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Conflict of interest statement

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A 9-year follow-up study of the natural progression of upper limb performance in myotonic dystrophy type 1: a similar decline for phenotypes but not for gender.

ABSTRACT

This study aimed to document and compare the decline of upper limb performance among adults with myotonic dystrophy type 1 according to phenotype and gender. A longitudinal descriptive design compared upper limb performance at baseline and follow-up of 70 women and 38 men with the late-onset or adult phenotypes. Grip strength and pinch strength as well as gross dexterity and fine dexterity were assessed. All four performance measures decreased significantly ($p < 0.001$). The decline over time was similar for individuals with the late-onset and adult-onset phenotypes, but differed according to gender. For late-onset and adult-onset phenotypes respectively, women lost less grip strength than men: 0.4 and minus 0.8 kg (2.0% and -9.4%) in women vs. minus 7.4 and minus 3.1 kg (-19.2% and -30.7%) in men. A similar situation was found for gross dexterity: minus 3.0 and minus 3.2 blocks (-4.6% and -5.9%) in women vs. minus 12.4 and minus 8.7 blocks (-19.4% and -16.6%) in men. Pinch gauge had the smallest standard deviations and was one of the only measurement tools with significant detectable changes in relation to the standard error of measurement. Given these results, health professionals and researchers should consider phenotype and gender differently when planning health services or future studies. Indeed, as their upper limb strength and dexterity differed, even if their decline was similar, the phenotypes should not be pooled. Finally, the use of the pinch gauge to assess long-term change in upper limb ability seems preferable to the three other measurements.

Abbreviations

DM1, myotonic dystrophy type 1; CTG, cytosine-thymine-guanine; MDC, minimal detectable change; MIRS, Muscular Impairment Rating Scale; RM ANOVA, repeated measures analysis of variance.

1. INTRODUCTION

Myotonic dystrophy type 1 (DM1), an autosomal dominant disease, results from the expansion of an unstable trinucleotide cytosine-thymine-guanine (CTG) repeat mutation located in the 3' untranslated region of a gene (19q13.3), encoding the myotonin protein kinase (*DMPK*) [1]. DM1 is often compared to premature aging [2, 3]. Several systems are affected, especially the muscular, cardiac, respiratory, ocular, gastrointestinal, reproductive, and central nervous systems [4]. Of these, the muscular system plays a key role in the accomplishment of daily activities and social roles [5]. In DM1, symmetric muscle wasting is generally observed in the neck and distal upper/lower limbs, which slowly progresses to the trunk [6, 7]. A delay in muscle relaxation (myotonia) is also observed [8].

Although a common general pattern of muscle wasting progression is observed, the severity of the disease varies widely among individuals and across affected systems. In addition, from a clinical standpoint, impairments and disabilities are also highly heterogeneous, making planning of health services challenging. This phenomenon, although only partly understood, has given rise to a plethora of clinical pictures. These pictures exist on a continuum of severity that is classified into the following four phenotypes: late onset, adult (classic), childhood onset and congenital [9]. Although no international consensus is yet available, a juvenile phenotype was recently considered in the continuum [10]. Compared with the late onset and adult phenotypes, the childhood onset and congenital phenotypes are generally associated with more severe symptoms and younger age at onset [9].

These impairments and disabilities have important personal and financial consequences for people with DM1, since they lead to restriction in social participation [11], reduction of quality of life [12, 13], and medical and indirect costs amounting to (US)$32 236 per year [14]. Among potential explanatory factors, muscle weakness of the upper limbs and difficulty performing tasks that require fine manual dexterity were respectively demonstrated to be associated with social participation restrictions [5] and activity limitations [15]. Indeed, individuals with DM1 reported difficulties handling, lifting and grasping objects, opening doors or jars, and reaching objects over their head, all of which are associated with moderate to severe restrictions in the accomplishment of daily activities [16]. Moreover, upper limb disabilities have been shown to be associated with household-related needs and, specifically, hand weakness was reported to be a criterion for referral to rehabilitation services [17]. However, to adopt a prognostic approach, i.e., offer rehabilitation interventions and services in a timely manner, it is important to have a better understanding of the progression of disabilities over time. In addition, according to the Food and Drug Administration (FDA), studies of the natural history of disease are a key aspect of upcoming clinical trials [18]. Describing the decline of upper limb performance over a long time period will lead to a better understanding of the natural progression of DM1. In addition, the characterization of muscle strength impairment over time according to adult vs. late-onset phenotype has been reported as essential to facilitate monitoring in clinical settings [19].

Although previous studies have advanced knowledge of DM1, little is known about the decline of upper limb performance over time. To our knowledge, no study has investigated gross and fine manual dexterity decline. Moreover, studies investigating

muscle strength decline showed conflicting results. On the one hand, a two-year longitudinal study showed a non-significant decrease in grip strength and a significant increase in lateral pinch strength, with no gender effect [20]. On the other hand, a cross-sectional study that took disease duration into account reported a significant rate of decline for grip strength and lateral pinch strength, with a gender effect [6]. For each year of disease, a rate of decline of 2% for women and 3% for men for grip strength, and a rate of decline of 1.6% for women and 2.5% for men for lateral pinch strength were found [6]. These discrepancies raise questions about the expected decline in grip and pinch strength over time as well as the gender effect on the rate of decline. Although recommended, none of these studies distinguished between DM1 phenotypes in their analyses [19]. This study aimed to document and compare the decline in upper limb performance among adults with DM1 according to phenotype and gender.

2. MATERIALS AND METHODS

2.1 Participants

This study used a longitudinal descriptive design comparing data from baseline (2002–2004) with data from follow-up (2011–2013). Participants were recruited through the Saguenay Neuromuscular Clinic registry (Québec, Canada). Individuals with DM1 (late-onset and adult phenotypes) confirmed by genetic analysis and 18 years of age or older were invited to participate (n = 416). Since they presented with more severe impairments and different prognoses, individuals with the childhood or congenital phenotype of DM1 were excluded as were those with another disease influencing upper limb performance (e.g., stroke). A sample of 200 subjects was then drawn randomly from this subset of the 416 individuals; the baseline sample selection criteria and process has been published

previously [5, 11, 13, 21-24]. The study was conducted at the Neuromuscular Clinic and at the participant's home by trained healthcare professionals. The Ethics Review Board of the *Centre intégré universitaire de santé et de services sociaux du Saguenay–Lac-St-Jean*, approved the study protocol.

2.2 Measures

The equipment was the same and calibrated by the manufacturer before each data collection (baseline and follow-up). Although two different raters collected data at baseline and follow-up, the first rater trained the second rater and a standardized procedure and instruction to participant were used to minimize bias. The time of the year of the data collection was kept as constant as possible for most participants. Given the constraints of rater and participants, it was not possible to be consistent in time of the day for all participants.

2.2.1 Sociodemographic and clinical characteristics of participants: Sociodemographic characteristics of participants were assessed with a generic questionnaire for age, gender, employment status, and age at onset of symptoms. The number of CTG repeats was also reported for each participant. Overall progression of muscular impairment was measured using the DM1-specific Muscular Impairment Rating Scale (MIRS) with five stages based on manual muscle testing and the detection of myotonia [25]. Stage 1 indicates no muscular impairment while stage 5 indicates severe proximal weakness [25]. Information on phenotype was collected from the medical file. Patients are classified as late-onset phenotype if they met at least two of the following three criteria at the time of their diagnosis: (i) CTG < 200; (ii) MIRS score of 1 (no muscular impairment) or 2 (minimal signs); (iii) age at onset of symptoms > 40 years.

2.2.2 Strength: As they are both related to accomplishment of activities [17], grip and lateral pinch strength were measured. **Grip strength** was documented using the mean of three trials and following a standardized procedure with a Jamar dynamometer [26, 27]. The Jamar dynamometer has very good to excellent intra-rater reliability in the DM1 population (intra-class coefficient [ICC]: 0.87–0.98) [20]. In healthy population, inter-rater reliability is excellent (ICC: 0.98) [28]. **Lateral pinch strength** was assessed using the mean of three trials and following a standardized procedure with a B&L pinch gauge [26]. Excellent intra-rater reliability (ICC: 0.93–0.96) has been documented in the DM1 population [20]. In healthy women population, inter-rater reliability is excellent (ICC: 0.99) [27].

2.2.3 Manual dexterity: Two dexterity measurements were assessed: gross and fine dexterity. **Gross dexterity** was measured with the Box and Block Test following standardized instructions [29]. This test consists of moving, one at a time and as fast as possible, in a 60-second period, the maximum number of blocks from one side to the other of a box that is separated in the middle. Excellent intra-rater reliability (ICC: 0.97) has been shown with an aging population [30]. Good inter-rater reliability (ICC: 0.80) was found in healthy population [31]. No psychometric values were available for individuals with DM1. **Fine dexterity** was assessed with the four subtests of the Purdue Pegboard Test: right hand; left hand; both hands; assembly [32]. These tests involve placing small pins on a board as quickly as possible in a 30- or 60-second period. The assembly subtest involves coordinating both hands, with specific instructions to alternate hands when placing the pins. Scores are the mean of two trials. In DM1, good intra-rater reliability (ICC: 0.63 and 0.67) and moderate to good inter-rater (ICC: 0.73 and 0.47) has

been shown for the right and left hand subtests respectively [33]. Intra-rater reliability for the assembly subtest was excellent (ICC: 0.91) [25].

2.3 Data analysis

Descriptive statistics were first used to define sample characteristics. Participants' characteristics and upper limb test scores were compared between phenotypes and gender using the Mann-Whitney U-test or Chi-square test. Repeated measures analysis of variance (RM ANOVA) were used to compare follow-up (T2) to baseline (T1) and also to compare means of the four upper limb test scores for the phenotype and gender subgroups respectively. This comparison was carried out with the Test of within-participant effects and the Test of between-participant effects for both phenotype and gender subgroups. For within-participant effects, a significant *p*-value indicated the presence of an interaction, i.e., a difference in the rate of decline. For between-participant effects, a significant *p*-value indicated the presence of a confounding variable, i.e., different means for subgroups. To assist in interpreting these effects, graphic illustration was provided. As post-hoc analysis, the Wilcoxon rank-sum test was also used to compare decline between T1 and T2 for a small cluster composed of phenotype-by-gender subgroups. Decline between T1 and T2 in raw scores (i.e., mean of delta = score at T2 - score at T1) was estimated for each phenotype-by-gender subgroup and relative decline using percentage of loss. Spearman's correlations between upper limb performance decline with participant age using phenotype subgroups were performed in order to determine if there was an association between aging and decline. Also, Spearman's correlations between baseline performance of grip and lateral pinch strength and their decline over the 9-year period according to phenotype subgroups were

performed to determine if there was an association between strength at baseline and rate of decline. Standard errors of measurement (SEM) were calculated based on the ICC of intra-rater reliability for the right hand subtest using concordant standard deviation (SD) for each measurement scale with the following formula: $SEM_{95\%} = 1.96 * (SD * \sqrt{(1 - ICC)})$ [34]. Then, delta scores were compared to $SEM_{95\%}$ to determine if the change observed is larger than what would be expected to occur in relation to the standard error of measurement (minimal detectable change (MDC)). The statistical analyses were performed using SPSS software (version 21.0 for Windows) and a significant *p*-value was set at 0.01.

3. RESULTS

3.1 Demographics

Of the 200 participants at baseline (2002–2004), 92 participants did not attend the follow-up: 59 passed away, 14 refused (lack of interest: 23%; personal reasons: 77%), 12 were excluded for health reasons or for geographical remoteness, and seven others had incomplete data. There were no dropped out of the study. The 108 participants who completed the study (2011–2013) were similar to the 92 who withdrew in terms of gender, CTG repeats, and phenotype proportion but, at baseline, they were younger (43.6±10.6 vs. 51.0±11.8 years, $p < .01$) and had better strength (grip strength 12.7±10.4 vs. 8.3±9.4 kg; pinch strength 6.0±2.2 vs 5.0±2.2 kg) and better dexterity (gross dexterity 55.8±11.1 vs. 46.9±12.5 blocks; fine dexterity 12.5±2.1 vs 10.1±3.1 pins, $p < .01$). At baseline, the 108 participants were aged between 20 and 77 years and the majority were female and had the adult phenotype (Table 1). All the participants were right-handed. Gender proportion was similar for both phenotypes (Table 2). While the mean age of the

late-onset phenotype was higher than that of the adult phenotype at both measurements ($p < .001$), no difference was found in age according to gender for each phenotype.

Please insert Tables 1 and 2 about here

3.2 Upper limb performance over time

All strength and dexterity test scores decreased significantly for the total sample (see RM ANOVA, Table 3). No significant interaction within phenotypes was found, i.e., the decline over time was approximately the same for the late-onset and adult phenotypes. Interactions within gender were found for grip strength and gross dexterity, i.e., men showed greater decline over time than women (see Comparison of subgroup effects, Table 3). For example, when decline per year for right-hand strength was approximated linearly, the mean decline in grip strength was 0.06 kg/year for women and 0.41 kg/year for men ($p < .001$). However, for lateral pinch strength, the mean decline was 0.17 kg/year for women and 0.21 kg/year for men ($p = .13$). Comparison between phenotypes showed that the late-onset and adult subgroups were distinct from each other for all upper limb performance measurements, i.e., the late-onset phenotype had higher scores than the adult phenotype, except for the assembly subtest in the Purdue Pegboard Test (Figures 1–4; Table 3). In addition, except for gross dexterity, male and female subgroups were distinct from each other for all test scores, i.e., for some tests, women had higher scores than men and vice versa. However, interactions between phenotype and gender subgroups were found for grip and lateral pinch strength, which made the interpretation more complex and required graphic illustration of effects of estimated mean (Figures 1–4; Table 3).

Please insert Table 3 and Figures 1–4 about here

On the one hand, the adult phenotype showed a significant decrease in their upper limb strength and dexterity, except for grip strength in women (see Wilcoxon rank-sum test, Table 3). On the other hand, the late-onset phenotype only showed a significant decrease in some tests or subtests. Specifically, women with the late-onset phenotype showed a significant decrease only for pinch strength and the both hands and assembly subtests for fine dexterity. Men with the late-onset phenotype showed a significant decrease only for pinch strength, gross dexterity, and the assembly subtest for fine dexterity (see Wilcoxon rank-sum test, Table 3). Moderate negative relationships between baseline performance of grip and lateral pinch strength and their decline over the 9-year period were found for all strength values, except for lateral pinch for the late-onset phenotype (Table 4). A high variability in rate of decline was found for all upper limb performance measurements (Supplementary Appendix). Only gross and fine dexterity decline for the adult phenotype showed a significant but low correlation with age ($r_{\text{gross dexterity}}$ = -.31; $r_{\text{fine dexterity}}$ = -.32, p < .01; data not shown in table).

Please insert Table 4 about here

3.3 Standard error of measurement and minimal detectable change

Changes beyond the measurement error were detected statistically for two of the four tests (Table 5).

Please insert Table 5 about here

4. DISCUSSION

This study aimed to document and compare the decline of upper limb performance among adults with DM1 according to phenotype and gender. As observed in clinical practice, grip and pinch strength as well as gross and fine dexterity decreased

significantly over a 9-year period, except for grip strength for late-onset female. However, when considering the standard error of measurement (SEM), two out of four upper limb test scores decreased beyond the measurement error for the total sample. This study also demonstrated a gender difference for performance scores and decline in some types of upper limb performance. In addition, a DM1 phenotype difference was observed only for performance scores, and not for decline in upper limb performance. Not all functions decline similarly, an important finding for selection of outcome measures in upcoming clinical trials.

Although a similar absolute decline over nine years was observed for the late-onset and adult phenotypes, the clinical impact of this decline differed. In fact, as individuals with the adult phenotype had lower strength and dexterity scores, the relative decline may have greater functional effects than in people with the late-onset phenotype. For example, men with late-onset phenotype lost 7.4 kg (19.2%) while men with adult phenotype lost 3.1 kg (30.7%) for the right-hand grip strength. As, to our knowledge, no minimum clinically important difference (MCID) has been determined yet in upper limb performance for DM1 individuals, this hypothesis has to be verified. Therefore, as the relative rate of decline differs according to the clinical phenotype, future research including clinical trials should distinguish phenotypes and analyze data from late-onset and adult phenotypes separately. In addition, as late-onset, adult, juvenile, infantile, and congenital phenotypes exist on a continuum of severity, more longitudinal studies that compare all phenotypes are needed.

Performance scores and decline in strength and dexterity varied according to gender. In our study, men lost more grip strength and gross dexterity than women, whereas a similar

rate of decline was observed in men and women for lateral pinch strength and fine dexterity. As reported by a recent study, muscular impairment differed according to gender for individuals with DM1, with men having more marked muscular impairment [10]. However, this study pooled all phenotypes and since interactions for gender and phenotype were found in the present study, future comparisons must take these effects into account during data interpretation. In addition, moderate negative relationships were found between grip and lateral pinch strength baseline performances and their respective decline. This result suggests that stronger participants tend to show a bigger decline. Since most men were stronger at baseline it may not be a gender effect but only related to the baseline performance. Otherwise, at second measurement, late onset males (66.8 ± 10.6 y.o.) are on average eight years older than the females (59.1 ± 13.5 y.o.), thus an age effect cannot be overruled to explain this gender difference. In Switzerland population's reference values, which used the same instruments and standardized position and instruction we did, decline in strength appeared to happen around 75 years old [35], and some of the late onset from both gender reached this age in our study. It is noteworthy that women with late-onset phenotype presented unexpected results. In fact, contrary to what could be hypothesis with a progressive neuromuscular disorder such as DM1, they remained stable. It also contrasts with normative data, where healthy women of similar age group tended, albeit not significantly, to loose strength (50-54 y.o. had 33.7 ± 4.5 kg and 60-64 y.o. had 28.7 ± 5.5 kg) [35]. This phenomenon might be explained by combination of factors. First, only 17 women with late-onset phenotype were included in our sample which may not be representative of the population. Second, limiting factors such as pain or lack of mobility in the fingers could have influenced the measure of the

strength. Finally, methodological aspects should be considered (please see limitation section for more details).Health professionals and researchers should consider phenotype and gender differently when planning health services or future studies. Health professionals could inform DM1 patients about the risk of decline, which seems higher for men and the adult phenotype, and use a personalized approach to plan interventions to minimize the impact on their daily activities and social roles. Moreover, by maintaining abilities [36], teaching alternative methods or adapting the environment at the appropriate time [37], rehabilitation professionals could optimize the accomplishment of activities in this population. For example, rehabilitation professional could use the result of the current study to help increase motivation of men with late-onset to implement an exercise program at home. However, more studies are needed, as few interventions have been documented as effective in reducing or preventing disabilities in people with DM1 [36, 38].

To our knowledge, no follow-up studies on dexterity change over time are available for populations with DM1, and cross-sectional studies assessing performance have not considered gender difference [15, 17]. Nevertheless, in general population studies, women had better dexterity, particularly fine dexterity [39], which is consistent with the current findings.

The decline observed for strength is partially consistent with previous studies [6, 20, 40], as we found a gender difference for grip strength with a linearly estimated mean decline of 0.06 kg/year for women and 0.41 kg/year for men, but no difference for pinch strength, with a mean decline of 0.17 kg/year for women and 0.21 kg/year for men. Nevertheless, since decline may not be linear, these rates of decline might not be totally accurate. A

recent retrospective study that considered disease duration showed a decline of 0.24 kg/year for grip strength for the non-congenital DM1 phenotype [40], which is relatively similar to our results. In addition, although there are important methodological differences between the two studies, the results of the current study were not entirely consistent with the cross-sectional study by Mathieu et al. [6]. In fact, Mathieu et al.'s study found a gender difference in decline for both types of strength, whereas the current study only found a gender difference for grip strength. Furthermore, along with the results of our study, the findings of the two-year longitudinal study by Nitz et al. [20] revealed the very slow decline of the disease, not observable within two years, and the importance of using the SEM.

Since lateral pinch strength had the smallest standard deviations and since it showed a significant decrease for both phenotypes by gender subgroup, the pinch gauge could, of the four measurement tools used in this study, be the best tool health professionals could use to assess long-term change or for studies on upper limb performance. To measure the natural progression of the disease within a short period of time, our results indicated that change might not be beyond the SEM considering the very slow progression of the disease. However, the use of a computerized pinch gauge or hand grip dynamometer, which reduces reading errors, is another way to increase the responsiveness to change of these measurement tools [41]. Indeed, outcome measurement selection should be revised after more extensive study of these computerized tools. Sensitivity to change of the measures should also be documented in relation to potential interventions such as antimyotonia drug.

4.1 Strengths and limitations

This study assessed long-term change in upper limb strength and dexterity and to compare decline between DM1 phenotypes and gender. As few studies had been carried out to date, health professionals may better inform individuals with the adult and late-onset phenotypes about the risk of decline over time. This study also involved a large cohort of patients who had a relatively rare diagnosis over a long period of time which, given the very slow progression of the disease, made it possible to detect any change [6]. This study, however, had some limitations. A survival bias might give a more positive portrait, as participants who completed both time measurements had better upper limb ability scores at T1. Thus, sample may not reflect adequately the whole population. Statistical comparison with normative values were not performed notably because of the low number of women and men of late-onset subgroup with highly variable age (32 to 77 y.o. for women and 42 to 72 y.o. for men for late-onset at baseline). In addition, pairing participants with normal control have been impossible given the timeframe of the study. Even if the same standardized procedure and instruction to participant were used for both measurements, a reduced effort, distraction, or difference in encouragement at T1 compared to T2 could have influenced data and consequently reduced the observed decline. Also, due to the limited precision of 2 kg step scale for Jamar dynamometer and 0.5 kg for pinch gauge, reading error could have occurred. In addition, decrease in the active range of flexion of the finger joints due to a severe weakness might limits the strength measured by the dynamometer. Using subgroups (phenotype and gender) with a low number of participants for each subgroup affected the power of the statistical analysis, specifically for the late-onset phenotype. Such restricted statistical power limits the conclusion about the expected decline over time for subgroups, e.g., the decrease in

grip strength for men with the late-onset phenotype is beyond the SEM (-7.4 ± 2.6 kg) but was not statistically significant (p = 0.13). Multiple tests were carried out and the level of statistical significance was tightened to reduce statistical type I errors. Although the decline over nine years should have been compared with the MCID, this information was not available for people with DM1 and only comparison with the SEM was performed. Also, even though most of the measurement instruments demonstrated good to excellent psychometric proprieties with the DM1 population, intra-rater reliability used to calculate the SEM for gross dexterity was not based on this population and caution must be taken when interpreting change smaller than the measurement error. In addition, the rate of decline is presented only for participants with around 30 years of disease duration and may be different for shorter disease duration.

5. CONCLUSION

This study used a large cohort of individuals with DM1 to assess decline in four measures of upper limb performance according to phenotype and gender. It showed that grip and pinch strength as well as gross and fine dexterity decreased significantly among DM1 participants over a 9-year period and that the decline differed according to gender for specific tests. Baseline performances of the strength may be a possible explanation for the observed gender difference in the decline, and further studies should explore this hypothesis. The use of the pinch gauge to assess long-term change in upper limb performance could be preferable considering that it had the smallest SDs and SEM over the other three measurements. These results will help clinicians and researchers to choose accurate tools to assess upper limb performance as well as to understand the decline of the disease for phenotype and gender. To better understand the natural progression of

DM1, further studies need to assess the progression of impairment in the infantile and congenital phenotypes and use repeated measures designs with more than two follow-up periods also as including normal population data.

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REFERENCES

[1] Mahadevan M, Tsilfidis C, Sabourin L, et al. Myotonic dystrophy mutation: an unstable CTG repeat in the 3' untranslated region of the gene. Science. 1992;255:1253-55.

[2] Brisson D, Houde G, St-Pierre J, et al. The pleiotropic expression of the myotonic dystrophy protein kinase gene illustrates the complex relationships between genetic, biological and clinical covariates of male aging. Aging Male. 2002;5:223-32.

[3] Mateos-Aierdi AJ, Goicoechea M, Aiastui A, et al. Muscle wasting in myotonic dystrophies: a model of premature aging. Front Aging Neurosci. 2015;7:125-. 10.3389/fnagi.2015.00125

[4] Harper P. Myotonic dystrophy : a multisystemic disorder. In: Harper P, Van Engelen, B, Eymard, B, et al. ed. Myotonic Dystrophy: present management, future therapy. Oxford: Oxford University Press, 2004: 3-13.

[5] Gagnon C, Mathieu J, Jean S, et al. Predictors of Disrupted Social Participation in Myotonic Dystrophy Type 1. Arch Phys Med Rehabil. 2008;89:1246-55. 10.1016/j.apmr.2007.10.049

[6] Mathieu J, Boivin H, Richards CL. Quantitative motor assessment in myotonic dystrophy. Can J Neurol Sci. 2003;30:129-36.

[7] Hebert LJ, Remec JF, Saulnier J, et al. The use of muscle strength assessed with handheld dynamometers as a non-invasive biological marker in myotonic dystrophy type 1 patients: a multicenter study. BMC Musculoskelet Disord. 2010;11:72. 10.1186/1471-2474-11-72

[8] Hogrel JY. Quantitative myotonia assessment using force relaxation curve modelling. Physiol Meas. 2009;30:719-27.

[9] Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. J Neurol Neurosurg Psychiatry. 2010;81:358-67. 10.1136/jnnp.2008.158261

[10] Dogan C, De Antonio M, Hamroun D, et al. Gender as a Modifying Factor Influencing Myotonic Dystrophy Type 1 Phenotype Severity and Mortality: A Nationwide Multiple Databases Cross-Sectional Observational Study. PLoS One. 2016;11:e0148264. 10.1371/journal.pone.0148264

[11] Gagnon C, Mathieu J, Noreau L. Life habits in myotonic dystrophy type 1. J Rehabil Med. 2007;39:560-6. 10.2340/16501977-0091

[12] Peric S, Stojanovic VR, Basta I, et al. Influence of multisystemic affection on health-related quality of life in patients with myotonic dystrophy type 1. Clin Neurol Neurosurg. 2013;115:270-5. 10.1016/j.clineuro.2012.05.015

[13] Laberge L, Mathieu J, Auclair J, et al. Clinical, Psychosocial, and Central Correlates of Quality of Life in Myotonic Dystrophy Type 1 Patients. Eur Neurol. 2013;70:308-15. 10.1159/000353991

[14] Larkindale J, Yang W, Hogan PF, et al. Cost of illness for neuromuscular diseases in the United States. Muscle Nerv. 2013;49:431-8. 10.1002/mus.23942

[15] Kierkegaard M, Harms-Ringdahl K, Holmqvist LW, et al. Functioning and disability in adults with myotonic dystrophy type 1. Disabil Rehabil. 2011;33:1826-36. 10.3109/09638288.2010.549287

[16] Heatwole C, Bode R, Johnson N, et al. Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1). Neurology. 2012;79:348-57. 10.1212/WNL.0b013e318260cbe6
[17] Raymond K, Auger L-P, Cormier M-F, et al. Assessing upper extremity capacity as a potential indicator of needs related to household activities for rehabilitation services in people with myotonic dystrophy type 1. Neuromuscul disord. 2015;25:522-9. 10.1016/j.nmd.2015.03.015
[18] Food and Drug Administration, *Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases Including Strategic Plan: Accelerating the Development of Therapies for Pediatric Rare Diseases.*, in *Public Workshop Report*. 2014, U.S Department of Health and Human Services. p. 86.
[19] Petitclerc É, Hébert LJ, Desrosiers J, et al. Lower limb muscle impairment in myotonic dystrophy type 1: The need for better guidelines. Muscle Nerve. 2015;51:473-8. 10.1002/mus.24521
[20] Nitz JC, Burns YR, Jackson RV. A longitudinal physical profile assessment of skeletal muscle manifestations in myotonic dystrophy. Clin Rehabil. 1999;13:64-73.
[21] Laberge L, Veillette S, Mathieu J, et al. The correlation of CTG repeat length with material and social deprivation in myotonic dystrophy. Clin Genet. 2007;71:59-66. 10.1111/j.1399-0004.2 007.00732.x
[22] Gagnon C, Chouinard MC, Jean S, et al. Health supervision and anticipatory guidance in adult myotonic dystrophy type 1. Neuromuscul Disord. 2010;20:847-51.
[23] Jean S, Richer L, Laberge L, et al. Comparisons of intellectual capacities between mild and classic adult-onset phenotypes of myotonic dystrophy type 1 (DM1). Orphanet J Rare Dis. 2014;9.
[24] Jean S, Richer L, Mathieu J, *Intellectual functioning in a large sample of adult and late-onset DM1 patients*, in *6th International Myotonic Dystrophy Consortium Meeting*. 2007: Milan, Italy.
[25] Mathieu J, Boivin H, Meunier D, et al. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. Neurology. 2001;56:336-40.
[26] American Society of Hand Therapist, Clinical assessment recommendations. 2nd edition ed. 1992, Chicago: Author.
[27] Mathiowetz V, Weber K, Volland G, et al. Reliability and validity of grip and pinch strength evaluations. J Hand Surg [Am]. 1984;9:222-6.
[28] Peolsson A, Hedlund R, Oberg B. Intra- and inter-tester reliability and reference values for hand strength. J Rehabil Med. 2001;33:36-41.
[29] Mathiowetz V, Volland G, Kashman N, et al. Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther. 1985;39:386-91.
[30] Desrosiers J, Bravo G, Hebert R, et al. Validation of the Box and Block Test as a measure of dexterity of elderly people: reliability, validity, and norms studies. Arch Phys Med Rehabil. 1994;75:751-5.
[31] Canny ML, Thompson JM, Wheeler MJ. Reliability of the Box and Block Test of Manual Dexterityfor Use With Patients With Fibromyalgia. American Journal of Occupational Therapy. 2009;63:506-10.

[32] Tiffin J, Asher EJ. The Purdue Pegboard : Norms and studies of reliability and validity. J Appl Psychol. 1948;32:234-47.
[33] Aldehag A, Jonsson H, Littorin S, et al. Reliability of hand function testing instruments in patients with muscular dystrophies. Int J Ther Rehabil. 2008;15:211-18.
[34] Leong FTL, Huang JL, Standard Error of Measurement. Encyclopedia of Research Design.;dx.doi.org/10.4135/9781412961288. 2010, Thousand Oaks, CA: SAGE Publications, Inc. 1428-31.
[35] Werle S, Goldhahn J, Drerup S, et al. Age- and gender-specific normative data of grip and pinch strength in a healthy adult Swiss population. J Hand Surg Eur Vol. 2009;34:76-84. 10.1177/1753193408096763
[36] Brady LI, MacNeil LG, Tarnopolsky MA. Impact of Habitual Exercise on the Strength of Individuals with Myotonic Dystrophy Type 1. Am J Phys Med Rehabil. 2014;93:739-50. 10.1097/PHM.0000000000000088
[37] Cup EHC, Sturkenboom IHW, Pieterse AJ, et al. The evidence for occupational therapy for adults with neuromuscular diseases: a systematic review. OTJR: Occupation, Participation & Health. 2008;28:12-8. 10.3928/15394492-20080101-02
[38] Aldehag A, Jonsson H, Lindblad J, et al. Effects of hand-training in persons with myotonic dystrophy type 1 - a randomised controlled cross-over pilot study. Disabil & Rehab. 2013;35:1798-807. 10.3109/09638288.2012.754952
[39] Thorley T, McDaniel M, *Mean sex differences in Psychomotor Ability: A meta-analysis*, in *28th Annual Conference of the Society for Industrial and Organizational Psychology*. 2013: Houston.
[40] Bouchard J-P, Cossette L, Bassez G, et al. Natural history of skeletal muscle involvement in myotonic dystrophy type 1: a retrospective study in 204 cases. J Neurol. 2015;262:285-93. 10.1007/s00415-014-7570-x
[41] Allen D, Barnett F. Reliability and validity of an electronic dynamometer for measuring grip strength. Int J Ther Rehabil. 2011;18:258-64. 10.12968/ijtr.2011.18.5.258

Table 1: Description of participants' characteristics for the total sample

	Total sample (n = 108)	
	Baseline (T1)	**Follow-up (T2)**
Interval (months), mean (SD) [range]	107 (4) [96–125]	
Age (y), mean (SD) [range]	43.6 (10.6) [20–77]	52.2 (10.6) [29–85]
Gender, n (%)		
Female	70 (64.8)	
Male	38 (35.2)	
Phenotype, n (%)		
Adult	83 (76.9)	
Late onset	25 (23.1)	
CTG repetition, n (%)		
50 to 199	20 (18.5)	13 (12.0)
200 to 1000	56 (51.9)	35 (32.4)
> 1000	32 (29.6)	60 (55.6)
MIRS, n (%)		
Grade 1 (no muscular impairment)	6 (5.6)	1 (0.9)
Grade 2	14 (13.0)	5 (4.6)
Grade 3	27 (25.0)	23 (21.3)
Grade 4	56 (51.9)	63 (58.3)
Grade 5 (severe muscular impairment)	4 (3.7)	13 (12.0)
Missing data	1 (0.9)	3 (2.8)
Disease duration (y), mean (SD) [range]	19.6 (8.0) [3–35]	28.5 (8.0) [12–44]
Missing data (n = 33)		
Employment status, n (%)		
Unemployed / at home	63 (58.3)	65 (62.9)
Part-time job/study	15 (13.9)	6 (5.6)
Full-time job/study	17 (15.8)	13 (12.0)
Retired	11 (10.2)	23 (21.3)
Other/unknown	2 (1.9)	1 (0.9)

CTG, cytosine-thymine-guanine; MIRS, Muscular Impairment Rating Scale.

Table 2: Comparison of age between genders according to phenotype

			Gender†		*p*-value*
			Female	**Male**	
Age (y), mean (SD) [range]	**Late onset**	**T1**	50.6 (13.6) [32–77]	58.4 (10.6) [42–72]	.14
		T2	59.1 (13.5) [41–85]	66.8 (10.6) [50–81]	.16
	Adult	**T1**	40.7 (8.2) [20–58]	40.8 (7.3) [20–59]	.83
		T2	49.4 (8.2) [29–67]	49.4 (7.3) [29–68]	.79

† **Late onset**: *Female* n = 17 (68.0%), *Male* n = 8 (32.0%); **Adult**: *Female* n = 53 (63.9%), *Male* n = 30 (36.1%), $p = .70$.

***** Mann-Whitney U-test comparison between genders for both baseline and follow-up according to phenotype.

Table 3: Comparison of raw scores of upper limb performance at baseline and follow-up for the total sample (n = 108) and comparison for phenotype and gender with raw scores and delta decline

			Grip strength (kg) Mean (SD)		Lateral pinch strength (kg) Mean (SD)		Gross dexterity (# blocks) Mean (SD)		Fine dexterity (# pins) Mean (SD)			
			R	L	R	L	R	L	R	L	Both hands	Assem-bly
Total (n = 108)		T1	12.8 (10.1)	12.3 (10.2)	6.1 (2.3)	5.9 (2.1)	55.8 (11.1)	54.9 (10.3)	12.5 (2.1)	12.0 (2.0)	9.9 (1.9)	29.7 (6.5)
		T2	11.1 (9.1)	10.8 (9.4)	4.5 (2.1)	4.2 (2.0)	50.4 (11.7)	50.2 (11.8)	11.6 (3.3)	10.6 (3.2)	8.5 (2.9)	24.2 (9.4)
RM ANOVA† (*p*-value)			< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001
Late onset (n = 25)	Female (n = 17)	T1	20.1 (4.5)	18.5 (4.7)	7.8 (1.2)	7.4 (1.2)	64.6 (13.7)	63.4 (11.1)	14.3 (1.6)	13.9 (1.6)	12.0 (1.5)	35.4 (7.1)
		T2	20.5 (4.4)	19.5 (5.0)	6.1 (1.2)	5.5 (1.3)	61.6 (11.7)	61.9 (12.3)	14.4 (2.3)	13.1 (2.5)	11.0 (2.2)	29.1 (11.0)
		Δ§	0.4 (4.4)	0.8 (4.5)	-1.7* (1.3)	-1.9* (1.4)	-3.0 (13.5)	-1.5 (9.5)	0.1 (1.8)	-0.8 (1.7)	-1.0* (1.4)	-6.3* (8.9)
		%	2.0	4.3	-21.8	-25.7	-4.6	-2.4	0.7	-5.8	-8.3	-17.8
	Male (n = 8)	T1	38.5 (9.9)	37.1 (10.3)	11.0 (2.3)	10.2 (1.9)	63.8 (8.0)	60.0 (8.6)	11.8 (1.3)	11.8 (1.3)	9.3 (1.2)	25.9 (5.3)
		T2	31.1 (13.9)	31.7 (12.4)	9.1 (2.6)	8.8 (2.8)	51.4 (12.2)	51.8 (12.7)	10.4 (3.2)	10.1 (3.1)	8.1 (2.7)	20.3 (8.1)
		Δ§	-7.4 (11.8)	-5.4 (10.1)	-1.9* (1.4)	-1.3* (1.4)	-12.4* (6.4)	-8.3* (6.5)	-1.4 (2.6)	-1.7 (3.0)	-1.2 (2.4)	-5.7* (6.4)
		%	-19.2	-14.6	-17.3	-12.7	-19.4	-13.8	-11.9	-14.4	-12.9	-22.0
Adult (n = 83)	Female (n = 53)	T1	8.5 (5.7)	7.9 (5.6)	4.9 (1.3)	4.8 (1.4)	53.8 (9.4)	53.1 (8.8)	12.8 (1.9)	12.0 (1.4)	9.8 (1.6)	30.1 (5.5)
		T2	7.7 (4.4)	7.1 (4.3)	3.6 (1.2)	3.2 (1.0)	50.6 (8.9)	49.7 (8.9)	12.0 (2.8)	10.8 (2.9)	8.8 (2.3)	25.5 (8.4)
		Δ§	-0.8 (4.2)	-0.8 (4.0)	-1.3* (0.9)	-1.6* (0.9)	-3.2* (9.0)	-3.4* (8.1)	-0.8* (2.2)	-1.2* (2.3)	-1.0* (1.8)	-4.6* (5.7)
		%	-9.4	-10.1	-26.5	-33.3	-5.9	-6.4	-6.3	-10.0	-10.2	-15.3
	Male (n = 30)	T1	10.1 (7.5)	9.7 (7.7)	6.0 (1.6)	5.7 (1.6)	52.3 (9.6)	51.7 (9.9)	11.1 (2.0)	10.7 (2.3)	9.1 (2.0)	26.8 (5.7)
		T2	7.1 (5.3)	7.0 (5.9)	4.1 (1.5)	3.8 (1.4)	43.6 (11.2)	43.9 (11.4)	9.6 (3.3)	9.0 (3.4)	6.7 (3.3)	20.3 (9.1)
		Δ§	-3.1* (3.4)	-2.8* (3.9)	-1.9* (1.1)	-1.9* (0.9)	-8.7* (11.0)	-7.8* (9.7)	-1.6* (2.3)	-1.8* (2.4)	-2.3* (2.3)	-6.5* (5.7)
		%	-30.7	-28.9	-31.7	-33.3	-16.6	-15.1	-14.4	-16.8	-25.3	-24.3
Comparison of subgroup effects (*p*-value)												
Phenotype	Within-participants¥		.21	.66	.34	.71	.49	.74	.30	.62	.25	.78
	Between-participants		< .001	< .001	< .001	< .001	< .001	< .001	< .01	< .01	< .01	.24
Gender	Within-participants¥		< .001	< .001	.13	.53	< .01	< .01	.03	.19	.12	.68
	Between-participants		< .001	< .001	< .001	< .001	.03	.02	< .001	< .001	< .001	< .001
Phenotype x Gender	Within-participants¥		.02	.06	.41	.09	.44	.59	.48	.75	.23	.43
	Between-participants		< .001	< .001	< .01	< .01	.77	.48	.25	.35	.17	.14

† RM ANOVA, Repeated measures analysis of variance.

§ Δ = T2-T1, use of a negative sign implies a decrease in the score over nine years.

* Significant decline between baseline and follow-up using the Wilcoxon rank-sum test ($p < .05$), the level of significance was set at 5% considering the low number of participants in each cluster.

¥ Effects are analyzed within progression over 9 years.

Table 4: Correlation between baseline performance and decline for strength

	Phenotype	Hand	Spearman's Rho	*p*-value
Grip strength	Late onset	R	-.54	< .01
		L	-.51	< .01
	Adult	R	-.62	< .001
		L	-.48	< .001
Lateral pinch strength	Late onset	R	-.35	.08
		L	.07	.74
	Adult	R	-.45	< .001
		L	-.62	< .001

Table 5: Standard error of measurement (SEM) for *right hand* in upper limb performance and change over minimal detectable change (MDC)

	ICC right hand	SEM $_{95\%}$	Change over MDC
			Total sample n = 108
Grip strength (kg)	0.98[1]	± 2.6	no
Lateral pinch strength (kg)	0.96[1]	± 0.9	yes
Gross dexterity (# of blocks)	0.97[2]	± 3.8	yes
Fine dexterity (# of pins)	0.67[3]	± 2.4	no

[1] Nitz et al. [20];[2] Desrosiers et al. [30];[3] Aldehag et al. [33].

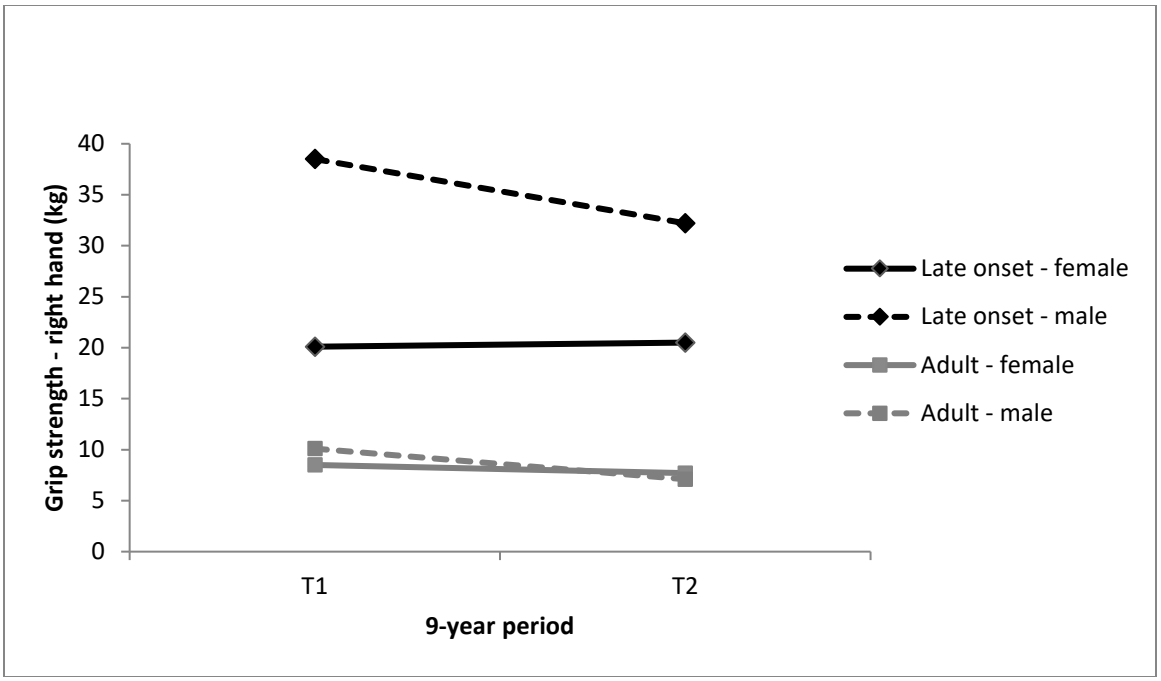

Figure 1: Phenotype and gender effects of estimated mean with RM ANOVA for right-hand grip strength.

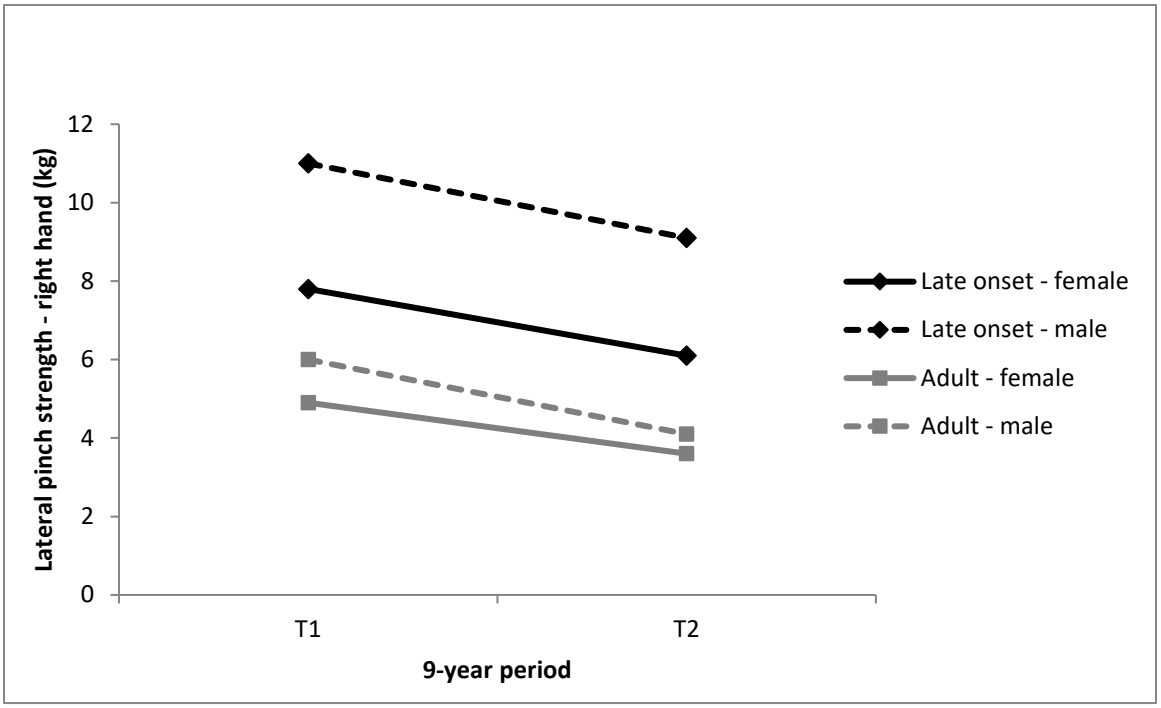

Figure 2: Phenotype and gender effects of estimated mean with RM ANOVA for right-hand lateral pinch strength.

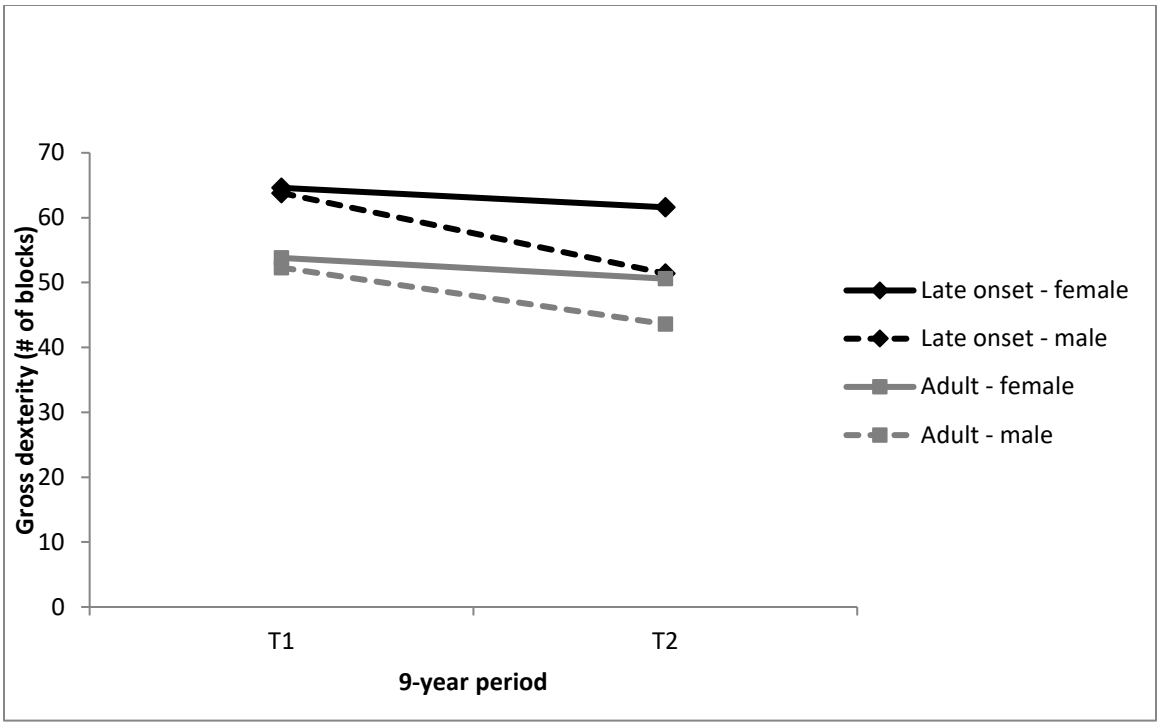

Figure 3: Phenotype and gender effects of estimated mean with RM ANOVA for right-hand gross dexterity.

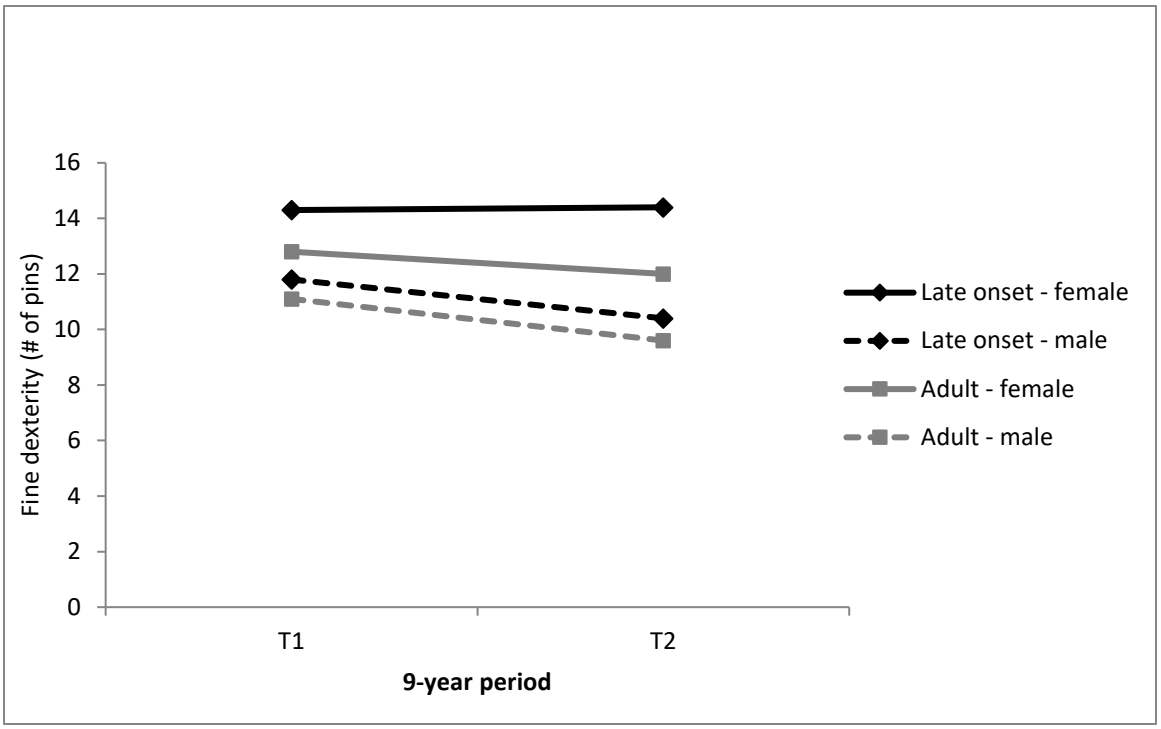

Figure 4: Phenotype and gender effects of estimated mean with RM ANOVA for right-hand fine dexterity.

SUPPLEMENTARY APPENDIX**:**

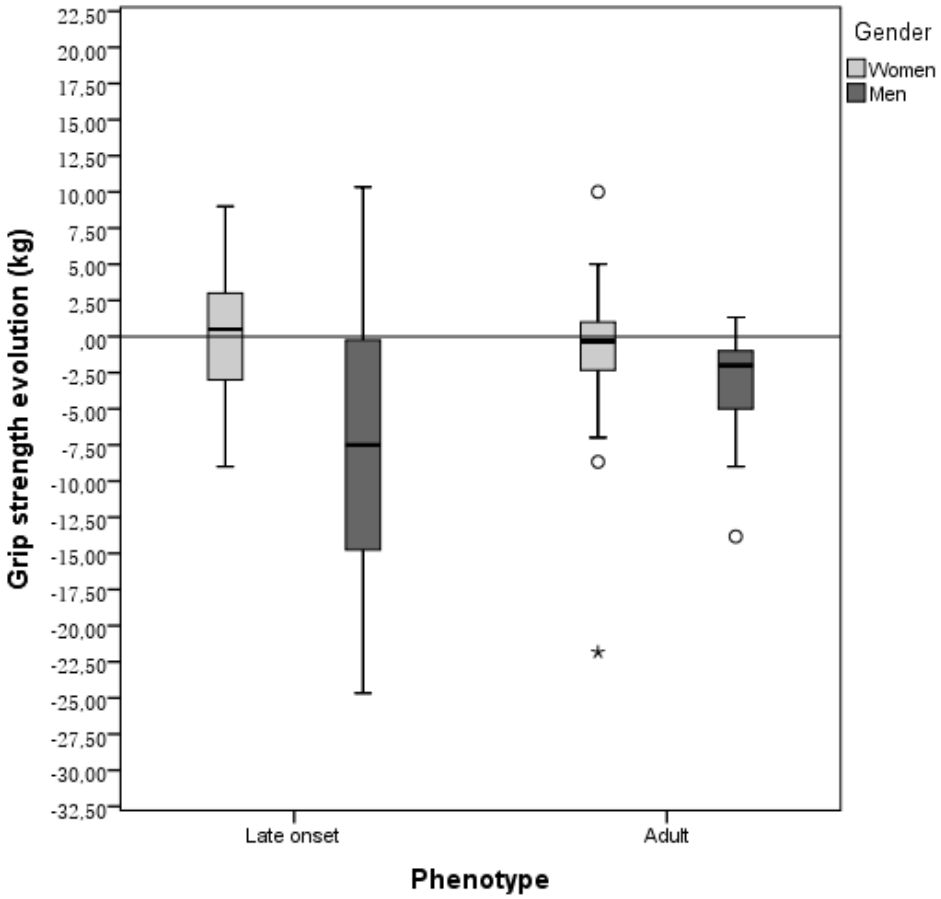

Figure A.1: Raw score decline in right-hand grip strength from baseline to follow-up.
Black lines represent the median (Q2). The box goes from the first quartile (Q1) to the third quartile (Q3) and lower and upper whiskers represent length to min-max non-outliers. Outliers (°) represent cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box and extreme outliers (*) represent cases with values more than 3 box lengths from the upper or lower edge of the box.

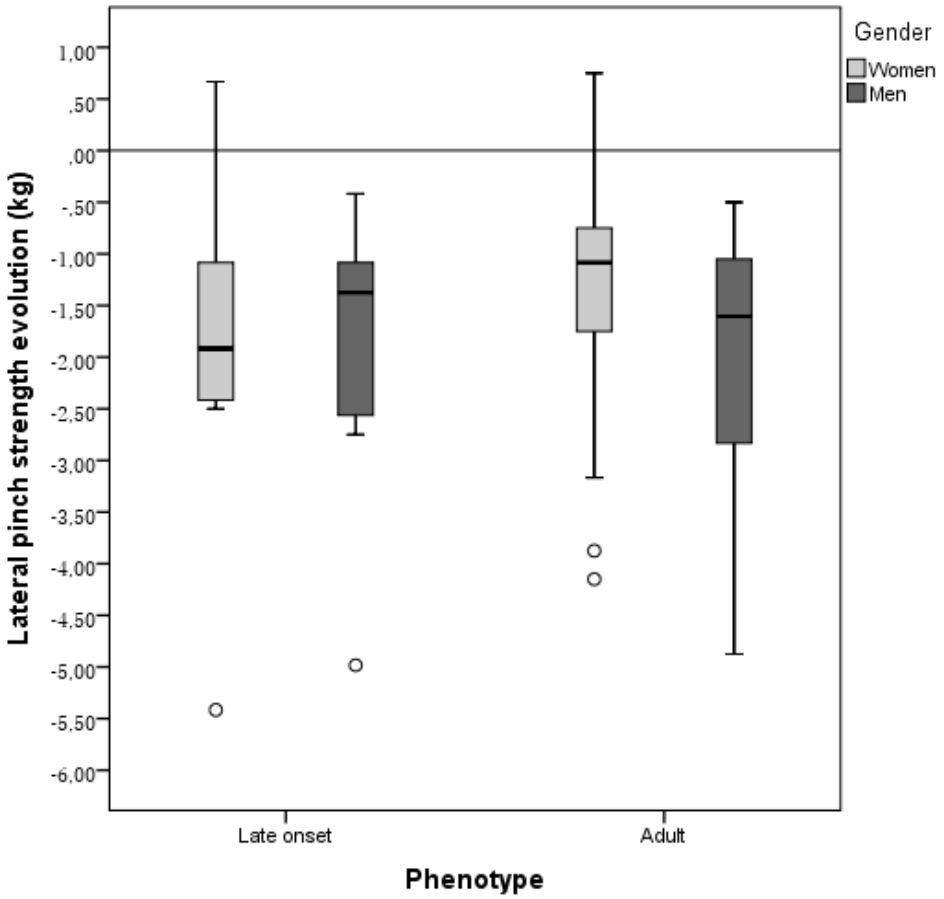

Figure A.2: Raw score decline in right-hand lateral pinch strength from baseline to follow-up.
Black lines represent the median (Q2). The box goes from the first quartile (Q1) to the third quartile (Q3) and lower and upper whiskers represent length to min-max non-outliers. Outliers (°) represent cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box and extreme outliers (*) represent cases with values more than 3 box lengths from the upper or lower edge of the box.

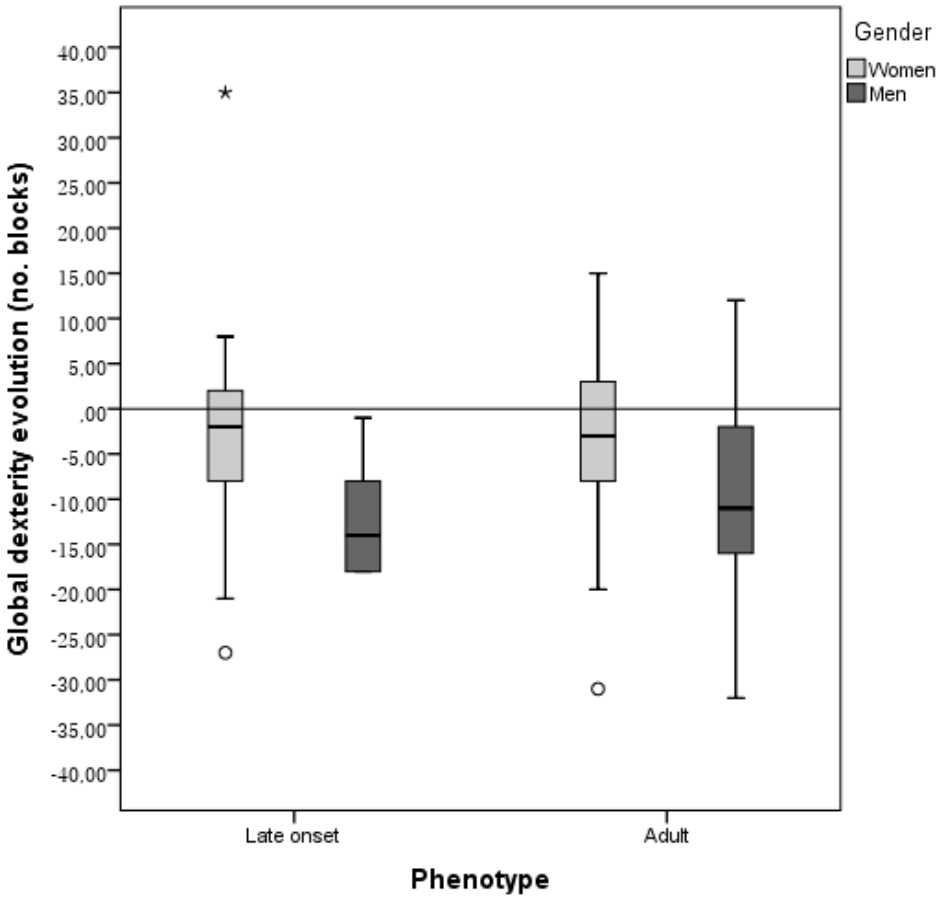

Figure A.3: Raw score decline in right-hand gross dexterity from baseline to follow-up.
Black lines represent the median (Q2). The box goes from the first quartile (Q1) to the third quartile (Q3) and lower and upper whiskers represent length to min-max non-outliers. Outliers (°) represent cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box and extreme outliers (*) represent cases with values more than 3 box lengths from the upper or lower edge of the box.

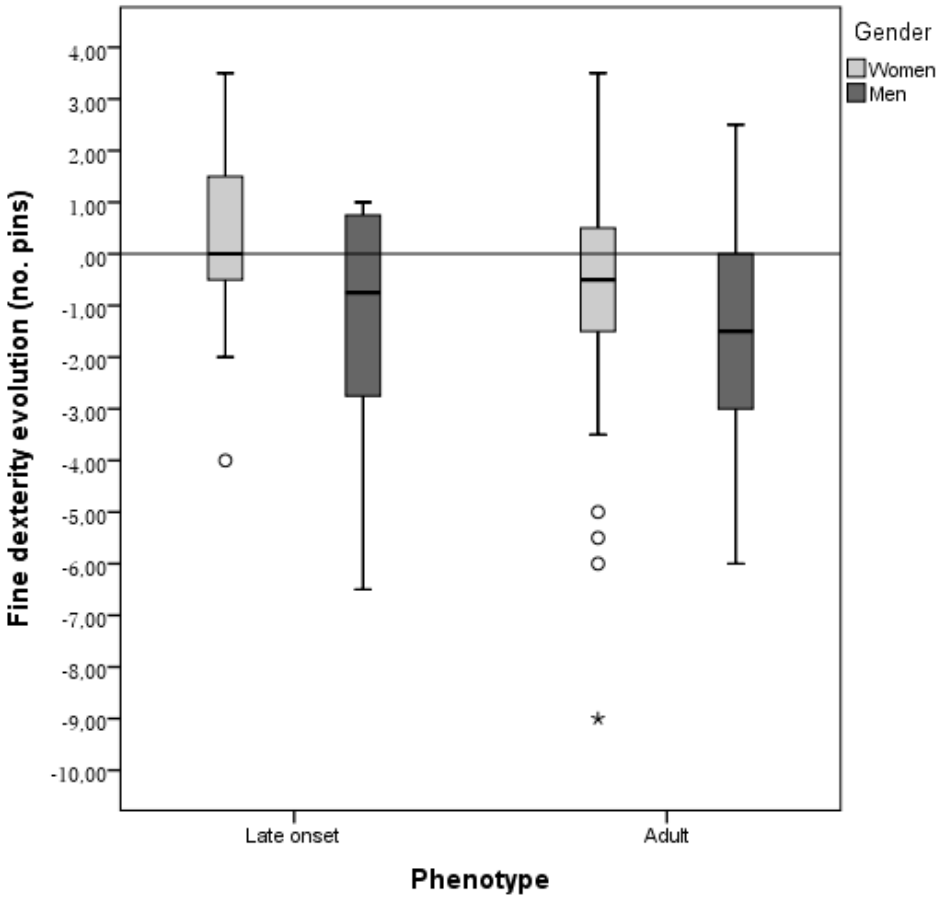

Figure A.4: Raw score decline of right hand test for fine dexterity from baseline to follow-up.
Black lines represent the median (Q2). The box goes from the first quartile (Q1) to the third quartile (Q3) and lower and upper whiskers represent length to min-max non-outliers. Outliers (°) represent cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box and extreme outliers (*) represent cases with values more than 3 box lengths from the upper or lower edge of the box.