkersen K, Kessels RP, Groenewoud J, van Engelen B, Knoop H and Raaphorst J (2019) Affective symptoms and apathy in myotonic dystrophy type 1 a systematic review and meta-analysis. *Journal of Affective Disorders* **250**, 260–269. DOI: [10.1016/j.jad.2019.03.036](https://doi.org/10.1016/j.jad.2019.03.036).
- Van Heugten C, Meuleman S, Hellebrekers D, Kruitwagen-van Reenen E and Visser-Meily J (2018) Participation and the role of neuropsychological functioning in myotonic dystrophy type 1. *Journal of Neuromuscular Diseases* **5**, 205–214. DOI: [10.3233/JND-170246](https://doi.org/10.3233/JND-170246).
- Van Spaendonck KP, Ter Brugge JP, Weyn Banningh EW, Maassen BA, Van de Biezenbos JB and Gabriëls FJ (1995) Cognitive function in early adult and adult onset myotonic dystrophy. *Acta Neurologica Scandinavica* **91**, 456–461. DOI: [10.1111/j.1600-0404.1995.tb00446.x](https://doi.org/10.1111/j.1600-0404.1995.tb00446.x).
- Wahbi K and Furling D (2020) Cardiovascular manifestations of myotonic dystrophy. *Trends in Cardiovascular Medicine* **30**, 232–238. DOI: [10.1016/j.tcm.2019.06.001](https://doi.org/10.1016/j.tcm.2019.06.001).
- Wenninger S, Montagnese F and Schoser B (2018) Core clinical phenotypes in myotonic dystrophies. *Frontiers in Neurology* **9**, 303. DOI: [10.3389/fneur.2018.00303](https://doi.org/10.3389/fneur.2018.00303).
- Winblad S, Jensen C, Månsson J-E, Samuelsson L and Lindberg C (2010) Depression in myotonic dystrophy type 1: clinical and neuronal correlates. *Behavioral and Brain Functions: BBF* **6**, 25. DOI: [10.1186/1744-9081-6-25](https://doi.org/10.1186/1744-9081-6-25).
- Yum K, Wang ET and Kalsotra A (2017) Myotonic dystrophy: disease repeat range, penetrance, age of onset, and relationship between repeat size and phenotypes. *Current Opinion in Genetics & Development* **44**, 30–37. DOI: [10.1016/j.gde.2017.01.007](https://doi.org/10.1016/j.gde.2017.01.007).