

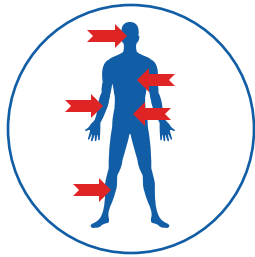


Module 3

What are the clinical manifestations and impact of myotonic dystrophy type 1 (DM1)?

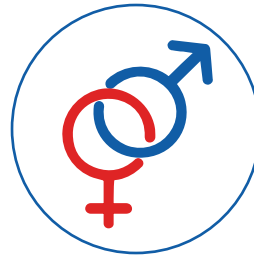


Module summary



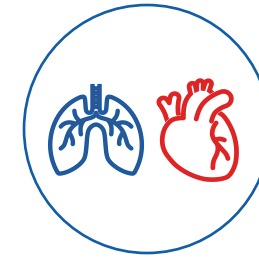
Spliceopathy drives the multi-system clinical manifestations of DM1¹

There are skeletal muscle, ocular, respiratory, cardiac, CNS, GI, and endocrine features of DM1, and risk of cancer and pregnancy-related complications is elevated^{2–10}



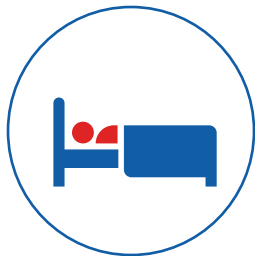
Gender influences DM1 clinical profile and severity of disease¹¹

Features more prevalent in women include thyroid disorder, and urinary and anal incontinence; while respiratory features, severe myotonia, and facial dysmorphism are more prevalent in men¹¹



DM1 leads to significant morbidity and reduced life expectancy^{12,13}

Respiratory disease is the leading cause of mortality in DM1, followed by cardiac arrhythmias^{12–14}



Muscle weakness, fatigue, and daytime sleepiness are the most prevalent and impactful symptoms reported by individuals with DM1¹⁵

Individuals with DM1 have challenges performing daily activities such as using stairs, handling objects, and staying alert and awake¹⁵



Comorbidities cause under-appreciated symptoms that require medical attention, resulting in significantly higher healthcare resource utilization¹⁶

The most impactful comorbidities include GI symptoms, cardiac dysrhythmias, and sleep disorders¹⁶



Individuals with DM1 have lower labor force participation and annual income than the general population, despite comparable educational attainment^{15,17}

In one US study, approximately half of the overall respondents were unable to work due to DM1¹⁵

DM1, myotonic dystrophy type 1.

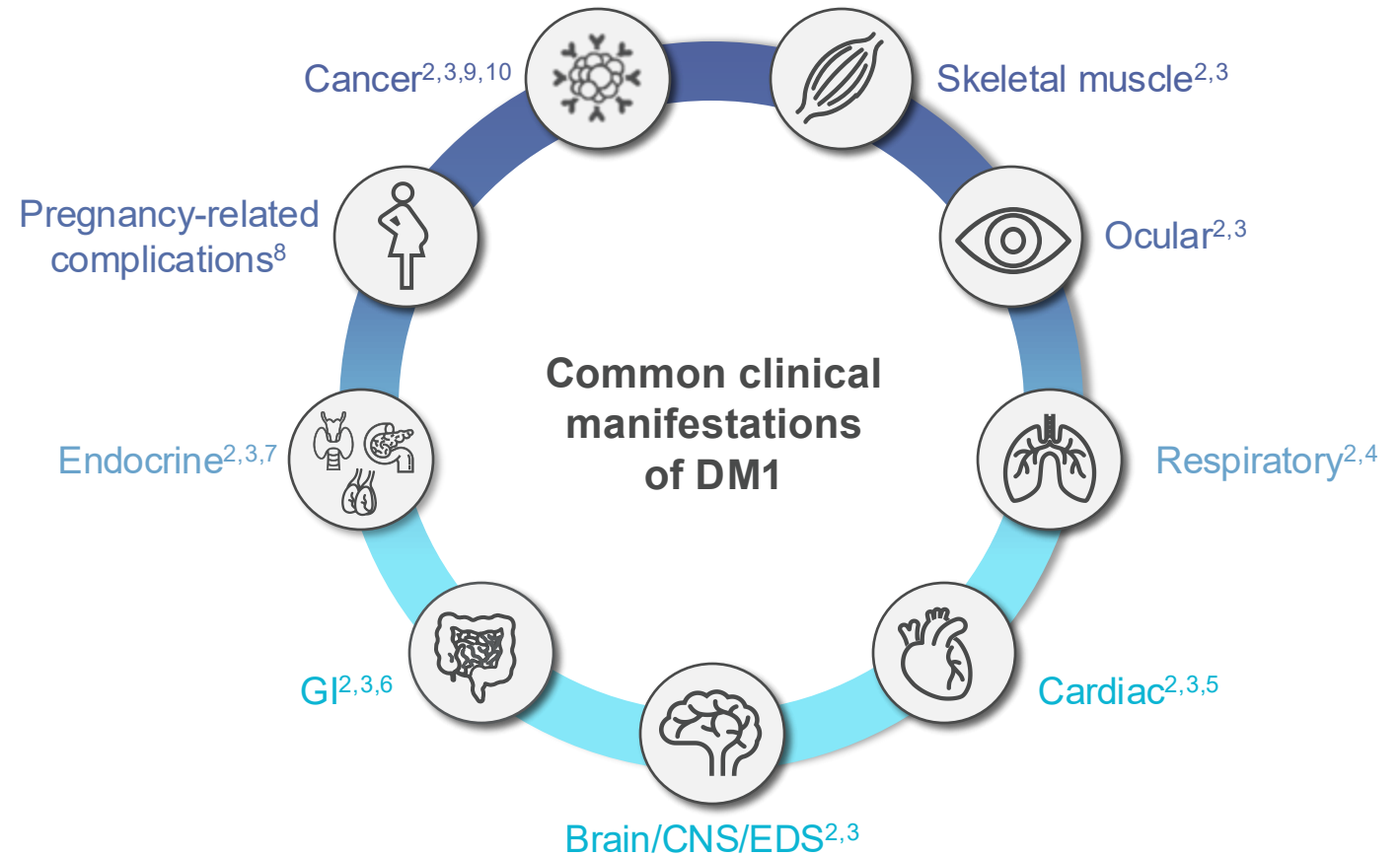
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What clinical manifestations arise from spliceopathy in DM1?

Spliceopathy drives the multi-system clinical manifestations of DM1¹

Examples of genes that are alternatively spliced in DM1:¹

- Myotonia and muscle weakness**
CLCN1, DTNA, PKM2, MBNL1, BIN1, CACNA1S, RyR1, SERCA1, TNNT3, DMD, CAPN3, NEB, MTMR1, ATP5MC2, NCOR2, SOS1, NFIX
- Cardiac conduction complications**
SERCA2, LDB3, SCN5A, TNNT2, TTN, MYOM1, ALPK3, RBFOX2
- Cognitive impairment**
MAPT, NMDAR1, APP, MBNL1, MBNL2



Skeletal muscle-, cardiorespiratory-, and CNS-related effects of DM1 are the main determinants of function and survival^{2,3}

CNS, central nervous system; DM1, myotonic dystrophy type 1; EDS, excessive daytime sleepiness; GI, gastrointestinal. Figures from BioRender.

Table adapted from López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.3390/genes11091109.

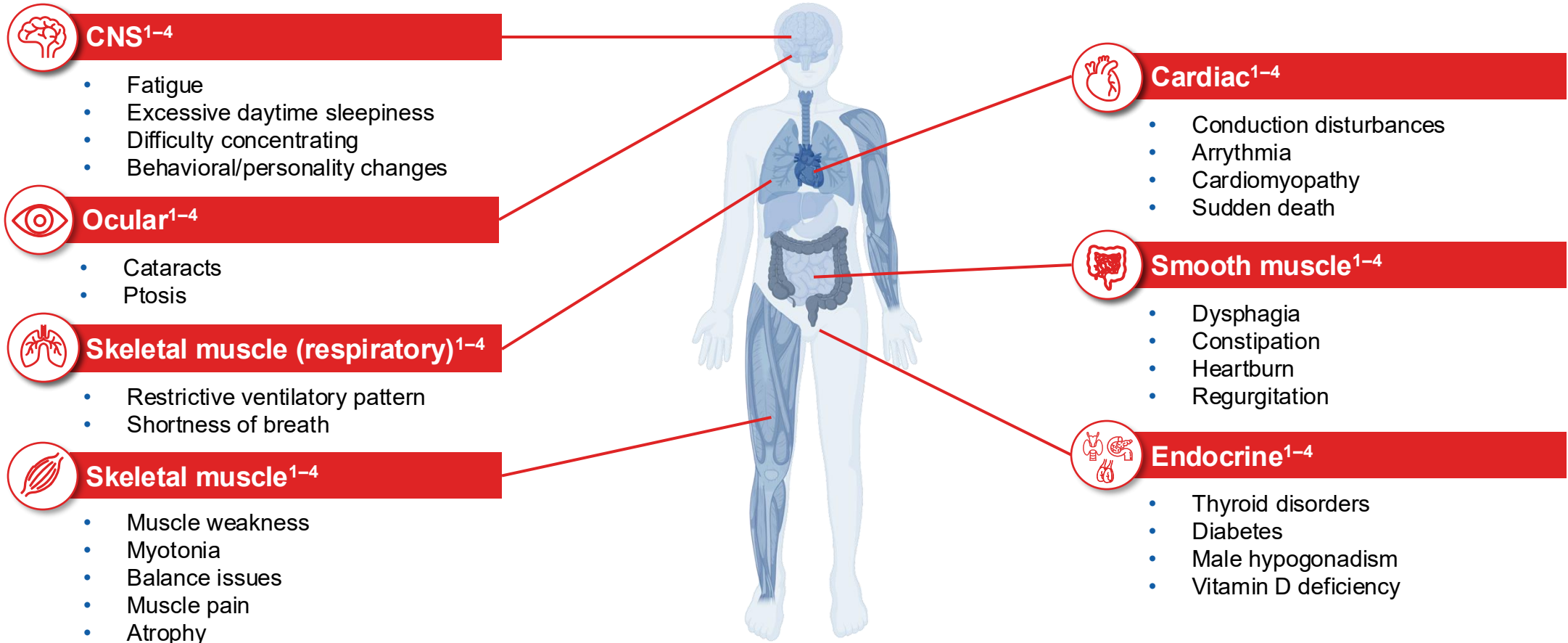
1. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109; 2. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet].

Seattle (WA): University of Washington, Seattle; 1993–2022; 3. Thomson CA. *Neurol Clin*. 2014;32:705–719; 4. Hartog L, et al. *Front Neurol* 2021;12:658532; 5. Wahbi K, Furling D. *Trends Cardiovasc Med*. 2020;30:232–238;

6. Bellini M, et al. *World J Gastroenterol*. 2006;12:1821–1828; 7. Peric S, et al. *Acta Myol*. 2013;32:106–109; 8. Johnson NE, et al. *J Neuromuscul Dis*. 2015;2:447–452; 9. Gadalla SM, et al. *JAMA*. 2011;306:2480–2486;

10. Win AK, et al. *Mayo Clin Proc*. 2012;87:130–135.

Which organs and tissues are affected by DM1?



DM1 affects virtually all organs and tissues¹⁻⁴

Slide does not represent an exhaustive list of symptoms.

CNS, central nervous system.

Figure from BioRender.

1. Thornton CA. *Neurol Clin*. 2014;32:705–719; 2. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 3. Hageman KA, et al. *Muscle Nerve*. 2019;59:457–464;

4. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed)*. 2020;35:185–206.

Which organs and tissues are affected by DM1?

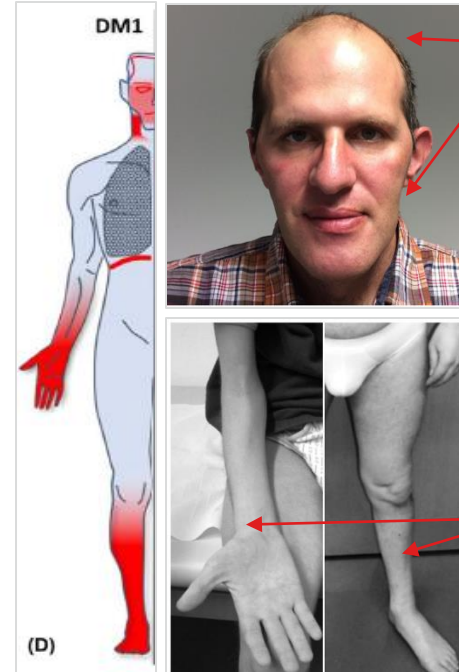


Skeletal muscle features

Myotonia, muscular weakness, and atrophy are the most prominent musculoskeletal features^{1,2}

- **Myotonia** (impaired muscle relaxation) **occurs in 88%** of individuals with DM1, but only **50% report a significant impact** on daily life²⁻⁴
 - Myotonia mainly affects the fingers (grip myotonia), jaw, and tongue^{2,4}
 - Myotonia in DM1 is thought to arise due to increased excitability of muscle fibers, leading to continuous discharges of repetitive action potentials after mechanical stimulation or voluntary contraction²
- **Muscle weakness is reported in 94%** of adults with DM1 and is considered the symptom with the **highest impact**, with 75% stating it has a significant impact* on their daily life^{3,4}
 - Distally predominant **muscular weakness and atrophy** are characteristic, mainly involving finger flexors, wrist flexors, and foot extensors²
 - In individuals with DM1, muscle biopsy demonstrates variability in muscle fiber size, rows of internal nuclei, fibrosis, aberrant myofibril orientation, and type I fiber atrophy⁵
- **Muscular imbalance secondary to weakness causes pain-related complications associated with disease progression²**

Typical musculoskeletal symptoms²



'Myopathic face' is a prominent early feature of DM1:
Long face, temporomandibular wasting, balding forehead and ptosis

Weakness and atrophy of facial muscles may falsely indicate a tired, sad, or emotionless individual²

Distal muscular atrophy

*Defined as major or moderate impact.

DM1, myotonic dystrophy type 1.

Images from Wenninger S, et al. *Front Neurol*. 2018;9:303, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.3389/fneur.2018.00303.

1. LoRusso S, et al. *Neurotherapeutics*. 2018;15:872–884; 2. Wenninger S, et al. *Front Neurol*. 2018;9:303; 3. The Christopher Project. Report to the Myotonic Dystrophy Community. Accessed February 12, 2025. https://www.myotonic.org/sites/default/files/pages/files/Christopher_Project_Full_Report.pdf; 4. Hagerman KA, et al. *Muscle Nerve*. 2019;59:457–464; 5. Tumer C, Hilton-Jones D. *J Neurol Neurosurg Psychiatry*. 2010;81:358–367.

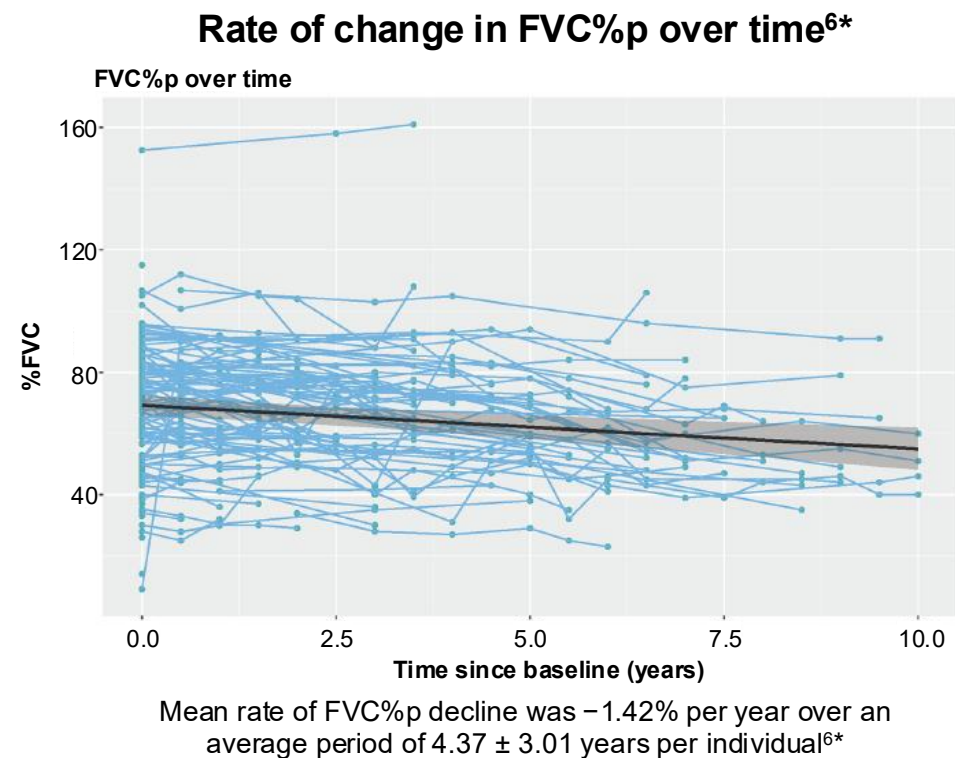
Which organs and tissues are affected by DM1?



Respiratory features

Respiratory disease is the primary cause of mortality in DM1^{1–3}

- Respiratory disease typically occurs in adults between 50–60 years of age **and accounts for mortality in 31–51% of individuals with DM1**^{1–4}
- **Restrictive ventilatory pattern** is the predominant ventilatory function abnormality in DM1, with forced vital capacity (FVC) and vital capacity (VC) being most commonly impaired^{5,6}
- **Reduced cough efficiency** in DM1 is due to weakness of the inspiratory and expiratory muscles. This leads to impaired airway clearance and an increased risk of aspiration and pulmonary infections⁴
- **Restrictive respiratory impairment in DM1 is slowly progressive, but requires appropriate management because of high risk of mortality**⁶



*FVC over time ($r = -1.421$, Wald statistic = 13.92 [$p < 0.001$], $n = 152$ subjects with 522 observations).

DM1, myotonic dystrophy type 1; FVC%p, percent predicted forced vital capacity.

Image adapted from Hartog L, et al. *Front Neurol.* 2021;12:658532, licensed under a CC-BY 4.0 Creative Commons license; doi: doi.org/10.3389/fneur.2021.658532.

1. Mathieu J, et al. *Neurology.* 1999;52:1658–1662; 2. de Die-Smulders CEM, et al. *Brain.* 1998;121:1557–1563; 3. Groh WJ, et al. *Muscle Nerve.* 2011;43:648–651; 4. Boentert M, et al. *Respiration.* 2020;99:360–368; 5. Hawkins AM, et al. *Neuromuscul Disord.* 2019;29:198–212; 6. Hartog L, et al. *Front Neurol.* 2021;12:658532.

Which organs and tissues are affected by DM1?

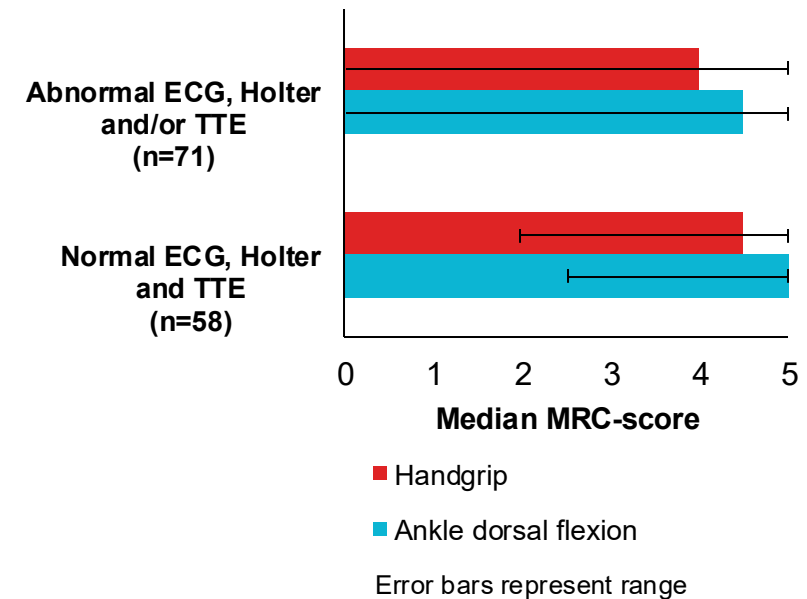


Cardiac features

Cardiac arrhythmias are the second leading cause of mortality in DM1¹

- Cardiac abnormalities are detected in **>50% of individuals** with DM1 and account for 20–35% of deaths in individuals with DM1^{1–4}
 - Individuals with DM1 have a three-fold higher risk of sudden cardiac death than age-matched controls^{4,5}
- Conduction disturbances, arrhythmias, cardiomyopathy, and sudden death** are the most common cardiac manifestations in DM1^{6–8}
 - Myocardial fibrosis, occurring in up to 40% of individuals, reflects an increased tendency for the development of cardiomyopathy⁹
 - Left ventricular (LV) dysfunction is ~4.5-fold higher than in the general population⁹
 - Cardiac conduction disorders in DM1 are likely caused by myocyte hypertrophy, interstitial fibrosis, and fatty infiltration⁴
 - Misregulation of SCN5A alternative splicing has been shown to contribute to arrhythmias and conduction delay in a preclinical mouse model, two predominant features of myotonic dystrophy¹⁰
- Abnormal cardiac findings correlate with weaker muscle strength compared with normal cardiac findings⁴
- A cardiologist, working alongside a team of specialists, can help manage the cardiac symptoms of DM1⁶**

Relationship between cardiac involvement and peripheral strength^{4*}



*Large single-center study of 129 unselected individuals with DM1 (49.6% men), mean (SD) age 44 (14.7) years.

DM1, myotonic dystrophy type 1; ECG, electrocardiogram; MRC, Medical Research Council; SD, standard deviation; TTE, transthoracic echocardiogram.

1. de Die-Smulders CEM, et al. *Brain*. 1998;121:1557–1563; 2. Mathieu J, et al. *Neurology*. 1999;52:1658–1662; 3. Groh WJ, et al. *Muscle Nerve*. 2011;43:648–651; 4. Petri H, et al. *Int J Cardiol*. 2014;174:31–36; 5. Russo V, et al. *J Clin Med*. 2023;12:1947; 6. McNally EM, Sparano D. *Heart*. 2011;97:1094–1100; 7. McNally EM, et al. *J Am Heart Assoc*. 2020;9:e014006; 8. Groh WJ, et al. *N Engl J Med*. 2008;358:2688–2697; 9. Russo V, et al. *J Card Fail*. 2020;26:849–856; 10. Freyermuth F, et al. *Nat Commun*. 2016;7:11067.

Which organs and tissues are affected by DM1?

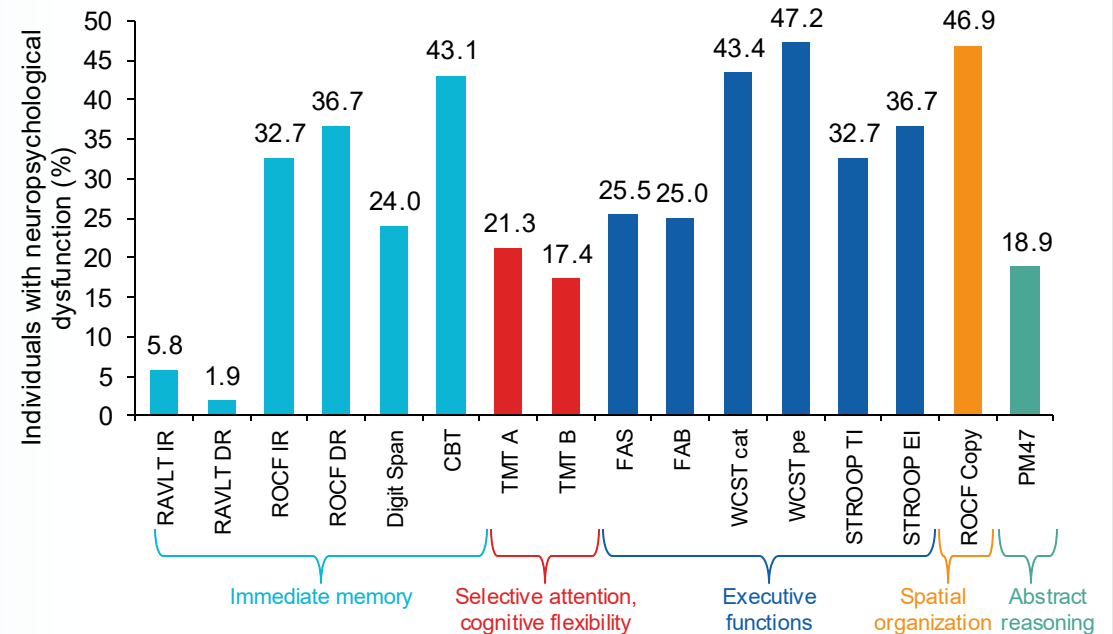


Brain features

DM1 is associated with a decline in cognitive function^{1,2}

- DM1 causes changes to the brain structure due to protein deposits and mutant RNA accumulations in the nuclei of brain cells, cellular alterations (including neuronal loss and gliosis), and white matter changes that result in cognitive effects³
- In adults with DM1, varying degrees of cognitive dysfunction, characterized by a dysexecutive syndrome with predominant frontotemporal involvement, may occur that can result in **behavioral-personality changes, fatigue, and excessive daytime sleepiness**¹⁻⁷
- Mild-to-moderate intellectual disability and developmental delays are common in individuals with congenital or childhood/juvenile DM^{18,9}
- DM1 profoundly affects cognition, behavior, and quality of life, underscoring the need for holistic, multi-disciplinary care beyond managing muscular symptoms**^{5,6,10}

Percentages of DM1 individuals with clinically relevant neuropsychological dysfunctions (N=65)^{5*}



*Percentages of impairment (%) are related to available cut-off scores of normality ($\geq 95\%$ of the tolerance limit of the normal population distribution).

CBT, Corsi's block test; DM1, myotonic dystrophy type 1; DR, delayed recall; EI, error interference; FAB, frontal assessment battery; FAS, controlled oral word association test (COWAT); IR, immediate recall; PM47, progressive matrices 47; RAVLT, Ray auditory verbal learning test; RNA, ribonucleic acid; ROCF, Rey-Osterrieth complex figure; TI, time interference; TMT, trail making test; WCST cat, Wisconsin card sorting test (categories); WCST pe, Wisconsin card sorting test (perseverative errors). Image adapted from Baldanzi S, et al. *Orphanet J Rare Dis*. 2016;11:34, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.1186/s13023-016-0417-z.

1. Modoni A, et al. *J Neurol*. 2008;255:1737–1742; 2. White M. *Ther Innov Regul Sci*. 2020;54:1010–1017; 3. Weijs R, et al. *Neuropathology*. 2021;41:3–20; 4. van der Velden BG, et al. *J Affect Disord*. 2019;250:260–269; 5. Baldanzi S, et al. *Orphanet J Rare Dis*. 2016;11:34; 6. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 7. Sansone V, et al. *J Clin Sleep Med*. 2021;17:2383–2391; 8. Steyaert J, et al. *Am J Med Genet*. 2000;96:888–889; 9. Jacobs D, et al. *Am J Med Genet*. 2016;174B:359–366; 10. Landfeldt E, et al. *J Neurol*. 2019;266:998–1006.

Which organs and tissues are affected by DM1?

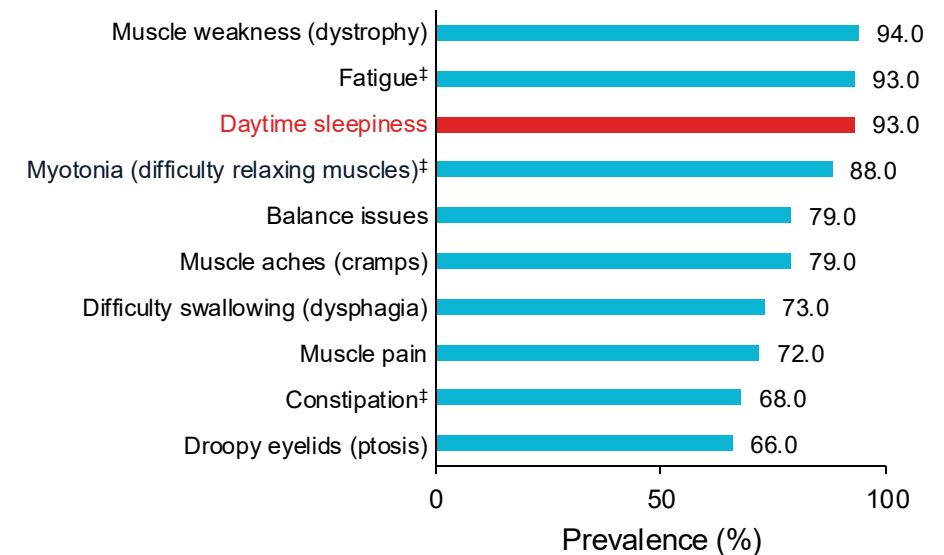


Brain features

EDS is among the most common non-neuromuscular manifestations of DM1^{1,2}

- **EDS** is a common feature due to a central dysfunction of sleep regulation and **has a prevalence of 93%** among individuals with DM1^{1,2}
- EDS is one of the most impactful symptoms, with 66% of individuals reporting a significant impact* on their daily life^{*1,3}
- Individuals with DM1 experience increased total sleep, greater fragmentation of sleep, and altered sleep architecture (greater time spent in slow wave and REM sleep) compared with healthy controls^{4,5}
- Alterations in brain structure seem to occur in regions linked to cognitive deficits and EDS^{6,7}
- **CNS involvement in myotonic dystrophy profoundly affects cognition, behavior, and quality of life, underscoring the need for holistic, multi-disciplinary care beyond managing muscular symptoms⁸**

Top 10 most commonly reported DM1 symptoms^{1†}



*Defined as major or moderate impact. †Respondents were from the United States and Canada. Statistics were controlled for age differences, and a Bonferroni correction for multiple comparisons was applied. Prevalence calculations were based on n=457. ‡Significantly higher prevalence or impact of symptoms in females (p<0.05).

DM1, myotonic dystrophy type 1; EDS, excessive daytime sleepiness; REM, rapid eye movement.

1. Hageman KA, et al. *Muscle Nerve*. 2019;59:457–464; 2. Hilton-Jones D. *Curr Opin Neurol*. 1997;10:399–401; 3. The Christopher Project. Report to the Myotonic Dystrophy Community. Accessed May 29, 2025.

https://www.myotonic.org/sites/default/files/pages/files/Christopher_Project_Full_Report.pdf; 4. Yu H, et al. *Sleep*. 2011;34:165–170; 5. Sansone V, et al. *J Clin Sleep Med*. 2021;17:2383–2391; 6. Baldanzi S, et al. *Neuroimage Clin*. 2016;12:190–197; 7. van der Plas E, et al. *J Neuromuscul Dis*. 2019;6:321–332; 8. Heatwole C, et al. *Neurology*. 2012;79:348–357.

Which organs and tissues are affected by DM1?



GI features

GI manifestations are common and occur along the entire digestive tract in individuals with DM^{1,2}

- At least one GI symptom is reported by 91% of individuals with myotonic dystrophy in North America, with 64% experiencing one or more symptoms that significantly impact their daily life (moderate-to-major impact)³
- Most individuals (79%, n=721/913) with DM1 enrolled in the DM and FSHD Registry (NCT00082108) reported a history of ≥ 1 GI manifestation, but only 1.3% of these individuals reported a GI problem as their initial manifestation²
- In the upper GI tract, dysphagia, heartburn, regurgitation, and indigestion are common symptoms, whereas in the lower GI tract, abdominal pain, bloating, and changes in bowel habits (constipation/diarrhea) are frequently reported^{1,2}
- GI symptoms in DM1 are generally attributed to motility disorders caused by striated and smooth muscle dysfunction. Neurologic alterations may also play a role¹
- Individuals with DM1 who are women, who have higher body mass index, or who have longer disease duration have a greater risk of developing GI symptoms^{2,4}
- **Regardless of the affected region, GI dysfunction reduces daily function and comfort, and in severe cases, it can be life-threatening⁵**

Percentages of individuals with DM1 who reported GI manifestations at enrollment in the registry²

GI manifestation	Total individuals reported, %
Trouble swallowing	55
Acid reflux	38
Constipation	33
Gallbladder problems	19
Liver problems	6
Stomach ulcers	4

Which organs and tissues are affected by DM1?



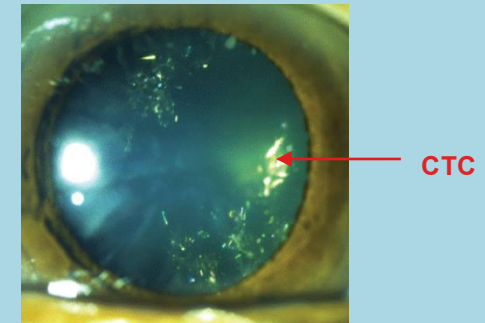
Ocular features

Cataract formation is the most common ocular feature in DM1¹

- **Christmas tree cataract (CTC)** occurs in nearly all individuals with myotonic dystrophy; however, only 16% of individuals with CTC are diagnosed with myotonic dystrophy¹
- CTC can cause vision impairment as it progresses¹
- Other ocular findings include ptosis, lower intraocular pressure, Fuchs' endothelial corneal dystrophy, pupillary light-near dissociation, ciliary body detachment, and reticular maculopathy¹
- Individuals with DM1 may present with early-onset cataracts as cataracts in DM1 may progress faster than usual cataracts²
- **Premature cataracts or a family history of cataracts in individuals <55 years old who also have muscle symptoms may be suggestive of myotonic dystrophy^{1,2,5}**

Cataracts in individuals with DM1^{3,4}

Early cataract
CTCs appear in the outer layer at the back of the lens as very fine and bright dust-like particles^{3,4}



Mature cataracts
Cortical spokes appear and increase in size over time and form star-shaped white regions that cloud the lens³

DM1, myotonic dystrophy type 1.

Image from El Moubarik N, et al. *Austin J Clin Ophthalmol*. 2023;10:1163, licensed under a CC-BY 4.0 Creative Commons license.

1. Moshirfar M, et al. *Clin Ophthalmol*. 2022;16:2837–2842; 2. MDF. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 1. Accessed February 14, 2025.

https://www.myotonic.org/sites/default/files/pages/files/MDF_Consensus-basedCareRecsAdultsDM1_1_21.pdf; 3. Myotonic Dystrophy Support Group. Myotonic Dystrophy and the Eye. Accessed February 14, 2025. <https://www.myotonicdystrophysupportgroup.org/myotonic-dystrophy-and-the-eye/>; 4. El Moubarik N, et al. *Austin J Clin Ophthalmol*. 2023;10:1163; 5. Thomson CA. *Neurol Clin*. 2014;32:705–719.

Which organs and tissues are affected by DM1?



Endocrine features

Various forms of progressive endocrine dysfunction can manifest in DM1¹

- Individuals with DM1 may present with endocrinopathies with the most prevalent being insulin resistance, hypogonadism, thyroid disorders, hydrocarbon metabolism abnormalities, and phosphocalcium metabolism abnormalities¹
 - The risk for type 2 diabetes is approximately three times higher in individuals with DM1 compared with individuals without DM1²
- Mutant DMPK mRNA is expressed in the testes, pituitary gland, thyroid, pancreas, and liver, and results in loss of function and abnormal processing of gene products, (e.g. the insulin receptor)³
- Reproductive abnormalities are widely recognized in DM1, with progressive testicular atrophy affecting approximately 80% of men, many of whom experience infertility⁴
- A higher percentage of hyperparathyroidism is seen in individuals with DM1 than the general population^{5,6}
- **The incidence of endocrine dysfunction increases with disease progression⁷**

Endocrine abnormalities in DM1¹

Endocrine dysfunctions	Common disorders
Male hypogonadism ^{1,5}	
Thyroid disorders ^{1,5}	
Alterations of hydrocarbon and phosphocalcium metabolism ¹	
Vitamin D deficiency ^{1,5-8}	
Diabetes mellitus ^{5,7}	
Primary hyperparathyroidism ¹	
Hypocortisolism ¹	
Hypercortisolism ¹	
Dyslipidemia ¹	
Electrolyte alterations ¹	

DM1, myotonic dystrophy type 1.

1. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed)*. 2020;35:185–206; 2. Alsaggaf R, et al. *Int J Cancer*. 2020;147:785–792; 3. Winters SJ. *J Clin Endocrinol Metab*. 2021;106:2819–2827; 4. Kim WB, et al. *Korean J Urol*. 2012;53:134–136; 5. Dahlqvist JR, et al. *Eur J Neurol*. 2015;22:116–122; 6. Terracciano C, et al. *J Neurol*. 2013;260: 2330–2334; 7. Wenninger S, et al. *Front Neurol*. 2018;9:303; 8. Passeri E, et al. *J Neurol Sci*. 2013;331:132–135.

Which organs and tissues are affected by DM1?

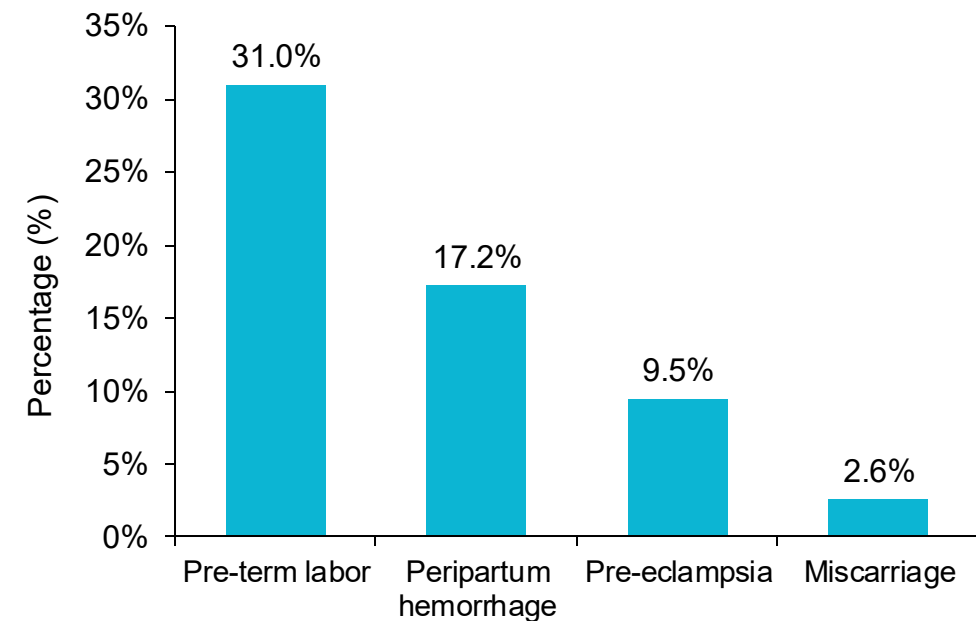


High-risk pregnancy features

Women with DM1 of childbearing age are at high risk for complications during pregnancy and childbirth^{1,2}

- Mothers with DM1 are likely to experience ectopic pregnancy, premature delivery, spontaneous abortions, prolonged labor, weakness during labor, retained placenta, postpartum hemorrhage, uterine over distention with polyhydramnios, diminished ovarian reserve, reactions to analgesia and cardiac complications^{1,2}
- Women with DM1 are at risk of having a child with a more severe form of the disease, and prenatal diagnosis can provide an estimate of disease severity based on CTG triplet repeat length¹
- Women with DM1 have high rates of miscarriage^{3,4}
- **Consultation and monitoring by a pediatric/neonatal subspecialist and obstetrician along with genetic counselling and family planning services are highly recommended²**

Complications associated with first pregnancy in mothers with DM1³



*Mothers with DM1 were recruited from one of two patient registries completed the Myotonic Dystrophy Health Index-Short Form (MDHI-SF) to measure their disease burden and identify the severity of select symptoms 6 months prior to, during, and 6 months after their first pregnancy (n=152 mothers; n=375 pregnancies).³

DM1, myotonic dystrophy type 1.

1. Gutierrez G, et al. *Neurologia (Engl Ed)*. 2020;35:185–206; 2. MDF. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 1. Accessed February 14, 2025.

https://www.myotonic.org/sites/default/files/pages/files/MDF_Consensus-basedCareRecsAdultsDM1_1_21.pdf; 3. Johnson NE, et al. *J Neuromuscul Dis*. 2015;2:447–452; 4. Ørngreen MC, et al. *J Neurol*. 2012;259:912–920.

Which organs and tissues are affected by DM1?



Cancer

DM1 is associated with a higher risk of cancer^{1,2}

- Overall, individuals with DM1 have a significantly higher risk of cancer than individuals without DM1^{1,2}
 - The individual cancers identified as having higher risk can vary across DM1 study cohorts^{1,2}
- Cancer risk may differ by disease severity and gender:
 - Greater risk in adult-onset DM1 versus late-onset DM1¹
 - Increased risk for women compared with men²
- While the molecular mechanisms underlying increased cancer risk are still being elucidated, there is evidence for significant downregulation of tumor suppressor genes in DM1²
- **Individuals with DM1 have a significantly higher overall cancer risk (disease severity and gender may be risk factors) with thyroid, brain, skin, uterine, endometrium, and ovarian cancers predominating^{1,2}**

Cancers with significantly elevated risks identified in different DM1 populations

Study by Alsaggaf and colleagues ¹	
Women (adult-onset DM1)	Both sexes (adult-onset DM1)
Uterus	Thyroid
	Melanoma
1.81-fold greater risk (95% CI 1.12–2.93) in adult-onset DM1 (n=500); 0.53-fold greater risk (95% CI 0.32–0.85) in late-onset DM1 (n=295) ^{1*}	
Study by Fernández-Torrón and colleagues ²	
Women	Both sexes
Ovary	Thyroid
Endometrium	Brain
1.81-fold greater risk (95% CI 1.37–2.36) in DM1 overall (N=424) ^{2†}	

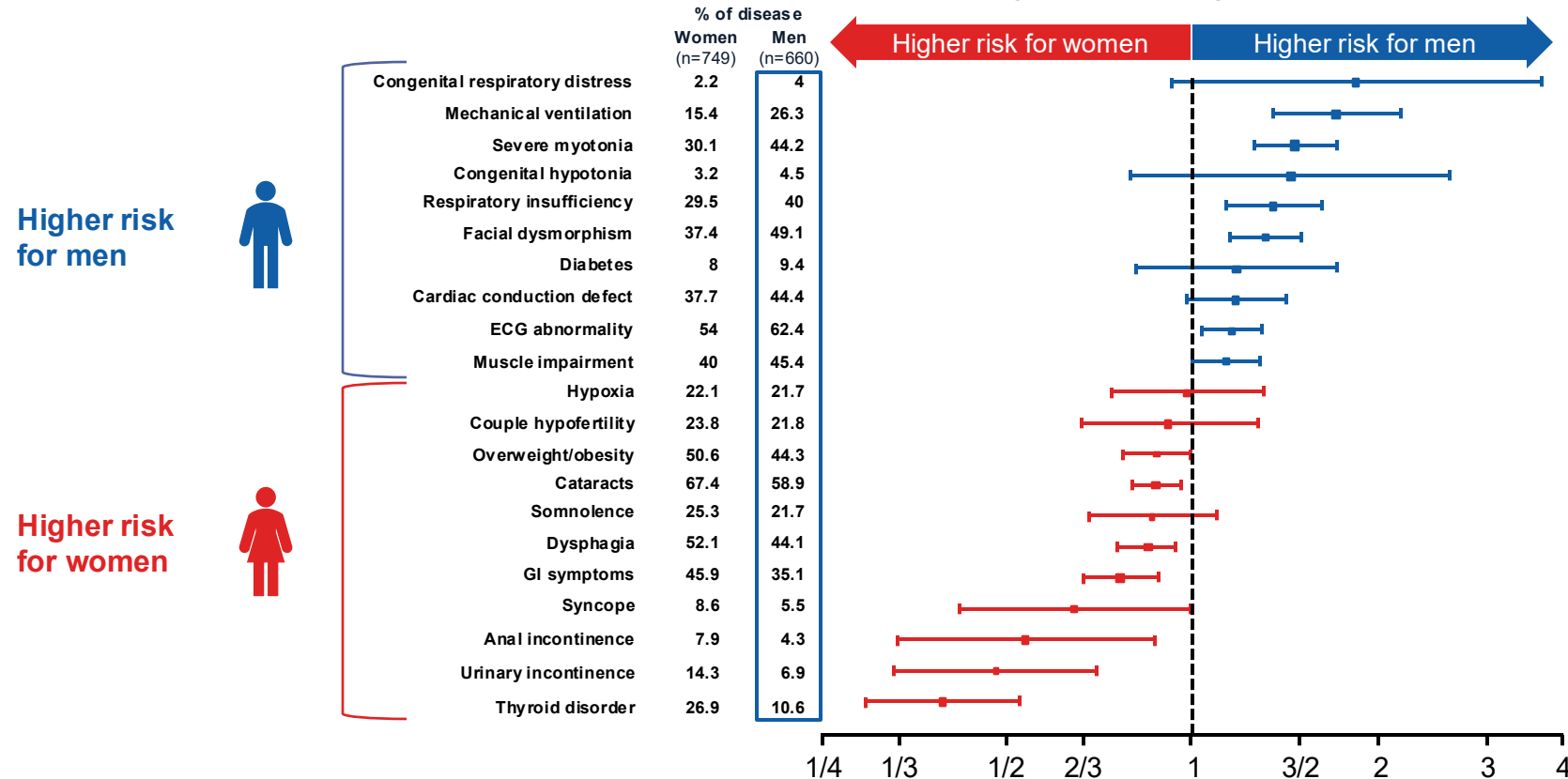
*Retrospective medical record analysis from the United Kingdom Clinical Practice Research Datalink (between January 1, 1988 and February 29, 2016). Hazard ratios were calculated to measure risk.¹ †Retrospective medical record analysis of the Gipuzkoa DM1 cohort (1985–2013). Standardized incidence ratios were calculated to measure risk²

CI, confidence interval; DM1, myotonic dystrophy type 1.

1. Alsaggaf R, et al. *JNCI Cancer Spectr*. 2018;2:pk052; 2. Fernández-Torrón R, et al. *Neurology*. 2016;87:1250–1257.

Are there gender differences in DM1 clinical presentation?

Gender impact on severity of DM1 symptoms*†



Gender influences DM1 clinical profile and severity of disease

*Cross-sectional analysis of the French DM-scope registry of adults with DM1 (>18 yrs, n=1409).

†A risk ratio is significant if the confidence interval does not cross the vertical line at value 1. The width of confidence interval depends on estimate standard deviation and consequently on observations number. Gender impact is expressed as risk ratio on 95% confidence interval.

DM1, myotonic dystrophy type 1; ECG, electrocardiogram; GI, gastrointestinal.

Image adapted from Dogan C, et al. *PLoS One*. 2016;11:e0148264, licensed under a CC-BY 4.0 Creative Commons license; doi: 10.1371/journal.pone.0148264.

Dogan C, et al. *PLoS One*. 2016;11:e0148264.

How does DM1 affect life expectancy?

In a 10-year follow-up study of 367 individuals with DM1:

Mean age at death was
53 years¹

Mortality was
7.3 times higher
compared with an age-matched
reference population¹

Respiratory failure and
cardiovascular disease was
the cause of death in 43% and
20% of participants,
respectively¹

In a longitudinal study of 83 individuals with adult-onset DM1:

Most individuals (63%) died
between the ages of
50 and 65 years²

The likelihood of surviving to 65
was significantly
**lower for those with DM1
(18%)** compared with those
without DM1 (78%)²

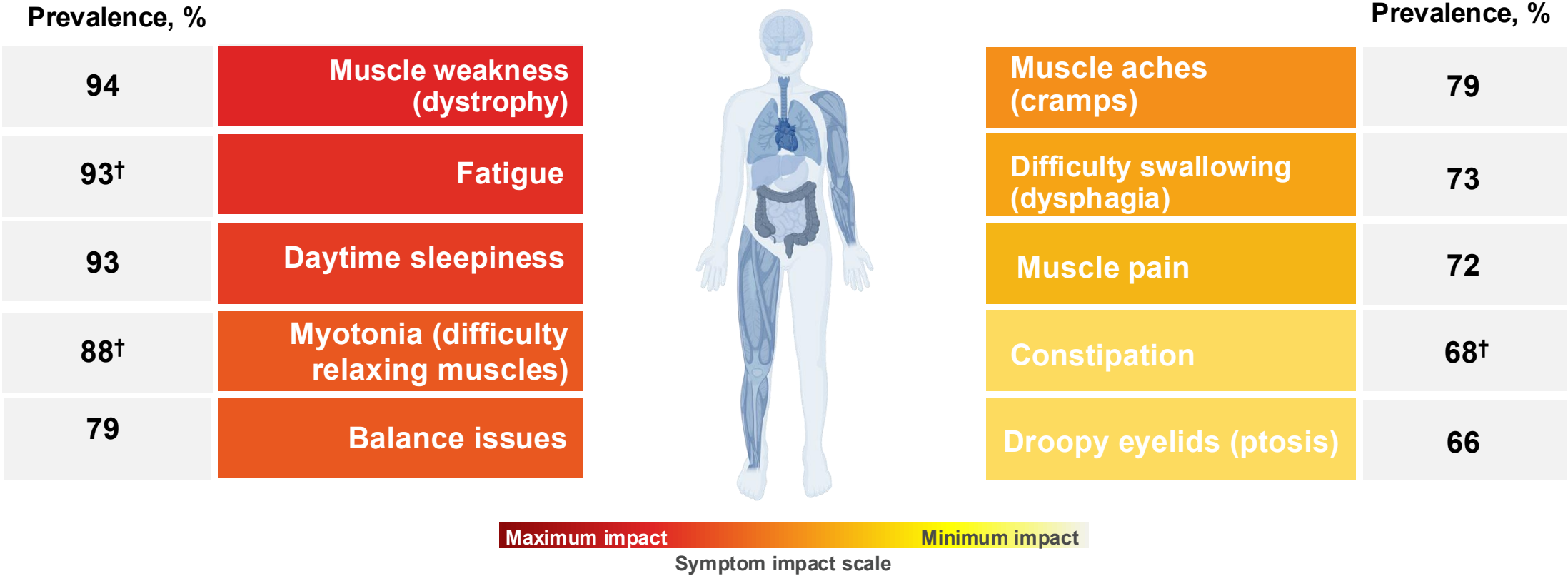
System	Manifestations
Skeletal muscle ³⁻⁵	Muscle weakness Myotonia
Cardiac ⁶⁻⁸	Conduction system disease Arrhythmias
Respiratory ^{1,2,8-10}	Respiratory insufficiency Pneumonia
Brain ¹¹⁻¹⁵	Neuropsychological Daytime sleepiness Fatigue
Gastrointestinal ¹⁶	Dysphagia Constipation Diarrhea
Ocular ¹⁷	Cataract
Endocrinal ^{18,19}	Insulin resistance Reduced fertility/infertility in men

DM1 leads to significant morbidity and reduced life expectancy^{1,2}

DM, myotonic dystrophy type .
1. Mathieu J, et al. *Neurology*. 1999;52:1658–1662; 2. de Die-Smulders CEM, et al. *Brain*. 1998;121:1557–1563; 3. LoRusso S, et al. *Neurotherapeutics*. 2018;15:872–884; 4. Wenninger S, et al. *Front Neurol*. 2018;9:303; 5. De Antonio M, et al. *Rev Neurol (Paris)*. 2016;172:572–580; 6. McNally EM, Sparano D. *Heart*. 2011;97:1094–1100; 7. McNally EM, et al. *J Am Heart Assoc*. 2020;9:e014006; 8. Groh WJ, et al. *N Engl J Med*. 2008;358:2688–2697; 9. Hawkins AM, et al. *Neuromuscul Disord*. 2019;29:198–212; 10. Hartog L, et al. *Front Neurol*. 2021;12:658532; 11. Modoni A, et al. *J Neurol*. 2008;255:1737–1742; 12. White M. *Ther Innov Regul Sci*. 2020;54:1010–1017; 13. van der Velden BG, et al. *J Affect Disord*. 2019;250:260–269; 14. Baldanzi S, et al. *Orphanet J Rare Dis*. 2016;11:34; 15. Ho G, et al. *World J Clin Pediatr*. 2015;4:66–80; 16. Bellini M, et al. *World J Gastroenterol*. 2006;12:1821–1828; 17. Moshirfar M, et al. *Clin Ophthalmol*. 2022;16:2837–2842; 18. Gutierrez Gutierrez G, et al. *Med Clin (Barc)*. 2020;153:82.e1-82.e17; 19. Kim WB, et al. *Korean J Urol*. 2012;53:134–136.

What are the most common and impactful symptoms of DM1?

Top 10 most commonly reported DM1 symptoms and their impact*



Muscle weakness, fatigue, and daytime sleepiness are the most prevalent and impactful symptoms reported by individuals with DM1

*Respondents were from the United States and Canada. Statistics were controlled for age differences, and a Bonferroni correction for multiple comparisons was applied. Prevalence calculations were based on n=457. Impact score ranged from 0 to 4. †Significantly higher prevalence or impact of symptoms in females (p<0.05).
DM1, myotonic dystrophy type 1.
Figure from BioRender.
Hagerman KA, et al. *Muscle Nerve*. 2019;59:457–464.

What is the impact on daily activities for people living with DM1?

Challenge prevalence and level of difficulty performing daily activities for individuals with DM1*

Challenge prevalence (%)	Relative degree of challenge	Mobility	Challenge prevalence (%)	Relative degree of challenge	Household activities
80	1.9	Standing for any length of time	88	2.1	Handling objects, opening jars, knobs
79	2.0	Going up or down stairs	70	1.5	Housekeeping, cleaning, laundry
74	1.7	Maintaining balance	64	1.1	Swallowing, eating, drinking
70	1.4	Stand up, sit down, bend down	57 [†]	1.1 [†]	Dressing, doing up buttons, zippers
70	1.5	Walking outside or inside	56	1.1	Using cutlery, kitchen utensils, preparing meals
Challenge prevalence (%)	Relative degree of challenge	Cognitive functioning	Challenge prevalence (%)	Relative degree of challenge	Communication
78	1.6	Alertness, difficulty staying awake	64 [†]	1.1 [‡]	Speaking, pronouncing words
64	1.1	Remembering things	52 [‡]	0.9 [‡]	Writing, holding a pen
61	1.0	Concentrating	Challenge prevalence (%)	Relative degree of challenge	Social
51	0.9	Putting thoughts into words	50 [†]	1.1 [‡]	Romantic, emotional, intimate life
41	0.7	Planning daily activities	49	0.9 [†]	Relationships/interactions with people

Individuals with DM1 have challenges performing daily activities

*Respondents were from the United States and Canada. Statistics were controlled for age differences, and a Bonferroni correction for multiple comparisons was applied. Prevalence calculations were based on n=457. Relative degree of challenge was scored from 0 to 4. [†]P<0.05. [‡]P<0.0001, significantly higher prevalence or degree of challenge in males.

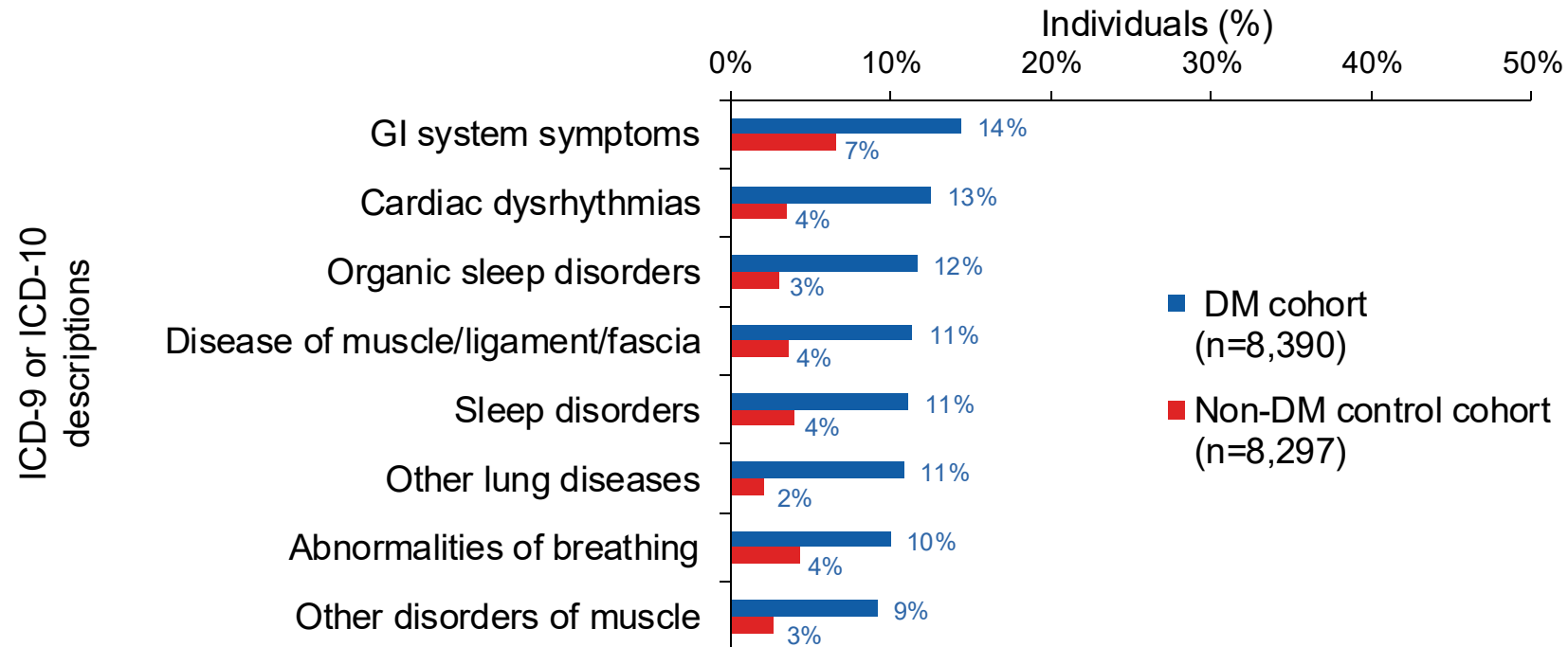
DM1, myotonic dystrophy type 1.

Hagerman KA, et al. *Muscle Nerve*. 2019;59:457–464.

What is the impact of DM1 based on US insurance claims data?

- US insurance claims data from 2012 to 2019 identified >2,000 comorbidities in individuals with DM

Most impactful comorbidities at 12-month follow-up*†



Comorbidities cause under-appreciated symptoms that require medical attention, resulting in significantly higher healthcare resource utilization (HCRU)

Based on US insurance claims data from 2012 to 2019. *Numbers include data for individuals with DM1 and DM2. Excludes ICD-9 359 (muscular dystrophies) and ICD-10 G71 (primary disorders of muscle) as these are the ICD codes for inclusion in the study. †Affects more than 5% of the DM cohort and at least 2x more than the controls with P value <0.0001 during the 12-months follow-up period.

DM, myotonic dystrophy; GI, gastrointestinal; ICD, International Classification of Diseases; US, United States.

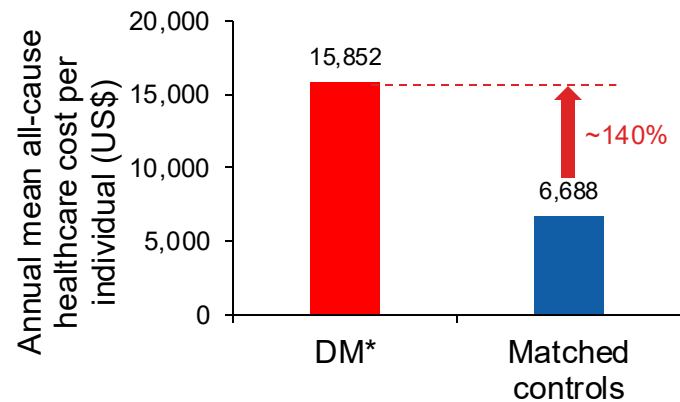
Howe SJ, et al. *Orphanet J Rare Dis.* 2022;17:79.

How does DM1 impact healthcare resource utilization?

- US insurance claims data from 2012–2019:¹

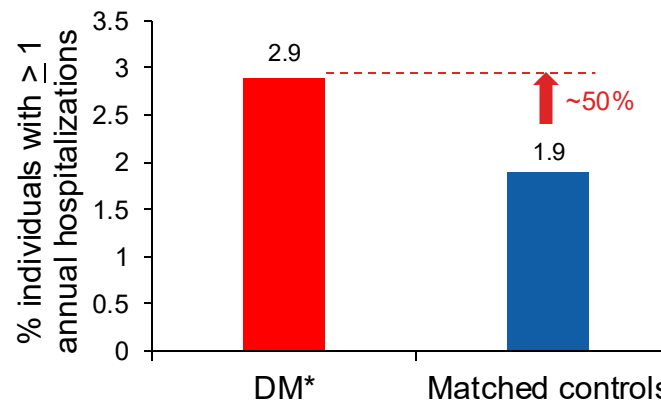
Healthcare cost*

The annual mean all-cause healthcare cost is **~140% higher** in individuals with DM compared with matched controls[†]



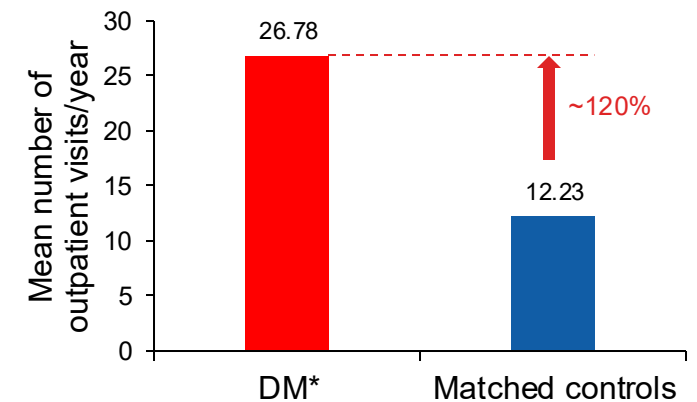
Hospitalizations*

Individuals with DM are at a **~50% increased risk** of having at least 1 annual hospitalization compared to those without DM[‡]



Outpatient visits*

The mean number of outpatient visits/year is **~120% higher** in individuals with DM compared with matched controls[‡]



- US insurance claims data from 2009–2018 (first-year post-diagnosis of DM):^{2 §}

3.9×

higher annual **health plan costs**

3.7×

higher probability to be **hospitalized**

2×

more **outpatient visits**

In the US, individuals with DM face significantly higher mean all-cause/health plan costs and HCRU per year than control patients^{1,2}

*Numbers include data for individuals with DM1 and DM2. †Averaged over a 4-year period. ‡Over a 12-month follow up period. §All p<0.0001.

DM, myotonic dystrophy; HCRU, healthcare resource utilization; US, United States.

1. Howe SJ, et al. *Orphanet J Rare Dis.* 2022;17:79; 2. Martinez-Thompson JM, et al. *Muscle Nerve.* 2025;71:972–978.

How does DM1 impact education, work and personal income?

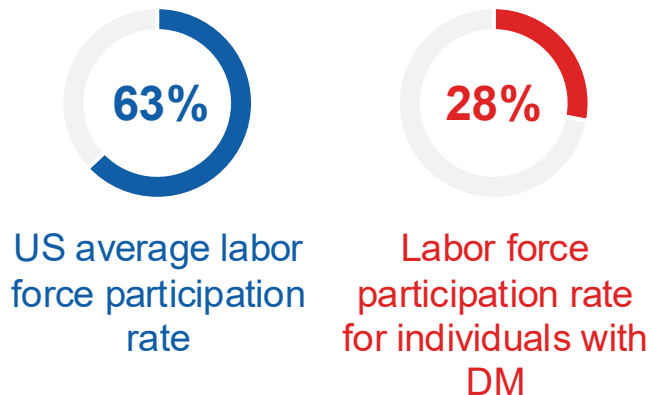
Educational attainment^{†1,2}

Generally aligned with the US and Canadian average (ages ≥25 years)



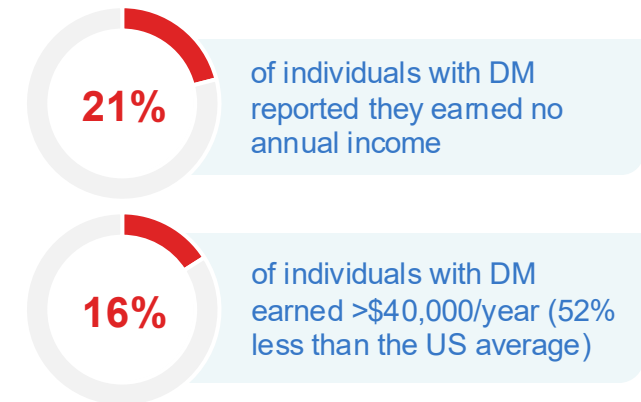
Labor force participation^{‡2}

56% lower than the US average



Annual personal income²

Was considerably lower compared with US national norms (ages 16–64)



Approximately half of the overall respondents were unable to work due to DM¹

Individuals with DM have lower labor force participation and annual income than the general population, despite comparable educational attainment^{*1,2}

^{*}Based on data from the Christopher Project, which included people with DM (n=1,180) (DM1, DM2, congenital DM) and their family members (n=402) across North America (US and Canada).

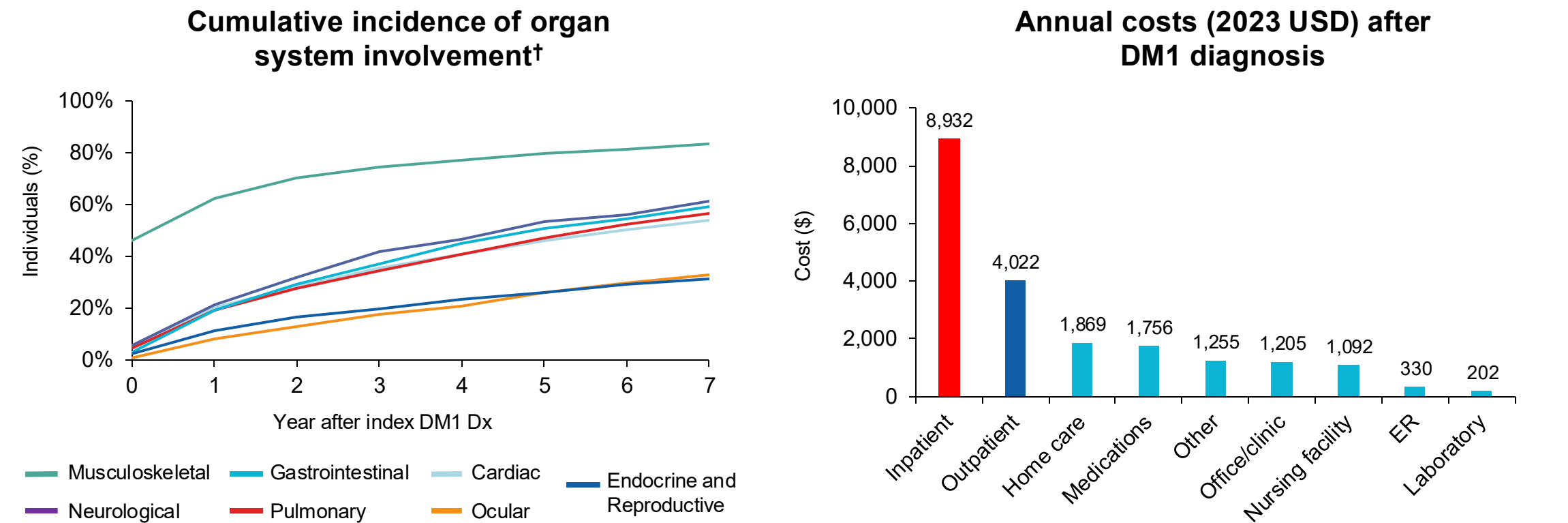
[†]Defined as the highest level of education a person has achieved. [‡]Defined as the percentage of people aged 16 to 64 who are employed (full-time or part-time) or actively looking for work.

DM, myotonic dystrophy; US, United States.

1. Hagerman KA, et al. *Muscle Nerve*. 2019;59:457–464; 2. The Christopher Project. Report to the Myotonic Dystrophy Community. Accessed May 29, 2025.

https://www.myotonic.org/sites/default/files/pages/files/Christopher_Project_Full_Report.pdf.

How do the multi-systemic manifestations of DM1 impact healthcare utilization and costs across settings?



Mean annual total cost of care post-DM1 diagnosis (2023) was \$20,687 (with inpatient care as the highest expense)

Organ system involvement increases over time in individuals with DM1, resulting in substantial HCRU and costs across settings*

*Real-world data analysis from the CARE-DM1 study in the United States (N=1343). Incident organ system involvement was estimated post DM1 diagnosis.
†Individuals with the respective organ system involvement prior to index were excluded to capture incident organ system involvement after DM1 Dx.
CI, confidence interval; DM1, myotonic dystrophy type 1; ER, emergency room; HCRU, healthcare resource utilization; USD, United States dollar.
Hamel JI, et al. Poster presented at: ISPOR; May 5–8, 2024; Poster EE255.