Voice of the Patient
Report

Summary report resulting from an Externally-led Patient-Focused Drug Development meeting, an effort to expand the benefits of the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative

Myotonic Dystrophy
Externally-Led
Patient-Focused Drug Development Meeting

September 15, 2016

Hosted by:

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Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

This report represents the first summary report composed by a patient advocacy organization as a result of an Externally-led Patient-Focused Drug Development meeting, a parallel effort to the FDA's Patient Focused Drug Development Initiative. This report reflects the Myotonic Dystrophy Foundation's account of the perspectives of patients and caregivers that participated in the public meeting.

Table of Contents

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I. Introduction

Five years ago, FDA began to prioritize the value of the patient perspective in drug development, and the need for a systematic way to collect information. A key part of U.S. regulatory decision-making is establishing the context in which a particular decision is made. For purposes of drug marketing approval, this includes an understanding of the severity of the treated condition and the adequacy of the available therapies.

Patients who live with a disease have a direct stake in the outcome of FDA's decisions and are in a unique position to contribute to the understanding of their disease. The patient voice was therefore formally brought into the U.S. regulatory process under the fifth authorization of the Prescription Drug User Fee Act (PDUFA). As part of that reauthorization, the Patient-Focused Drug Development (PFDD) Initiative was launched with a commitment to hold at least 20 FDA-led public meetings focused on specific diseases. Each meeting was designed to capture the voice of the patient, and elicit perspectives specific to each disease community from patients, caregivers, and patient advocates. Realizing that these would not cover all disease areas, especially rare diseases, FDA also created a mechanism to allow external groups to host similar meetings. The externally-led PFDD meeting for myotonic dystrophy (DM), presented by the Myotonic Dystrophy Foundation (MDF), was the first such meeting under that process.

a. Overview of the myotonic dystrophies and their treatment

DM is a progressive genetic disorder of muscles that affects multiple systems in the body. It is the most common type of adult-onset muscular dystrophy, with a presumed prevalence of about 1 in 8,000, although prevalence varies markedly across different geographic populations, and may actually be significantly higher. There are two major types: Type 1 (DM1) and Type 2 (DM2), which are caused by mutations in two different genes. There are also congenital and childhood-onset forms of DM1.

b. Genetics of Myotonic Dystrophy

DM1 and DM2 are members of a group of diseases termed RNA repeat diseases because the mutations appear as a replication of three or four nucleotides (cytosine, thymine and guanine, or CTG in DM1; and CCTG in DM2) in the RNA from either the DM1 or DM2 genes. The genes are on different chromosomes.

CTG repeats in the DM1 gene are present in all people. When the number of repeats exceeds 35, the disease is considered to be in pre-mutation. When the number of repeats exceeds 50, the disease is considered to be present, although affected individuals may be asymptomatic. The severity of disease roughly correlates with the number of repeats. The repeat number is

unstable and typically expands, both over a person's lifetime and when transmitted to the next generation. This in part: explains the variability in clinical expression, even within a family; impedes diagnosis; and has a substantial impact on families and how society relates to families. In DM2, there may be thousands of CCTG repeats, with unpredictable changes between generations.

c. Clinical characteristics of DM1

The clinical expression of DM1 varies considerably among individuals with the disease, but in almost all cases multiple systems throughout the body are affected. Symptom onset is typically in the early to mid-twenties. Skeletal muscles are most affected, resulting in atrophy, wasting and weakness. Muscle groups are affected according to a somewhat regular pattern, with mouth and jaw muscles affected first, causing problems with swallowing and communication; followed by muscles of the distal arms and legs, resulting in problems with mobility and manual dexterity. Wasting and weakness of breathing muscles may be very serious, even resulting in respiratory failure, which is the leading cause of death among people with DM1. Myotonia, often described as cramping, where muscles are stiff or slow to relax, may vary from slight to very severe. Muscle weakness and wasting may cause disfiguring cosmetic effects. In addition, weakness may result in a sedentary lifestyle, which can cause difficulties with weight control and may predispose patients to diabetes.

Heart defects also occur in DM1. Although heart failure is uncommon, arrhythmias can cause sudden death, and cardiac dysrhythmia is the second leading cause of death in DM1 patients. Arrhythmias may be preventable with pacemakers, although the optimal time for implantation is unclear.

The brain may also be affected to varying degrees, ranging from no or mild effects to what some people describe as "the worst part of the condition." Most common are disorders of sleep regulation, including excessive or fragmented sleep, and problems with alertness, attention, and concentration. Psychological problems, including anxiety, depression, and withdrawal from others are common, although it remains unclear whether these represent manifestations of, or reactions to, the illness, or both. Cognitive problems, including executive function impairment and problems with memory and mental efficiency are also reported.

Effects on the endocrine system include an increased prevalence of diabetes, low testosterone, and effects on fertility. The eyes may be affected by premature cataracts and weakness of the eyelid muscles, leading to drooping eyelids that may affect how a person is perceived in the workplace and society more generally. Smooth muscles of the gastrointestinal system are also commonly affected, either becoming overactive, causing diarrhea, or underactive, causing constipation. Patients report that this symptom has a significant impact on their social lives. Smooth muscle problems may also affect the uterus, gall bladder, and circulatory system, leading to an increased frequency of problems with childbirth, gallstones, and low blood pressure.

DM1 typically appears in adults, but there are also congenital and childhood-onset forms, which if severe can cause problems with breathing and feeding. Problems tend to be focused on the mouth, causing difficulties with communication and language learning. There is also a very high frequency of learning disabilities. Muscle weakness may improve over time, although muscles may not develop at a normal rate.

d. Clinical characteristics of DM2

DM2 symptoms typically appear in the early 40s, and DM2 is not believed to have congenital or childhood-onset forms. Like DM1, multiple systems are affected, particularly skeletal muscles, the heart, and brain. The muscles affected in DM2 tend to be those of the hips, shoulder, and neck. The mouth is typically not affected. Muscle pain is more conspicuous in DM2 than in DM1, and weakness can threaten mobility. As with DM1 there are problems with heart rhythm, but the risk of sudden death is lower. Psychological effects include anxiety, depression, and withdrawal from social interactions. Memory and mental efficiency are also often impaired.

e. Meeting overview

This externally-led PFDD meeting was convened by the Myotonic Dystrophy Foundation to provide FDA the opportunity to hear perspectives on DM and approaches to its treatment directly from patients and caregivers, and to catalogue this input to be referenced by FDA officials as part of their regulatory decision-making. The discussion focused on two key topics: (1) the experience of living with DM and the symptoms that are most burdensome to patients; and (2) perspectives on the effectiveness and burden of current symptom management strategies and preferences about what would constitute a clinically meaningful treatment.

The meeting was held in Beltsville, Maryland, within close proximity to FDA's headquarters in Silver Spring, Maryland, to facilitate FDA attendance. The meeting was also made available, via a simultaneous webcast, to interested parties unable to attend in person. James Valentine, J.D., M.H.S., moderated the meeting. Mr. Valentine is an attorney who previously worked in the FDA's Office of Health and Constituent Affairs, where he facilitated patient input in benefit-risk decision making and served as a liaison to stakeholders on a wide range of regulatory policy issues. While at FDA, he helped launch the PFDD initiative.

Patient and caregiver input was captured through a multi-part format. For each of the two themes described below, a panel of patients and caregivers presented brief summaries of their experiences. This was followed by a series of polling questions designed to capture systematic data from those in attendance as well as those participating online. Polling was followed by a moderated discussion based on questions discussed by the panels. For 30 days following the meeting, patients and caregivers were also able to submit comments to an online docket or over the telephone. To access video recordings of the meetings, visit:

- Part 1: http://www.myotonic.org/patient-focused-drug-development-meeting-part-1-2016-mdf-annual-conference
- Part 2: http://www.myotonic.org/patient-focused-drug-development-meeting-part-2-2016-mdf-annual-conference.

f. Report overview

The report summarizes input provided by DM1 and DM2 patients and caregivers during the meeting and during the 30-day open comment period following the meeting regarding their experiences living with DM. Not all attendees and online participants submitted input. This report includes responses from a total of 58 individuals: 25 adult-onset DM1 patients, 1 childhood-onset DM1 patient, 13 adult-onset DM1 caregivers, 10 childhood-onset DM1 caregivers, 6 individuals living with DM2, and 3 DM2 caregivers. Demographic characteristics of these respondents are summarized in Table 1. To the extent possible, verbatim comments from

attendees are included to most accurately articulate the debilitating nature of this disease and the physical, social, and emotional impact it has on patients' lives.

The two patient and caregiver panels consisted of 6 people with DM1 and two individuals living with DM2. Additional efforts to systematically collect DM2 patient input may be undertaken in the future, when DM2-specific therapies enter the pre-clinical development arena.

Table 1: Respondent characteristics*

		DM1†	DM2†
DM1	Onset after 12 years old	38	
	Onset 1-11 years old	11	
DM2			9
Age	0-3	1	
	4-8	1	
	9-12	3	
	13-18	6	
	18-25	5	
	26-35	1	
	36-45	5	
	45-55	10	3
	>55	7	1
	Not reported	10	5
Geographic location	Northeast US	12	2
	Southeast US	7	1
	Midwest US	9	2
	Southwest US	4	
	California	5	1
	Northwest/not California	1	
	Canada	1	
	Outside North America	1	
Age at diagnosis	0-3	6	
	4-8	5	
	9-12	1	
	13-18	3	
	18-25	5	
	26-35	10	
	36-45	6	2
	46-55	4	2
	After 55	1	1
Years living with DM diagnosis	1-5	3	
	6-10	6	1
	11-15	14	
	15-25	12	3
	26-35	1	1
	>35	2	1

*Includes those present at meeting, online during the meeting, and individuals who responded by email or telephone after the meeting. Not all respondents answered all questions.
†Includes patients represented by caregivers.

II. DM1

a. Key themes in DM1

- Patients and caregivers described DM1 as a heterogeneous disease with varying types of symptoms and degrees of severity. In the most severe cases, DM1 is a devastating disease that affects all aspects of patients' lives, severely limiting their ability to work or participate in everyday and social activities.
- Patients and caregivers reported that muscle weakness, wasting, pain, and myotonia cause substantial difficulties with activities of daily living, including opening bottles and jars, preparing meals, bathing and dressing, speaking, or taking a walk.
- While muscle weakness is the predominant symptom of DM1, many patients report that their lives are affected to an even greater extent by other symptoms, such as excessive daytime sleepiness, fatigue, and gastrointestinal, respiratory, or cognitive dysfunction.
- Because the disease advances with age, some people with DM1 described their great despair as they rapidly declined, progressing from being physically, socially, and intellectually active to being relatively sedentary, isolated, and cognitively impaired.
- Patients and caregivers indicated that children with juvenile-onset or congenital DM1 are likely to be permanently developmentally impaired.
- Patients reported limited benefits from the symptomatic therapies available. They hope for a treatment that will halt or slow disease progression, but ultimately hold out hope for a treatment that would reverse the degeneration that has robbed them of a normal life.

b. Topic 1 – Living with DM

The first panel of patients and caregivers included a caregiver with 3 adult sons who all have DM1, a 75-year-old woman with DM1 diagnosed 30 years ago, and an affected mother with two daughters with juvenile-onset DM1. A woman with DM2 also participated in the first panel. The panelists were asked to address three topics:

- What symptoms of DM have the most significant impact on your life? How do they affect you or your family member's daily quality of life on a typical day and on your worst day?
- Are there specific activities that are important to you that you can no longer do, or do as fully because of your condition?
- How have your symptoms changed over time?

These same topics were covered by the polling questions and in the subsequent open audience discussion and online docket submissions; thus, the perspectives below comprise both in-person and on-line responses.

The respondents reflect the diverse age range of those affected by DM1, as shown in Table 1. Epidemiologic data shows that 75% of patients develop symptoms in their 20s, 30s, or 40s, while some are affected congenitally or in childhood or adolescence[1]. The polling data showed a similar breakdown, with the majority between the ages of 18 and 55. Those responding to the

[1] Thornton CA. 2014. "Myotonic Dystrophy" *Neurologic Clinics* 32(3): 705-719.

polling questions also reported living with DM symptoms for between one and more than 35 years, with the greatest number of patients experiencing symptoms for between 11 and 25 years.

Perspectives on the most significant symptoms

The most significant symptoms experienced by individuals with DM1 vary from person to person and over a person's lifetime. This variability is seen both in terms of severity and the specific body systems affected. For example, one man described his three adult sons living with DM1. The oldest son, diagnosed at age 26 when he experienced life-threatening cardiac arrhythmia, is now 43 years old and the most severely affected. He has steadily declined, is now unable to work and has been declared permanently disabled. The middle son has been affected primarily with muscle weakness and gastrointestinal issues, and he and his younger brother have progressed much more slowly. Another patient, a 75-year-old woman with DM1 who began experiencing symptoms of myotonia and muscle weakness in her 20s, identified fatigue as the symptom that has most dramatically affected her life.

Muscle weakness and myotonia

According to patients with DM1 and their caregivers, muscle weakness, muscle wasting and myotonia (stiffness and inability of the muscles to relax) are the most predominant symptoms of DM1. They report that symptoms manifest in different ways depending on the muscle groups affected, and can include difficulty with mobility, using hands and arms, breathing, swallowing and speech, and coughing and clearing secretions. Weakness of the facial muscles and the resulting low affect may also affect social interactions.

Mobility problems are common, resulting in many falls and injuries:

> "I fell and fractured my fibula as a result of the disease. My health started to deteriorate and I went on Social Security Disability Insurance," said one man.
>
> Another woman with DM1 said: "[in my 30s] I was taking Jazzercise class and kept stumbling into my classmates. I also began falling more while walking."

Both patients and caregivers described how muscle weakness makes accomplishing everyday activities and communication more difficult:

> A caregiver said: "The disease presents many challenges in accomplishing the normal activities of everyday life, such as opening bottles and jars, preparing a meal, lifting young children or changing their diapers, helping infants dress, taking a simple walk with a spouse, or throwing a ball with a teenage son."
>
> Individuals with DM1 reported a variety of difficulties; for example one patient reported: "Picking up and holding things became more difficult, and holding the steering wheel in the car through a turn was scary, since sometimes I couldn't let it go quickly enough."
>
> "I can't lift my arms above the shoulder, and I can't wash my hair."
>
> "I can't shake hands, and lifting kids is tiring."
>
> "I can't walk with or take care of children."

> Caregivers also reported that muscle weakness causes problems with speech and language. The mother of a child with congenital DM1: “People couldn’t understand what [my 5-year old daughter] was saying because of her severe speech impediment.”
>
> Another caregiver reported that on her son’s worst days, “He can’t be understood due to speech problems.”

Myotonia is also a prevalent symptom for most patients:

> “My main symptoms are stiffness (myotonia) of many parts of my body, such as ankles, legs, and especially my hands.”

Fatigue

Many patients identified fatigue as an even more problematic symptom than muscle weakness, although the two symptoms are frequently difficult for patients to differentiate. For example, one caregiver said that her husband describes having pervasive tiredness throughout the day, even though he uses a wheelchair and stair lift. He also has weak neck muscles, which may contribute to his fatigue.

> An artist with DM1 commented: “When I could no longer stand at my easel, I sat in a wheelchair. When I began to slump over, my back and shoulder muscles tired from sitting, we would use a bungee cord to strap me into an upright position.”
>
> Another patient said: “[it is] challenging getting out of bed or out of a chair, or getting enough energy to take a shower.”

Excessive daytime sleepiness

Many patients and caregivers also reported that being sleepy or drowsy during the day affected the patient’s ability to work or participate in other daily activities:

> “Excessive daytime sleepiness results in lack of energy and motivation to accomplish even the simplest household tasks, such as handling mail or doing a load of laundry,” said one caregiver.

Gastrointestinal problems

Dysfunction of the muscles of the gastrointestinal system, leading to both constipation and diarrhea, are often severe and can be extremely embarrassing and stigmatizing. Preserving the patient’s dignity is therefore a major concern to patients and caregivers. One parent reported that because of frequent accidents, her 16-year-old son wears pullups. Another reported: “Many hours spent in the bathroom with cramping and pain have cost our son jobs and disrupted many family activities.”

A mother who herself also has DM1 reported daily battles to get her 14-year-old daughter with constipation to sit on the toilet and push. She also wears diapers to manage constipation, which has led to comments, such as a classmate calling her “diaper girl,” causing substantial distress and humiliation.

A man with DM1 said he cannot eat normally, can easily get an intestinal obstruction, and worries about contracting pneumonia from food aspiration.

Cognitive dysfunction

Problems with mental efficiency or memory were identified as the most problematic symptom by a few patients and many caregivers. For example, one parent commented about his son:

> "He has a college degree, yet his executive function has deteriorated over the past 10 years, most recently exhibited in failure to pay a Medicare Part D premium. He therefore lost medication reimbursement for most of a year."

Emotional or behavioral problems

Caregivers, more often than patients, report emotional and behavioral problems as among the most problematic symptoms, affecting both children and adults. For example, one mother of two children with congenital DM1 made the following comments:

> "The most significant symptom of DM that has affected my family's life has been, hands down, the emotional and psychiatric manifestations of the disease."

> "[Our oldest daughter] was diagnosed with autism at 22 months of age. She had all three main features of autism and at age 6 she started to have serious behavioral issues that quickly progressed to aggression, including scratching my face, throwing heavy objects at people and having tantrums severe enough to require that she be restrained. Over time she was diagnosed with co-morbid bipolar disorder, severe anxiety disorder, ADHD, and severe learning disorders."

> "At an early age [our other affected daughter] became increasingly anxious and was unable to separate from either myself or [my husband] at any class, party or social event."

A father of three adult sons with DM1 also cited emotional issues as most problematic for one son:

> "Frustration at his situation, as well as obsessive preoccupation with minor issues, results in a stressful and often difficult home atmosphere for the patient's wife and son."

This same father mentioned the stress experienced by his sons related to having children of their own:

> "With the desire not to pass this disease to subsequent generations and the desire to have children, very expensive as well as emotionally draining multiple IVF and preimplantation genetic diagnosis procedures have been required for two of our sons, while adoption was the solution for our third son."

Heart problems

Problems affecting the cardiovascular system were reported as most problematic by only a minority of patients and caregivers, despite the fact that cardiac dysrhythmia is the second

leading cause of death in DM1. Since symptoms may be "clinically silent" in the early stages[2], they may be discounted by patients. One woman said that her heart issues include "delayed pumping action."

Pain

Some patients cited pain as one of the three most problematic symptoms, including "severe back pain," "pain in the back and neck," and pain caused by a pacemaker with defibrillator.

Perspectives on what has been lost: things you can no longer do, or do as fully because of your condition

Patients spoke poignantly about how the loss of function has affected their lives, especially their ability to maintain an active lifestyle, perform well at work, care for themselves independently, and maintain an active social life. "There is no normalcy!" said one caregiver. A woman with DM1 said "My worst day is when I feel depressed as I think of what the disease has done to my life. It ruined my marriage and career and lifestyle. I also think about what it's going to do. Sadly, I feel that this disease strips a woman of her beauty and has disfigured me. The outlook in life is bleak." Another woman with DM1 summed it up this way: "I would like to be able to hug people, clap my hands, lift my arms over my head, dance, ride horses… things we take for granted."

Individuals with DM1 and caregivers gave other more concrete examples of their losses, including the following:

Maintaining an active lifestyle:

> "I used to love to dance. I lost so many things I used to love to do."
>
> "I can't tap dance. I used to walk everywhere but can't anymore."
>
> "The activities that I can no longer do are sports related: I can only walk for a short period, cannot bike anymore due to not being able to press the brakes with my hands or hold on to the handlebars very tightly, [and can no longer do] ATV riding, ice skating, baseball and badminton, which I loved playing."
>
> "I led an active life prior to the progression of the disease. I used to like taking care of the house, doing outside work, planting and maintaining the yard. I used to go to the gym for a vigorous workout and to maintain my weight. I used to play sports with my son and I cherish the time when I was more active with him. My social life is affected, as I don't have that much money and have a hard time getting around."
>
> "I am not painting much, and I've given up driving - I was getting lost too often. I take afternoon naps; I watch short TV shows with little plots like Animal Channel. I read or paint only for short times to rest my eyes."
>
> "My daughter was an accomplished equestrian but has lost that physical ability," said one caregiver.

[2] Lau JK et al. 2015. "Myotonic dystrophy and the heart: A systematic review of evaluation and management" *International Journal of Cardiology* 184: 600-608.

Caring for oneself independently:

> "As a young adult, being so dependent on others for such simple tasks such as straightening a collar or putting on socks is extremely frustrating and demoralizing," said one caregiver.
>
> Another said: "Our son… cannot lift his arms above his chest, is unable to completely dress himself, struggles with buttons, collars, shoes, and socks; and has difficulty with grooming, lifting a glass, and even using a knife and fork."

Socializing

> "Socializing with friends, going out together as a couple, taking a vacation, pursuing outside interests and relaxing, and watching our children mature, develop interests and become independent individuals will never truly be a part of our life story," said one woman who has DM1 and also cares for her affected children.
>
> Another person said, "I have suspended social time with friends because my humor is angry and I cannot enjoy visiting and engaging in activities that we once shared."

Perspectives on disease progression:

Nearly all individuals with DM1 reported disease progression, although the rate varied from patient to patient. Some patients reported experiencing earlier onset (early 20s or late teens) and typically also experience faster progression. Others experienced later and/or milder onset of symptoms, and their progression tends to be slower.

Patients also reported experiencing changes in progression rate as they age. For example, one person said his symptoms progressed slowly until the last year or two when they seemed to progress more rapidly. Another said her symptoms started in college and have progressed to include being: "more tired, droopy eyed, and having a sunken face." Other comments included:

> "The sad reality is that I can do so much less today than I could do 20, 10, or even 2 years ago."
>
> "What is really scary is knowing that if the disease continues to progress, I will simply not be functional in 5 or 10 years' time."
>
> "2 years ago I could ride my bike 5 miles; now I cannot ride a bike at all. I used to be able to lift a small suitcase to the overhead bin. I can still walk, but I'd like to run and dance."
>
> A caregiver added: "Each and every day brings a new challenge for all our children, and those challenges will certainly increase as the disease progresses."
>
> A woman who is both affected herself and a caregiver for her two daughters reported that: "Over the past 5 years [my two daughters and I] have had, combined, a total of two cholecystectomies, one cataract repair, palatal surgery to repair a velopharyngeal defect caused by DM, an abdominal hysterectomy for abnormal uterine cytology (which seems associated with DM), and a prolonged inpatient hospitalization for a severe gastrointestinal infection made worse by the GI manifestations of DM. Impending foot braces and pacemakers for two of us are likely. Sleep studies, PFTs, swallowing studies,

additional medications, more blood work, another round of specialist appointments . . . it just keeps getting more complicated and more serious."

A caregiver reported that her husband "has experienced a devastating decline over time. On his best days, he goes to the senior center."

A woman with DM1 said her symptoms have "progressed drastically. I cannot bend, my ankles are weak, I fractured my fibula, and I've had three episodes of atrial flutter. My face is now long, thin and triangular, my muscles overall are becoming flaccid. I am becoming weaker while gaining more weight. I have to use a ventilator, which I find highly uncomfortable."

A caregiver said her 21-year-old son "is unable to make executive decisions or care for himself."

c. Topic 2 – Current and future treatments

Patients and caregivers shared that there are currently no treatments that alter the progression of DM1. Respondents described that management, is therefore, aimed at preserving function and independence; providing symptomatic relief for myotonia, pain, excessive sleepiness, and gastrointestinal dysfunction; preventing cardiopulmonary complications including heart failure, arrhythmias, and respiratory insufficiency; and treating emotional and psychological sequelae of the disease, such as anxiety and depression.

Perspectives on current treatments

Patients and caregivers described a variety of strategies they use to manage their symptoms and preserve what function remains. The list below is a compilation of what patients and caregivers described as the treatment strategies they use.

Preserving function and independence

- Exercise was the most frequently mentioned strategy used to preserve skeletal muscle function.
- Physical therapy has been used to promote balance and endurance.
- Many patients reported using leg braces, canes, walking poles and/or canes to enable ambulation. One patient also uses a cushioned headband to prevent injury from falls.
- One patient described using a neck brace to manage profound muscle weakness in the head and neck.
- Another patient used a manual wheelchair to decrease fatigue and muscle atrophy, although as his muscle weakness progressed, he became unable to control the chair without assistance.
- One patient described receiving speech therapy to rebuild strength in the esophagus.
- Another patient has used hippotherapy (horseback riding) to improve balance and strength.
- To preserve independence, patients engaged in several strategies, including making lifestyle adjustments and work accommodations such as starting work later in the day to allow time for their extensive morning routines, avoiding large gatherings, ordering dishes at restaurants that are easy to pronounce, acquiring a service dog, and using communication augmentation devices.

Providing symptomatic relief for myotonia, excessive daytime sleepiness, pain, and gastrointestinal dysfunction

- Myotonia treatments that were mentioned by many patients included mexiletine (an anti-arrhythmic agent), anti-spasmodic agents, and cannabis.
- For daytime sleepiness and drowsiness, several patients and caregivers reported using modafinil (Provigil), Ritalin or Nuvigil.
- Melatonin was mentioned by one patient as a sleep aid.
- Patients reported a variety of treatments for pain, including exercise, ice, heat, oral and topical pain relievers, massage therapy, chiropractic care, opioids, and cannabis.
- To relieve symptoms from gastrointestinal dysfunction, patients have taken magnesium, probiotics, and antibiotics to treat bacterial overgrowth. Nectar-thick liquids have been used to prevent aspiration, and some patients required a G-tube. One mother described giving her daughter enemas every other day as a means of shrinking her colon and reactivating nerves.

Preventing cardiopulmonary complications

- Patients described taking many different medications to lower the risk of cardiac problems, including beta-blockers, Xarelto, and baby aspirin.
- Many patients with more advanced disease symptoms use pacemakers and defibrillators to manage arrhythmias.
- To augment breathing and ensure adequate oxygenation of the blood while sleeping, patients reported using Bilevel Positive Airway Pressure (BiPAP) machines.

Managing emotional and psychological sequelae of DM1

- Many patients rely on exercise and/or physical therapy to improve mood.
- Some patients mentioned using cannabis to relax.

Effectiveness and adverse consequences of current treatments

A large majority of caregivers and a majority of people living with DM1 said that medicines, equipment, and lifestyle changes have helped somewhat in managing the worst symptoms and improving quality of life. Some, however, reported limited effectiveness that wanes over time:

> One caregiver said that the use of a pacemaker, G-tube, and BiPAP has helped control some symptoms, although her family member's muscle weakness is getting worse.
>
> Another caregiver said "Cane and nectar-thick liquids to prevent aspiration have helped, but other treatments are just holding steady."

Many individuals with DM1 commented on the effectiveness of exercise as a treatment strategy, and on the fact that exercise could have negative consequences:

> "Exercise and yoga have helped me to maintain enough strength to function normally."
>
> "Working out helps maintain strength, but at the same time I realize I am battling a disease that will eventually take over and I will have to be inactive. In the meantime, I try to keep going and I feel better about it. It makes me feel better that I had a productive day and I am doing something about it."

> “Exercise provides me with psychological benefits, but it can lead to injuries.”
>
> “[Physical] activity now increases my pain.”

While several individuals with DM1 use BiPAP or other ventilation assistive devices, their effectiveness is unclear, and some patients said [these devices] were not effective or that they are non-compliant for other reasons:

> “I am not sure if the ventilator is working but I keep using it as it just makes me feel better that I am actually doing something about it even if I use it during the day,” said one person with DM1. “I find that I am more confined to my bed and my sleep cycle is extremely affected by it.”
>
> Another individual noted, “Who wants to go to bed with a mask on their face? I don’t. I cannot stand it. It also affected the romance in my life.”

A majority of patients reported success with regular exercise for skeletal muscle and mood stabilization, although injury from falls was a problem for many. One DM2 patient reported taking regular medications that require 21 injections and 3 oral tablets to manage his daily symptoms that included excessive daytime sleepiness, pain and cognitive issues. He tried hydrotherapy for pain and experienced elevated CK levels. Cymbalta for depression caused excessive sweating, and the pain meds he tried, including Celebrex, were of limited efficacy, difficult to get reimbursed and caused flat libido. Stimulants he took to stay awake caused “numerous side effects”. One patient took mexiletine but had to stop after having changes in heart rhythm. Another patient reported that magnesium sometimes caused diarrhea. One patient said her chest sometimes hurts if she smokes too much marijuana.

In addition to adverse effects, patients reported other problems with current treatments, including the lack of insurance coverage for alternatives such as hippotherapy, service dogs, and portable defibrillators.

Perspectives on ideal treatments for DM1

People with DM1 and their caregivers hope for a cure and treatments that will reverse the damage already experienced. As an interim measure, they desire treatments that will halt or slow disease progression. One patient put it this way: “Regarding an ideal treatment, the general theme is quality of life. I would love to put a marker in the sand and keep what we have now. Down the road pushing back would be fabulous.”

Patients and caregivers gave somewhat different responses to the polling question: “What would be the three most important impacts from a new DM treatment for you or your affected family member?” People with DM1 indicated that reducing fatigue, improving walking and stamina, and improving sleep or sleepiness issues were the most important, while caregivers selected making gastrointestinal and stomach issues better, improving thinking, and improving walking and stamina as most important.

Comments submitted at the meeting and via the post-meeting docket provided additional perspectives from patients. They expressed the desire for treatments that would reverse muscle wasting or maintain current levels of muscle strength, rebuild muscles, relieve pain, and stop progression. Other comments included:

"The goal is to maintain what I have left as I am near crippled," said one patient.

"An ideal treatment would be a medication that reverses the symptoms in all aspects of the disorder, including cognitive issues of executive function," said another.

"More than anything, I want to recapture the joy of life that can be lost to a neuromuscular disease that requires most of my energy to get through the day, leaving little reserve for the things that really matter."

d. Summary of comments

The comments of patients and caregivers highlight several key aspects of DM1 that must be considered in the design and evaluation of prospective treatments. These include:

- The multiple organ systems that may be affected
- Substantial heterogeneity in symptomatology
- The progressive nature of the disease
- The transgenerational impact of the disease

Patients also describe a loss of abilities and functions that many people take for granted, the challenge of managing symptoms, and the financial burden imposed by lack of coverage for necessary therapies, including alternative therapies.

III. DM2

Only two panelists and a few audience members commented on the experience of living with DM2. Nonetheless, a few themes emerged about this DM genotype.

In general, people with DM2 tend to be older, diagnosed later, and experience milder symptoms.

Perspectives on most significant symptoms in DM2

Nearly all DM2 patients and caregivers mentioned fatigue and muscle weakness as their most significant symptoms. One woman described persistent symptoms of nausea, weakness, and heart arrhythmia that began after being sick with the flu at age 32, yet she was not diagnosed until age 58 when her older son became sick with similar symptoms. Eventually her younger son would also be diagnosed with DM2 and she learned that her father also had the disease. The older son has more severe symptoms than other family members, including a substantial loss of body mass, pointing again to the wide variability of disease expression.

Pain and cognitive issues also emerged as significant problems for individuals with DM2. One patient said: "I was forced to go on disability because of a combination of excessive daytime sleepiness, pain, and cognitive issues. Of these three symptoms, I could not really say which one is most debilitating for me. It depends on what is going on that day and the physical demands of the previous day."

Fatigue and excessive sleepiness

One patient said: "fatigue steals the most." Another woman reported that she has breathing difficulties and her eyes go out of focus, which contribute to fatigue. Another patient said he has

excessive daytime sleepiness, and another commented that he needs “large amounts of sleep,” even though his symptoms are generally mild.

Muscle weakness

Muscle weakness contributes to fatigue, but was also mentioned for other effects it has on the daily life of people with DM2:

> “My first grandbaby is 8 months old and I can barely lift him,” said one patient.
>
> “Sometimes at the end of the day, I can barely lift my head,” mentioned one patient, noting that for her, muscle weakness has been progressive.
>
> Muscle weakness complicates even the simplest tasks for patients, with one noting that: “I am weaker than a normal person, can’t lift much, and have trouble climbing steep stairs.”
>
> “I have difficulty getting up from low chairs, and if I fall, I cannot get up again without assistance,” said another patient.

Pain

One patient described pain as one of her most significant symptoms:

> “The pain is everywhere! From migraines to burning pain in my feet. It hurts to breathe, to speak, to stand, to sit, to roll over in bed. There is dystonia in my neck and jaw and my pelvic and back joints sublux constantly, sometimes dislocating and locking out of place.”

Cognitive issues

One patient said she has memory problems and diminished intellectual capacity:

> “I had brain fog and kept getting lost driving home. My memory, which used to be so good, is terrible now.”

Perspectives on current treatments

One man said he takes 21 different medications by mouth as well as 3 by injection, resulting in many drug interactions and significant side effects. For example, he takes Cymbalta for depression, which exacerbates the excessive sweating he experiences as a DM2 symptom. An alternative anti-depressant led to a 60-pound weight gain in 9 months. He has also taken many different medications for pain, but some are not covered by insurance, while others have side effects including flat affect and loss of libido. Narcotics are most effective, but doctors are reluctant to write prescriptions for them out of concerns about abuse.

This patient also uses BiPAP as a treatment for sleep apnea, but still suffers from excessive daytime sleepiness, for which he has taken stimulants and medications to increase wakefulness (Nuvigil, Provigil), all of which had limited effectiveness. Amphetamines were associated with serious side effects.

IV. Conclusion

The externally led Patient-Focused Drug Development meeting on myotonic dystrophy provided an opportunity for FDA to hear first-hand the experiences of patients and caregivers regarding this progressive, disabling, multi-system disease. Organized by the Myotonic Dystrophy Foundation, the meeting aligned with the Patient-Focused Drug Development Initiative launched in response to the fifth authorization of the Prescription Drug User Fee Act (PDUFA). Meeting participants demonstrated the critical importance of the patient perspective in ensuring that drug development proceeds in a manner that will deliver therapies to patients that reflect the magnitude of the disease burden experienced and the impact deemed most important by those living with this disease.

Meeting participants included patients and caregivers, as well as representatives from FDA and many academic and industry professionals working to find effective treatments for DM. MDF is very grateful to the patients and caregivers who shared their personal experiences of living with DM and their perspectives on current and future treatments, and to FDA for bringing this initiative to life.

APPENDIX 1: Meeting Agenda

Myotonic Dystrophy Patient-Focused Drug Development

Externally-Led Meeting

Thursday, September 15, 2016

Sheraton College Park North Hotel

4095 Powder Mill Road, Beltsville, MD 20705

1:00 PM	Buses arrive, meeting attendees are seated
1:15 PM	Introduction & Meeting Overview – James Valentine, JD, MHS, Associate, Hyman, Phelps & McNamara, P.C.
1:25 PM	Disease Manifestations & Clinical Overview – Charles Thornton, MD, Professor, Department of Neurology and the Center for Neural Development and Disease, University of Rochester Medical Center
1:40 PM	Audience & Remote Polling – Attendee Demographics
1:50 PM	Panel #1: Living with DM Myotonic dystrophy (DM) patient and caregiver panel: • What 1-3 symptoms of DM have the most significant impact on your life? How do they affect your life on a typical day? On your worst day? • Are there specific activities that are important to you that you can no longer do or do as fully because of your condition?

- How have your symptoms changed over time?

2:10 PM Audience & Remote Polling – Panel 1 Questions

2:20 PM Moderated Audience Discussion – Panel 1 Questions

2:50 BREAK

3:00 PM FDA Welcome and Remarks – Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER), FDA

3:15 PM Film screening: Challenges of DM

3:25 PM Panel #2: Current & Future Treatments

DM patient and caregiver panel:

- What current treatments or therapies do you use for symptom management
- How well are these therapies or treatments working?
- What are the downsides, if any, to these treatments or therapies?
- What do you want from an ideal treatment?

3:45 PM Audience & Remote Polling – Panel 2 Questions

4:00 PM Moderated Audience Discussion – Panel 2 Questions

4:30 PM Meeting Summary – Jonathan Goldsmith, MD, FACP, Associate Director for Rare Diseases, Office of New Drugs, CDER, FDA

4:45 PM Close & Adjourn – Molly White, Chief Executive Officer, MDF

5:00 PM Board buses to return to conference hotel

APPENDIX 2: Meeting Participants

Myotonic Dystrophy Patient-Focused Drug Development Meeting

FDA, Expert and Panel Participants

FDA Attendees:

- **Larry, Bauer, M.A., R.N.**, Senior Regulatory Scientist, Rare Diseases Program, Office of New Drugs, Center for Drug Evaluation and Research, FDA
- **William Dunn, M.D.**, Director, Office of Drug Evaluation 1 – Division of Neurology Products, Office of New Drugs, Center for Drug Evaluation and Research, FDA
- **Jonathan Goldsmith, M.D., F.A.C.P.**, Associate Director, Rare Diseases Program, Office of New Drugs, Center for Drug Evaluation and Research, FDA (presenter)
- **Laurie Haughey,** Health Communications Specialist, Office of Operations, Office of the Center Director, Center for Drug Development and Research, FDA
- **Nicholas Kozauer, M.D.**, Medical Team Lead, Office of Drug Evaluation 1, Division of Neurology Product, Office of New Drugs, Center for Drug Evaluation and Research, FDA
- **Alyssa Polovoy,** Program Analyst, Office of Operations, Center for Drug Evaluation and Research, FDA
- **Gayatri Rao, M.D., J.D.**, Director, Office of Orphan Products Development, FDA
- **Graham Thompson,** Operations Research Analyst, Office of Strategic Programs, Center for Drug Evaluation and Research, FDA
- **Janet Woodcock, M.D.**, Director, Center for Drug Evaluation and Research, FDA (presenter)

Expert Participants:

- **Charles Thornton, M.D.**, Professor of Neurology, University of Rochester Medical Center

Panelists:

- Panel 1:
    - **Lee Baker**, living with DM1
    - **Sarah Clarke, M.D.**, self and daughters living with DM1
    - **Judy Marks, R.N.**, living with DM2
    - **Glen Wiggans, M.D.**, self & 3 sons living with DM1
    -
- Panel 2:
    - **Joachim Boekelman, J.D.**, living with DM1
    - **Patricia Dinsmore**, living with DM1
    - **Suzette Ison, R.N.**, son living with DM1
    - **Thomas McPeek**, living with DM2

APPENDIX 3: Moderated Discussion Questions

Myotonic Dystrophy Patient-Focused Drug Development Meeting

Moderated Discussion Questions

Panel 1 Questions:

1. Select the *top 3* myotonic dystrophy symptoms *that most impact* you or your affected family member's *daily quality of life*
2. Select *the most important thing* you or your affected family member *used to do* that you or your family member *now can't do as well* because of DM

Post-Panel 1 Moderated Discussion Questions:

1. For those of you who picked **weakness** as a top three worst symptoms, tell us more about that:
    a. How does weakness affect you?
    b. How has it affected your ability to work?
    c. How has it affected your finances?
    d. How does it affect your daily living (dressing, cleaning, cooking, etc.)
    e. How has it affected your family? Your caregiver?
    f. What favorite or important activities do you no longer do or do less often because of weakness?
    g. For those of you who picked 'other' as one of your top three symptoms, can you tell us what that is?
2. For those of you who picked myotonia and cramping as a top three worst symptoms, tell us more about that:
    a. How has it affected your ability to use your hands? Your ability to speak clearly? Your ability to chew and swallow foods?
    b. How has it affected your family? Your caregiver?
    c. What favorite or important activities do you no longer do or do less often because of myotonia and cramping?
3. For those of you who picked fatigue as a top three worst symptoms, tell us more about that:
    a. How has fatigue affected your ability to work? Your family finances?
    b. How has fatigue affected your relationships?
    c. How has it affected your ability to care for a child or other family member?

d. What favorite or important activities do you no longer do or do less often because of fatigue?

Panel 2 Questions:

1. Indicate *3 medicines, equipment or lifestyle changes* that you or your affected family member currently use to manage DM symptoms
2. In general, how much do these medicines, equipment or lifestyle changes improve your or your affected family member's quality of life
3. What would an ideal DM therapy do for you or your affected family member – pick your top 3 effects

Post-Panel 2 Moderated Discussion Questions:

4. For those of you who seen good improvement in your or an affected family member's symptoms due to medicines, equipment and lifestyle changes you currently use, tell us more:
    a. How has mexiletine helped your ability to use your hands? Walk, climb stairs and avoid falls? Speak clearly? Chew and swallow food without choking?
    b. Are there downsides to mexiletine that you or your family member experience?
    c. How has using a C-PAP, BiPAP or VPAP machine helped? Do you or your family member use it regularly? What are the downsides of using the machine?
    d. How has taking medicine or getting therapy for behavioral issues helped? Are there drawbacks to the medications you are using?
    e. How has medicine for daytime sleepiness helped? How much more alert or awake are you or your affected family member? What can you do that you couldn't do before you started the medication? What are the downsides of the medication?
    f. How helpful have orthotics, ankle/leg braces or AFOs been in helping with walking, standing and avoiding falls? What don't you or your affected family member like about wearing the braces or orthotics

5. Let's talk more about what you want to see in an ideal DM therapy:
    a. What activity that is really important to you or your affected family member will you be able to do or do better?
    b. What do you most miss in your life that having DM has taken away from you?
    c. What will the most important impact of the ideal treatment be on your caregiver? Your family members?
    d. How important is stopping or slowing progression of DM to you in terms of what a therapy might do?
    e. How much improvement in muscle strength would be enough for you from a therapy?
    f. How much improvement in your fatigue would be enough for you from a therapy?
    g. How much improvement in your myotonia and cramping would be enough for you from a therapy?
    h. What are you most worried about in terms of your future living with DM that you would like a therapy to address?
    i. As a caregiver, what do you most want to see from an ideal therapy, for your family member?

APPENDIX 4: Meeting Polling Questions

Myotonic Dystrophy Patient-Focused Drug Development Meeting

Polling Questions

DEMOGRAPHIC POLLING QUESTIONS (asked at beginning of meeting)

1. I am a (chose all that apply):
    a. person living with adult-onset DM1 (symptoms after age 12)
    b. person living with childhood-onset DM1 (symptoms appearing between 1-11 years of age)
    c. person living with congenital DM1 (symptoms at birth or the first 4 weeks)
    d. *caregiver* of someone living with adult-onset DM1
    e. *caregiver* of someone living with congenital or childhood-onset DM1 (child or adult)
    f. person living with DM2
    g. *caregiver* of person living with DM2
    h. not sure

2. Your age or, if you are a *caregiver,* the age of your affected family member (pick *one* to discuss):
    a. 0-3 years old
    b. 4-8 years old
    c. 9-12 years old
    d. 13-18 years old
    e. 18-25 years old
    f. 26-35 years old
    g. 36-45 years old
    h. 46-55 years old
    i. older than 55

3. Where do you currently reside?
    a. Northeastern US
    b. Southeastern US
    c. Midwestern US
    d. Southwestern US, incl. Texas
    e. California

f. Northwest US, not including California
g. Canada
h. Outside of North America

4. Age you or your affected family member was diagnosed:
    a. 0-3 years old
    b. 4-8 years old
    c. 9-12 years old
    d. 13-18 years old
    e. 18-25 years old
    f. 26-35 years old
    g. 36-45 years old
    h. 45-55 years old
    i. older than 55

5. Number of years you or your affected family member have been living with DM symptoms:
    a. 1-5 years
    b. 6-10 years
    c. 11-15 years
    d. 15-25 years
    e. 26-35 years
    f. More than 35 years living with DM symptoms

PANEL 1 POLLING QUESTIONS (asked after Panel 1 presentations)

1. Select the *top 3* myotonic dystrophy symptoms *that most impact* you or your affected family member's *daily quality of life*:
    a. Trouble using hands or arms
    b. Problems sleeping or being too sleepy
    c. Myotonia/muscle stiffness in hands or mouth (grip stiffness, swallowing, choking or speech difficulties, etc.)
    d. Gastrointestinal problems
    e. Mobility problems: difficulty walking, tripping, falls
    f. Heart problems
    g. Problems with mental efficiency or memory
    h. Emotional or behavioral problems
    i. Pain
    j. Fatigue

1a: Was there a *top 3* myotonic dystrophy symptom *that most impacts* you or your affected family member's *daily quality of life that was NOT listed in the prior question*?
    a. Yes
    b. No

2. Select *the most important thing* you or your affected family member *used to do* that you or your family member *now can't do as well*:
    a. Take a shower, bath or dress independently
    b. Eat solid food
    c. Go out to eat or visit friends and family

d. Perform well at a job or work
e. Take care of a family member
f. Be active (exercise, dance, etc)
g. Go up and down stairs, get in and out of a chair or bed
h. Drive
i. Open doors, drawers, bottles, jars
j. Other

PANEL 2 POLLING QUESTIONS (asked after Panel 1 presentations)

1. Indicate up to *3 medicines, equipment or lifestyle changes* that you or your affected family member currently use to manage DM symptoms:
    a. Mexiletine for myotonia and muscle stiffness (hands, mouth, etc.)
    b. Medicine for daytime sleepiness or attention
    c. Medicine for anxiety or depression
    d. Medicine for stomach and intestinal symptoms
    e. C-PAP, BiPAP or VPAP machine at night
    f. Ankle, leg or other braces
    g. Pureeing, softening or thickening food
    h. Changes in diet (e.g. gluten free, high fiber, dairy free, etc.)
    i. Cane, walking stick
    j. Tools to open jars, doors, etc.

2. In general, how much do these medicines, equipment or lifestyle changes improve your or your affected family member's quality of life:
    a. In general they have *really helped manage the worst symptoms* and *improving my or my family member's quality of life*
    b. In general they *have helped somewhat in managing the worst symptoms* and *improving my or my family member's quality of life*
    c. In general they *have not helped much at all in managing the worst symptoms* and improving my or my family member's quality of life

3. What would be the *most important impact* from a new DM treatment for you or your affected family member – pick your top 3 impacts:
    a. Reduce fatigue
    b. Improve walking and stamina
    c. Reduce myotonia/muscle stiffness of hands and mouth
    d. Make the GI and stomach symptoms better
    e. Make the anxiety and/or depression better
    f. Improve behavioral issues
    g. Improve your thinking
    h. Lessen your pain
    i. Improve your sleep or sleepiness issues
    j. Other

3a. How important to is having a therapy that slows the progression of your disease of that of your affected family member:
    a. Very important
    b. Important
    c. Not important

APPENDIX 5: Results of Meeting Polling Questions

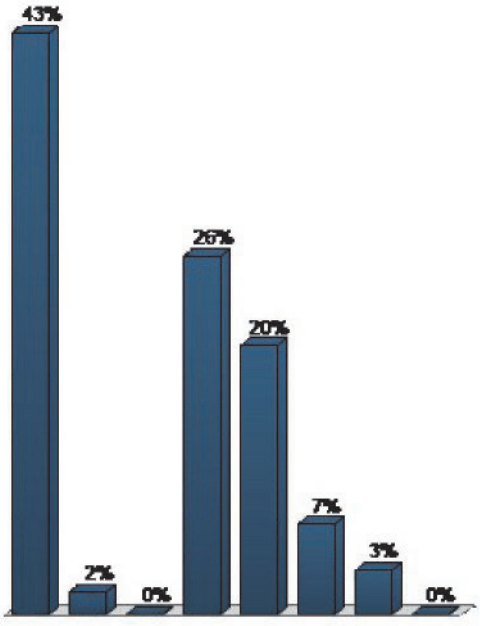
Session Name: MDF Wash DC 9-15-2016 4-49 PM

Date Created:	9/15/2016 12:46:15 PM	**Active Participants:**	118 of 118
Average Score:	0.00%	**Questions:**	11

Results by Question

1. I am a (choose one): (Multiple Choice)

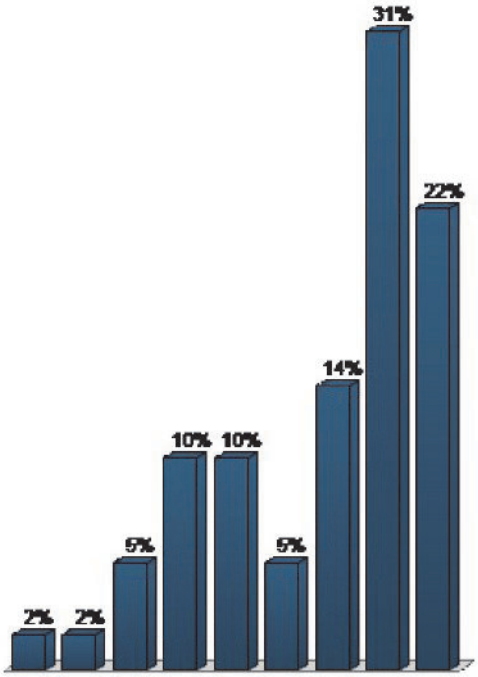
	Responses	
	Percent	**Count**
Person living with adult-onset DM1 (symptoms after age 12)	42.62%	26
Person living with childhood-onset DM1 (symptoms appearing between 1-11 years of age)	1.64%	1
Person living with congenital DM1 (symptoms at birth or the first 4 weeks)	0%	0
Caregiver of someone living with adult-onset DM1	26.23%	16
Caregiver of someone living with congenital or childhood-onset DM1 (child or adult)	19.67%	12
Person living with DM2	6.56%	4
Caregiver of person living with DM2	3.28%	2
Not sure	0%	0
Totals	**100%**	**61**



Question Statistics	
Mean	3.11
Median	4.00
Variance	3.87
Standard Deviation	1.97

2. Please indicate your age, or if you are a caregiver, the age of your affected family member (pick one to discuss): (Demographic Assignment)

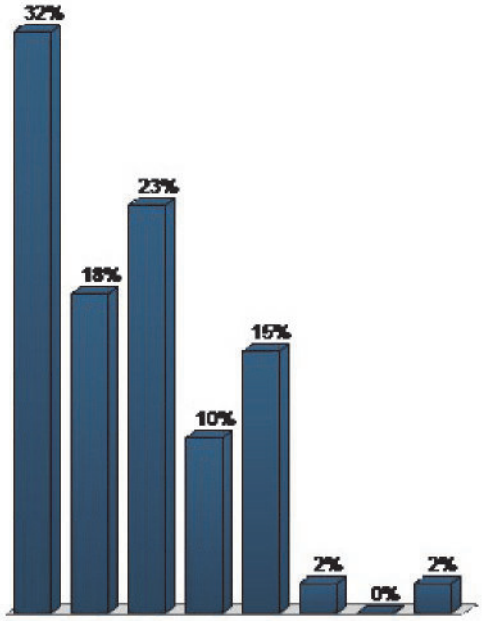
	Responses	
	Percent	**Count**
0-3 years old	1.69%	1
4-8 years old	1.69%	1
9-12 years old	5.08%	3
13-18 years old	10.17%	6
18-25 years old	10.17%	6
26-35 years old	5.08%	3
36-45 years old	13.56%	8
45-55 years old	30.51%	18
Older than 55	22.03%	13
Totals	**100%**	**59**



Question Statistics	
Mean	6.80
Median	8.00
Variance	4.37
Standard Deviation	2.09

3. Where do you or your affected family currently reside? (Demographic Assignment)

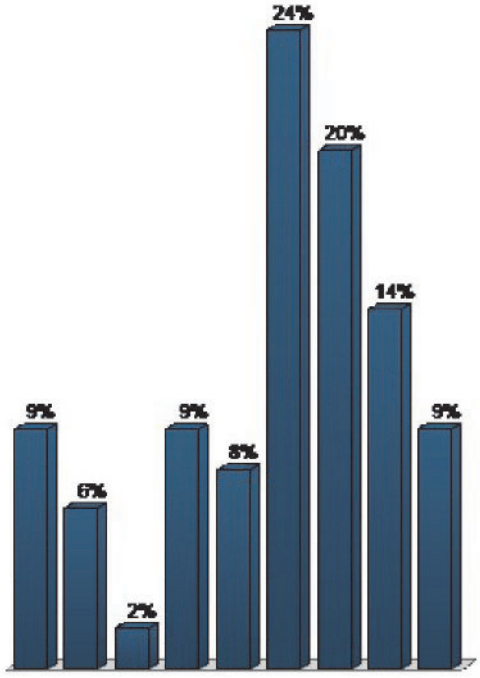
	Responses	
	Percent	**Count**
Northeastern US	32.26%	20
Southeastern US	17.74%	11
Midwestern US	22.58%	14
Southwestern US, incl. Texas	9.68%	6
California	14.52%	9
Northwest US, not including California	1.61%	1
Canada	0%	0
Outside of North America	1.61%	1
Totals	**100%**	**62**



Question Statistics	
Mean	2.69
Median	2.50
Variance	2.60
Standard Deviation	1.61

4. Age you or your affected family member was diagnosed: (Demographic Assignment)

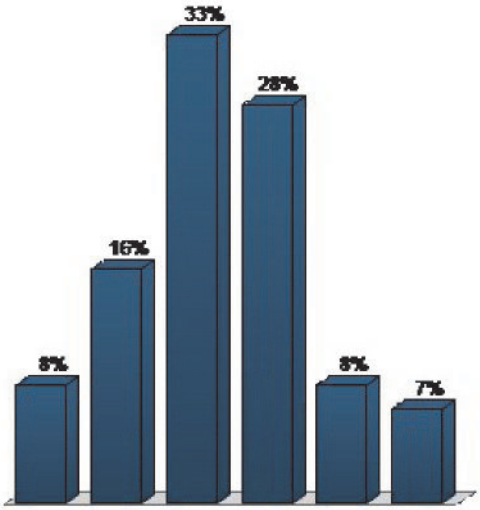
	Responses	
	Percent	**Count**
0-3 years old	9.09%	6
4-8 years old	6.06%	4
9-12 years old	1.52%	1
13-18 years old	9.09%	6
18-25 years old	7.58%	5
26-35 years old	24.24%	16
36-45 years old	19.7%	13
45-55 years old	13.64%	9
Older than 55	9.09%	6
Totals	**100%**	**66**



Question Statistics	
Mean	5.74
Median	6.00
Variance	5.31
Standard Deviation	2.30

5. Number of years you or your affected family member have been living with DM symptoms: (Demographic Assignment)

	Responses	
	Percent	Count
1-5 years	8.2%	5
6-10 years	16.39%	10
11-15 years	32.79%	20
15-25 years	27.87%	17
26-35 years	8.2%	5
More than 35 years living with DM symptoms	6.56%	4
Totals	**100%**	**61**

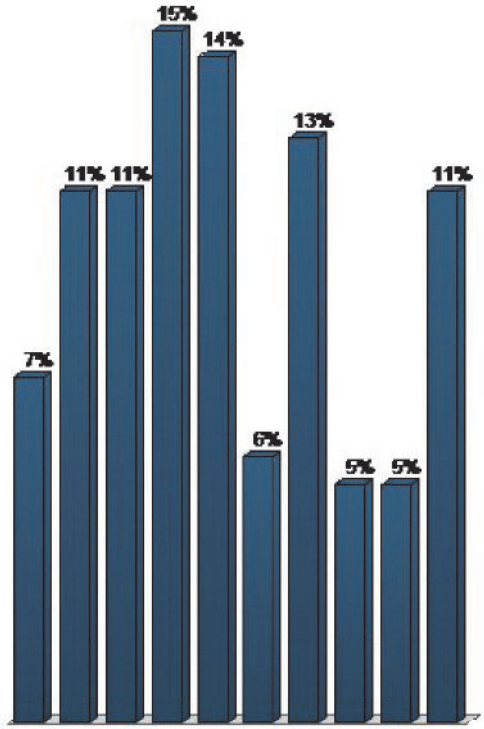


Question Statistics	
Mean	3.31
Median	3.00
Variance	1.59
Standard Deviation	1.26

6. Select the top 3 myotonic dystrophy symptoms that most impact you or your affected family member's daily quality of life: (Multiple Choice - Multiple Response)

	Responses	
	Percent	Count
Trouble using hands or arms	7.47%	13
Problems sleeping or being too sleepy	11.49%	20
Myotonia/muscle stiffness in hands or	11.49%	20

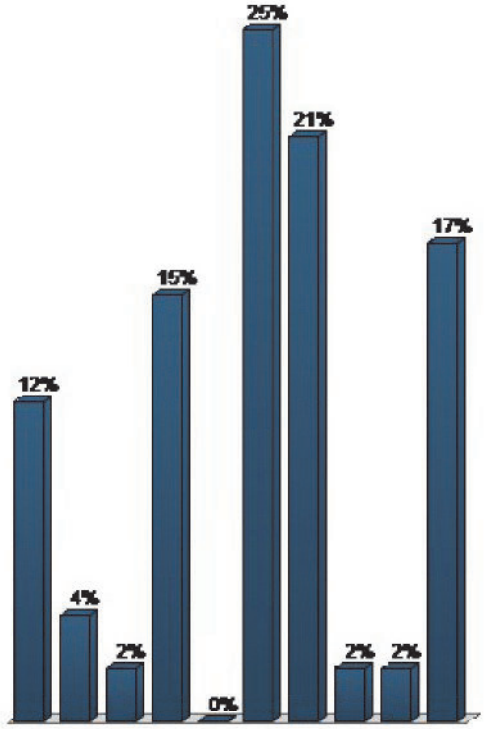
mouth (grip stiffness, swallowing, choking or speech difficulties, etc.)		
Gastrointestinal problems	14.94%	26
Mobility problems: difficulty walking, tripping, falls	14.37%	25
Heart problems	5.75%	10
Problems with mental efficiency or memory	12.64%	22
Emotional or behavioral problems	5.17%	9
Pain	5.17%	9
Fatigue	11.49%	20
Totals	**100%**	**174**



Question Statistics	
Mean	5.22
Median	5.00
Variance	7.52
Standard Deviation	2.74

7. Select the most important thing you or your affected family member used to do that you or your family member now can't do as well: (Multiple Choice)

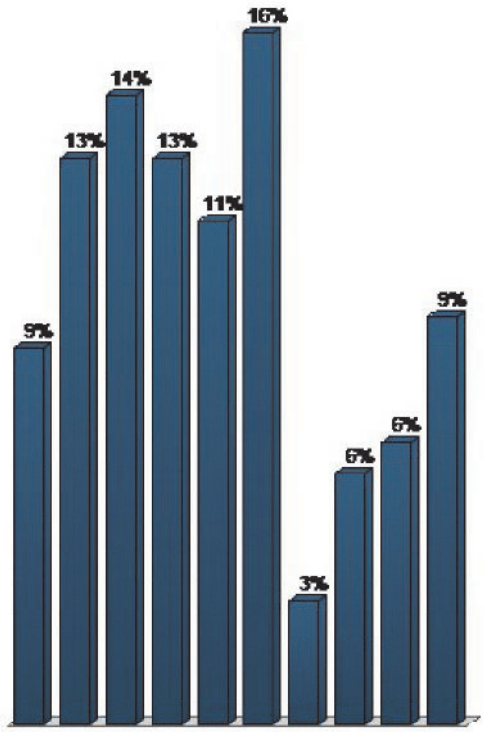
	Responses	
	Percent	Count
Take a shower, bath or dress independently	11.54%	6
Eat solid food	3.85%	2
Go out to eat or visit friends and family	1.92%	1
Perform well at a job or work	15.38%	8
Take care of a family member	0%	0
Be active (exercise, dance, etc.)	25%	13
Go up and down stairs	21.15%	11
Drive	1.92%	1
Get in and out of a chair or bed	1.92%	1
Open doors, drawers, bottles, jars	17.31%	9
Totals	**100%**	**52**



Question Statistics	
Mean	5.90
Median	6.00
Variance	7.51
Standard Deviation	2.74

8. Select up to 3 medicines, equipment or lifestyle changes that you or your affected family member currently use to manage DM symptoms (choose up to 3 - extra time provided): (Multiple Choice - Multiple Response)

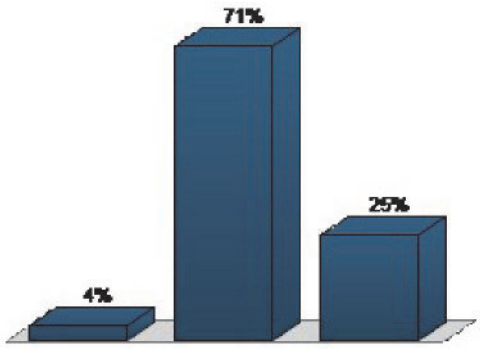
	Responses	
	Percent	Count
Mexiletine for myotonia and muscle stiffness (hands, mouth, etc.)	8.57%	12
Medicine for daytime sleepiness or attention	12.86%	18
Medicine for anxiety or depression	14.29%	20
Medicine for stomach and intestinal symptoms	12.86%	18
C-PAP, BiPAP or VPAP machine at night	11.43%	16
Ankle, leg or other braces	15.71%	22
Pureeing, softening or thickening food	2.86%	4
Changes in diet (e.g. gluten free, high fiber, dairy free, etc.)	5.71%	8
Cane, walking stick	6.43%	9
Tools to open jars, doors, etc.	9.29%	13
Totals	**100%**	**140**



Question Statistics	
Mean	4.96
Median	5.00
Variance	7.36
Standard Deviation	2.71

9. In general, how much do these medicines, equipment or lifestyle changes improve your or your affected family member's quality of life: (Multiple Choice)

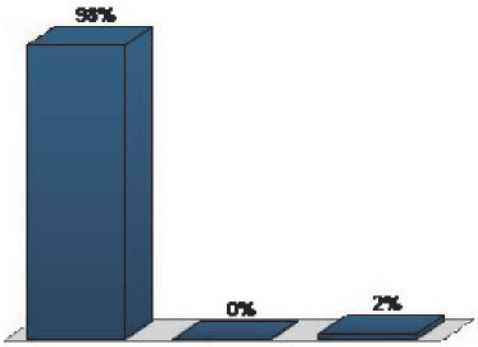
	Responses	
	Percent	Count
In general they have really helped manage the worst symptoms and improving my or my family member's quality of life	3.64%	2
In general they have helped somewhat in managing the worst symptoms and improving my or my family member's quality of life	70.91%	39
In general they have not helped much at all in managing the worst symptoms and improving my or my family member's quality of life	25.45%	14
Totals	**100%**	**55**



Question Statistics	
Mean	2.22
Median	2.00
Variance	0.24
Standard Deviation	0.49

10. How important is it to you or your affected family member to have a therapy that slows disease progression (choose one): (Multiple Choice)

	Responses	
	Percent	Count
Very important	98.28%	57
Important	0%	0
Not Important	1.72%	1
Totals	**100%**	**58**

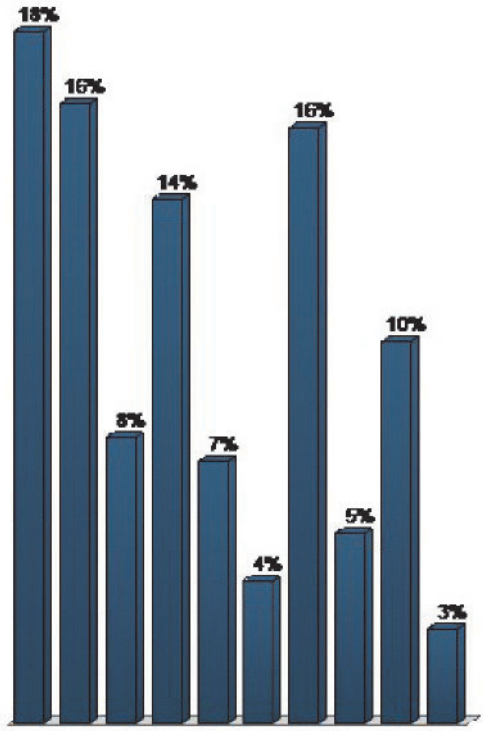


Question Statistics	
Mean	1.03
Median	1.00
Variance	0.07
Standard Deviation	0.26

11. What would be the 3 most important impacts from a new DM treatment for you or your affected family member (choose top 3 - extra time provided): (Multiple Choice - Multiple Response)

	Responses	
	Percent	Count
Reduce fatigue	18.24%	29
Improve walking and stamina	16.35%	26
Reduce myotonia/muscle stiffness of hands and	7.55%	12

mouth		
Make the GI and stomach symptoms better	13.84%	22
Make the anxiety and/or depression better	6.92%	11
Improve the behavioral issues	3.77%	6
Improve your thinking	15.72%	25
Lessen your pain	5.03%	8
Improve your sleep or sleepiness issues	10.06%	16
Other	2.52%	4
Totals	**100%**	**159**



Question Statistics	
Mean	4.52
Median	4.00
Variance	7.96
Standard Deviation	2.82

APPENDIX 6: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Myotonic Dystrophy

Introduction

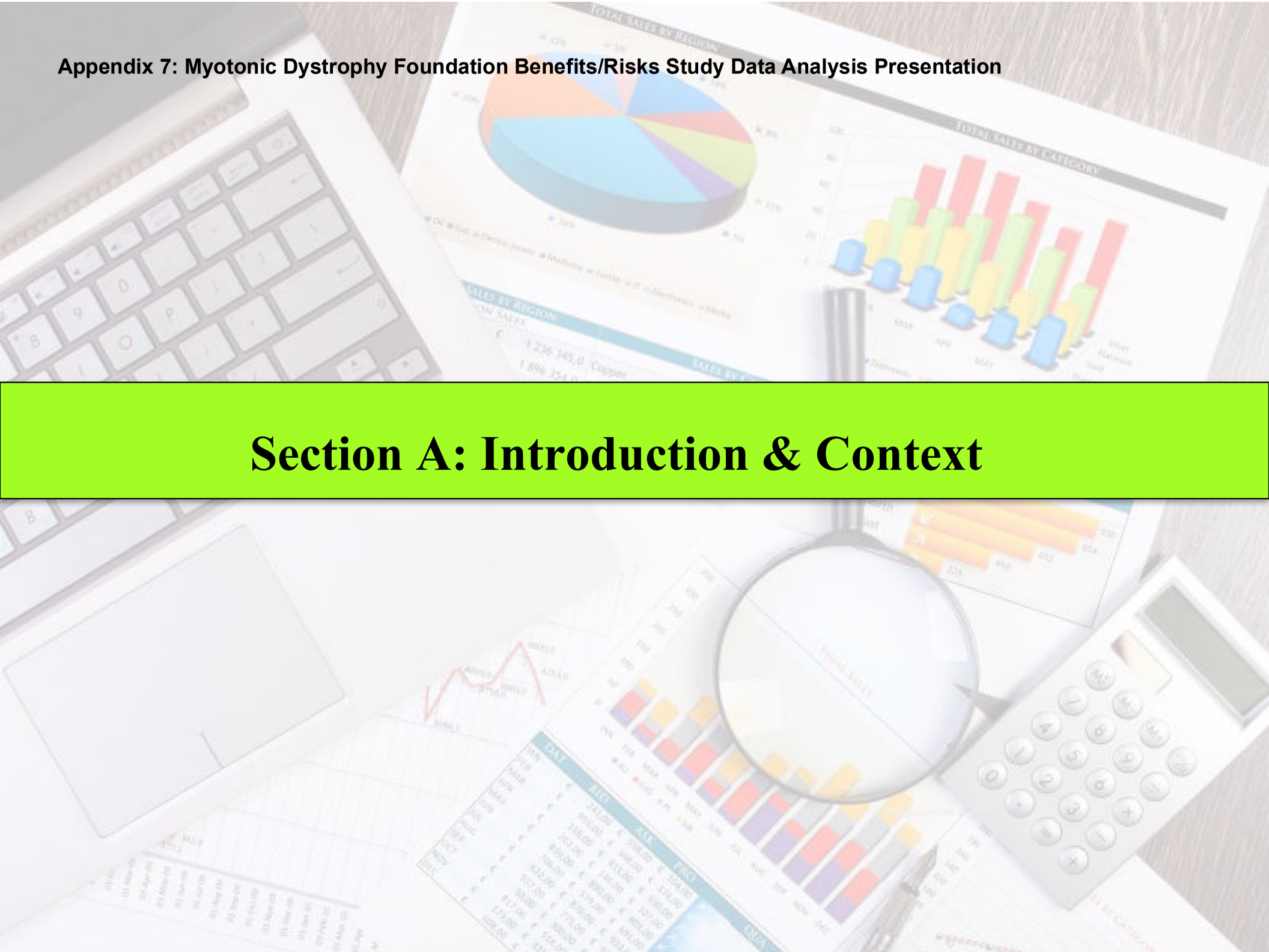
In 2013, the FDA published a draft implementation plan for a structured approach to benefit-risk assessment in drug regulatory decision making [1]. This framework calls for assessing five decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a specific product, it summarizes each decision factor and explains the FDA's rationale for its regulatory decision.

The input provided by patients and caregivers at the Myotonic Dystrophy Patient-Focused Drug Development meeting and docket, as well as other related surveys of patient experience, including the MDF Benefit/Risk Study conducted in 2015 (attached as Addendum 7) is compiled in the Voice of the Patient report and summarized here in this sample framework to provide an understanding of the benefit/risk aspects for two of these decision factors: Analysis of Condition, and Current Treatment Options. This sample framework is likely to evolve over time, and should be incorporated into a benefit-risk assessment framework for a drug under review.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Myotonic Dystrophy type 1 (DM1) is a highly heterogeneous, multi-systemic, progressive genetic disorder. It is the most common adult-onset form of muscular dystrophy, and may also occur as a childhood-onset or congenital disease. Severity ranges from mild to extremely severe and life-threatening. Muscle weakness, wasting, and myotonia (muscle stiffness) are among the most *common* symptoms, and may affect the upper and lower limbs as well as head, neck, and face muscles, leading to problems with mobility, daily activities, self-care, swallowing, eating, and breathing. Many patients also experience cognitive dysfunction. Fatigue and daytime sleepiness are common. Muscles of other organs including the heart and gastrointestinal tract may also be	DM1 is a progressive, multi-system, heterogeneous genetic disease that may cause serious disability and loss of function. It can substantially affect a patient's quality of life and place a large burden on the family.

[1] Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making. Draft PDUFA V Implementation Plan – February 2013. Fiscal years 2013-2017. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

	affected. Respiratory failure is the most common cause of death, followed by heart failure. Among the symptoms typically considered to be most *burdensome* are excessive daytime sleepiness, fatigue, GI and cognitive dysfunction. *See the Voice of the Patient report for a more detailed narrative*	
Current Treatment Options	-There is no cure for DM1 and no treatment that slows the progression of the disease. -Current treatment options may relieve some symptoms of the disease or enable patients to cope with the debilitating symptoms. -Current treatment options are only of limited effectiveness in helping patients manage their symptoms. *See the Voice of the Patient report for a more detailed narrative*	Drug treatments are available for some of the cardiac, gastrointestinal, and psychological manifestations of DM1 but are of limited effectiveness and do not address the underlying cause of the disease. There is substantial unmet medial need for therapies for DM1, and clinically meaningful benefit for DM1 patients, as defined by patients and caregivers, includes slowing of disease progression for the most burdensome symptoms and/or symptoms stabilization.



Section A: Introduction & Context

CONTENTS

Strategic Goals

The Myotonic Dystrophy Foundation commissioned Silicon Valley Research Group to design and conduct a quantitative survey of DM1 patients to uncover tradeoffs they make when considering the benefits anc risks associated with treating their symptoms.

The results will inform the Foundation on priorities for supporting the community and will also be presented to the FDA to guide support for treatment of the disease.

MYOTONIC DYSTROPHY FOUNDATION

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Selection of Methodology:

- Best/Worst Scaling, also known as Maximum Differential Scaling (Max-Diff), a subset of conjoint and discrete choice modeling, was selected as the survey methodology to quantitatively measure the risk/benefit tradeoffs

- The main reason for the selection of this methodology is that it provides higher discrimination and importance scaling between the tested attributes than with simple ratings and ranking questions and corrects for biases in individual variations in interpreting rating scales

- Research has shown that Best/Worst Scaling scores demonstrate greater discrimination among items and between respondents on the items than survey questions using standard scales. Since respondents make choices rather than expressing strength of preference using some numeric scale, there is no opportunity for scale use bias

- Lastly, several similar studies trading treatment benefits and risks have used this methodology. The FDA is familiar with this research design and in addition, several "research on research" studies have confirmed both the benefits and validity of the data obtained using this methodology design for medical patient studies

Survey Design & Process

- An online survey was created and respondents from the MDF Registry and General Database were invited via email to a link to the survey

- Respondents were also provided with telephone assistance for the survey (approx. 9% of the total sample requested and received additional support)

- A total of 267 respondents took the survey yielding a total sample accuracy of +/- 5.9% at the 95 % confidence level

- Survey was conducted between August 9th and August 23rd 2015

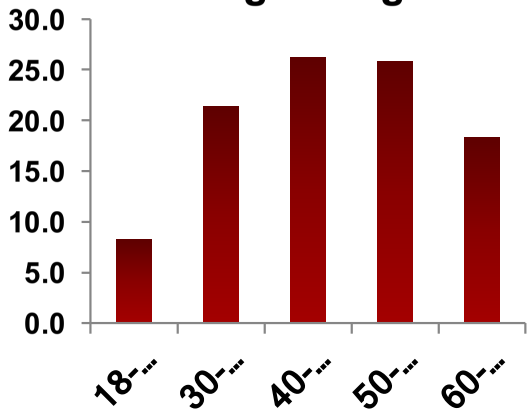
- Respondents took an average of 23 minutes to complete the survey with the range being between 15 and 35 minutes.

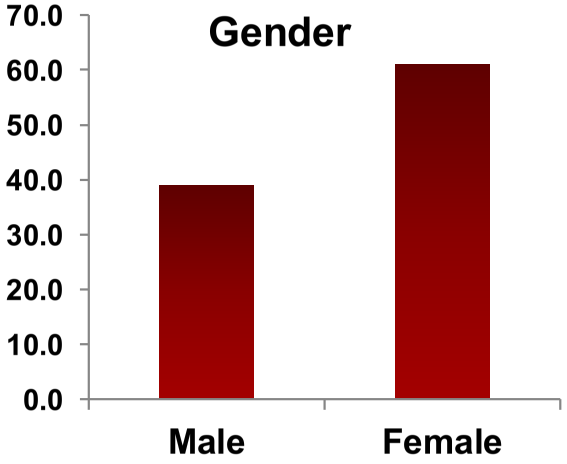
Screening Criteria

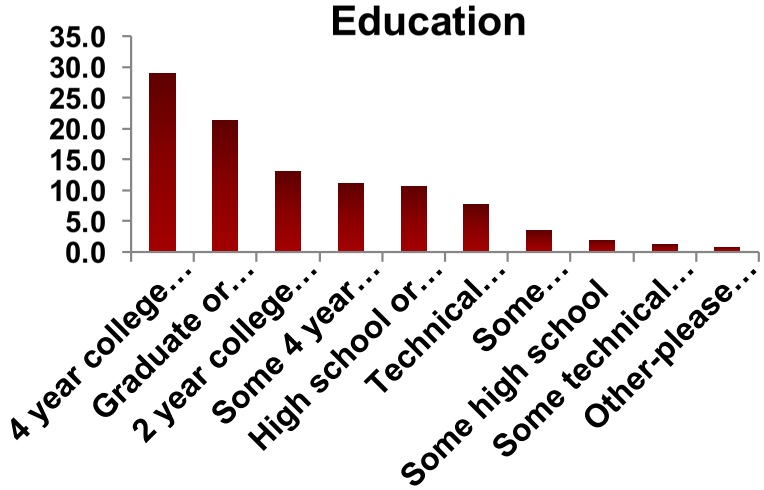
- Respondents were recruited into the study using the following screening criteria

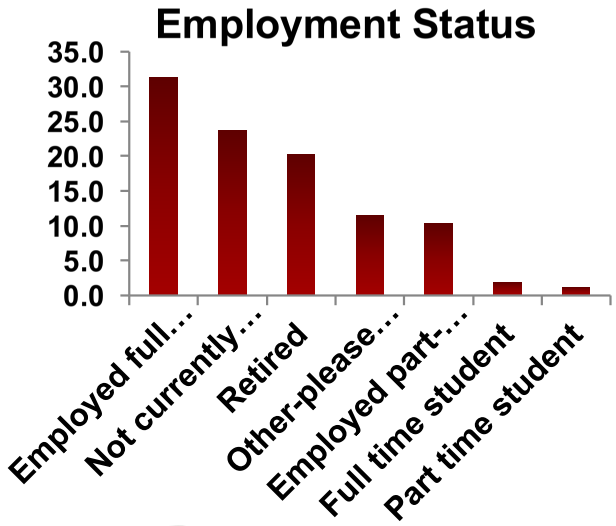
Screening Criteria/Cross Checks
Have been diagnosed with DM1
First experienced the symptoms associated with diagnosis at age 15 or older
Is between the ages of 18 and 70
Is the actual patient diagnosed with disease and not a caregiver or relative
Respondents with relatives who also suffered from the disease were asked to answer all questions from their personal perspective and not that of others
The results were checked for any significant effects the following factors may have had on the risk/benefit tradeoffs:
▪Presence of others in the household who also had the disease
▪Severity of symptoms using a validated scale developed by the University of Rochester and Dr. Chad Heatwole
▪Respondents' personal risk taking profile
▪Respondent's numeracy skills

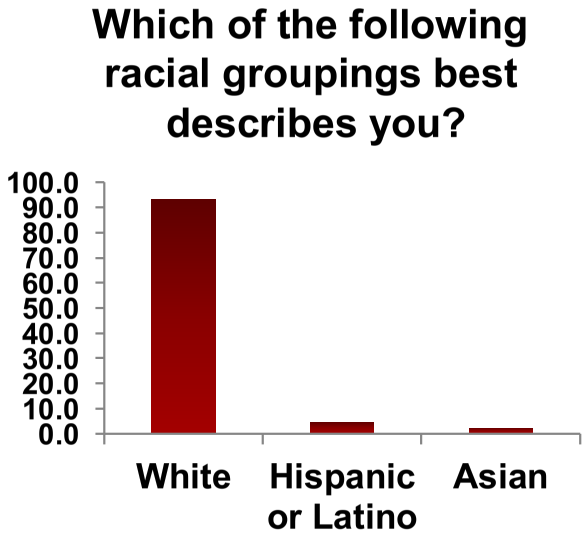
Demographic Snapshot of Survey Respondents (Details in Appendix)

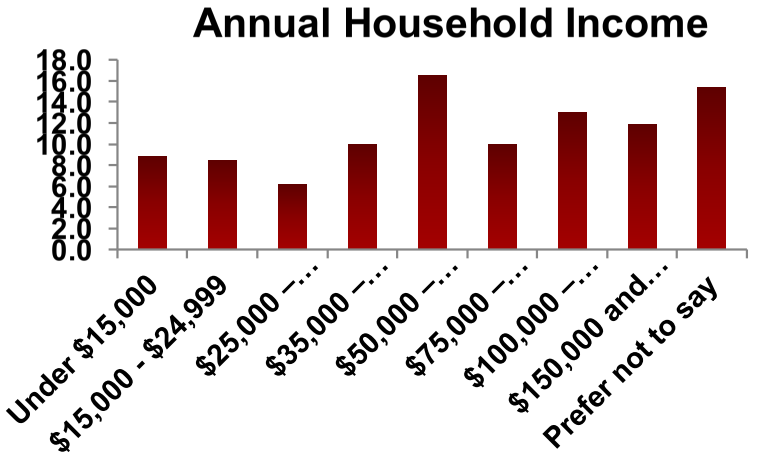












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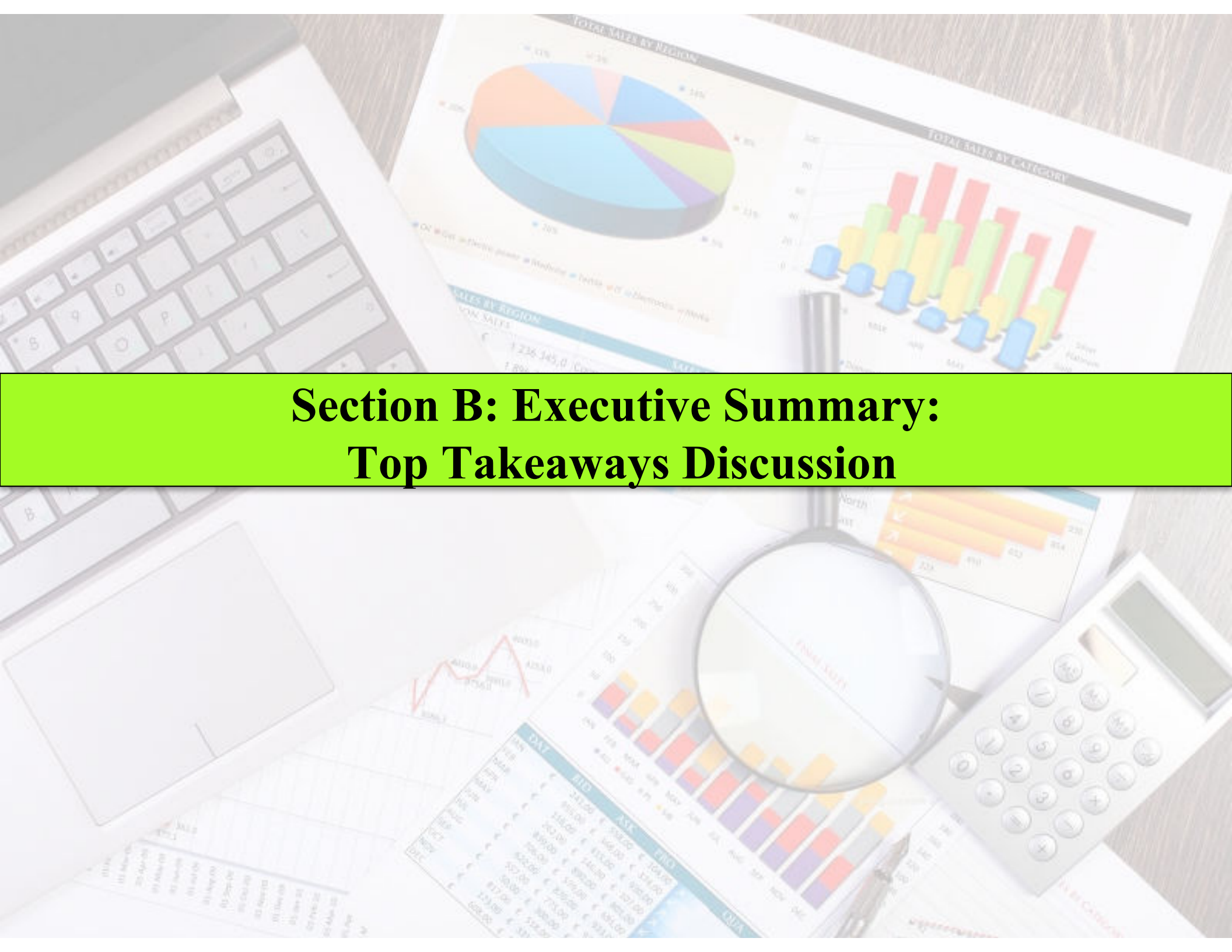
Reporting Notes

- The numerical data in this report is expressed as Bayesian averages which not only provide the rank prioritization of attributes but also contain within the number, several additional components:
  - Quantified scale indicating not just rank but magnitude of differences between attributes
  - Corrections in averages for number of times the item was voted best or last
  - Corrections for outliers
  - Takes into account each survey respondent's individual preference model as well as the preferences of the entire sample to come up with the average score

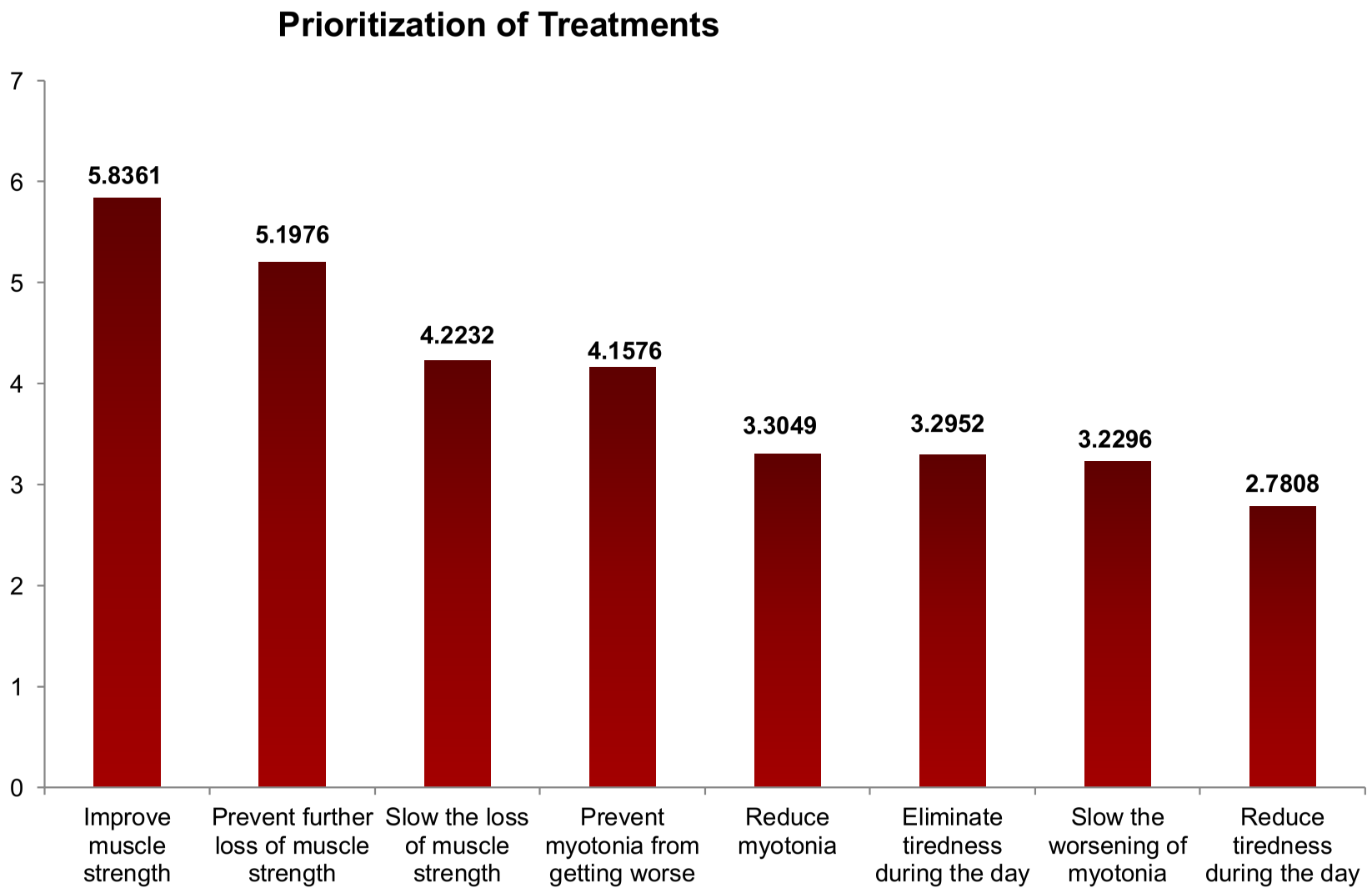
- Slides that contain major distinctions or implications are marked with a



Section B: Executive Summary: Top Takeaways Discussion

Prioritization of Benefits Sought

Overall Rank Ordering of Treatments or Benefits



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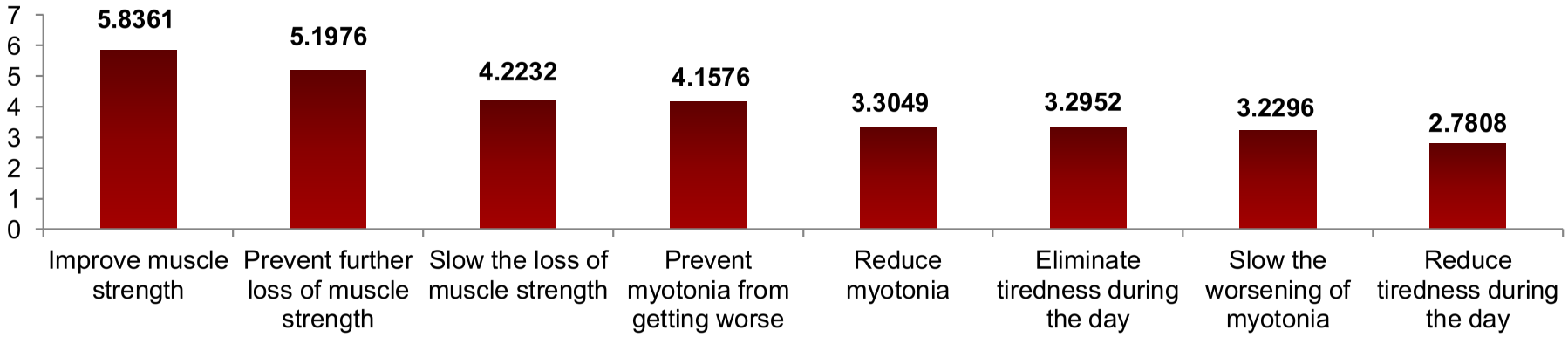
Interpretation of Benefit Rankings



- DM1 sufferers in our study prioritize dealing with muscle strength issues to any degree over all other benefits
- Preventing myotonia or reducing it are the next valued benefits
- Eliminating daytime tiredness however trumps slowing the worsening of myotonia

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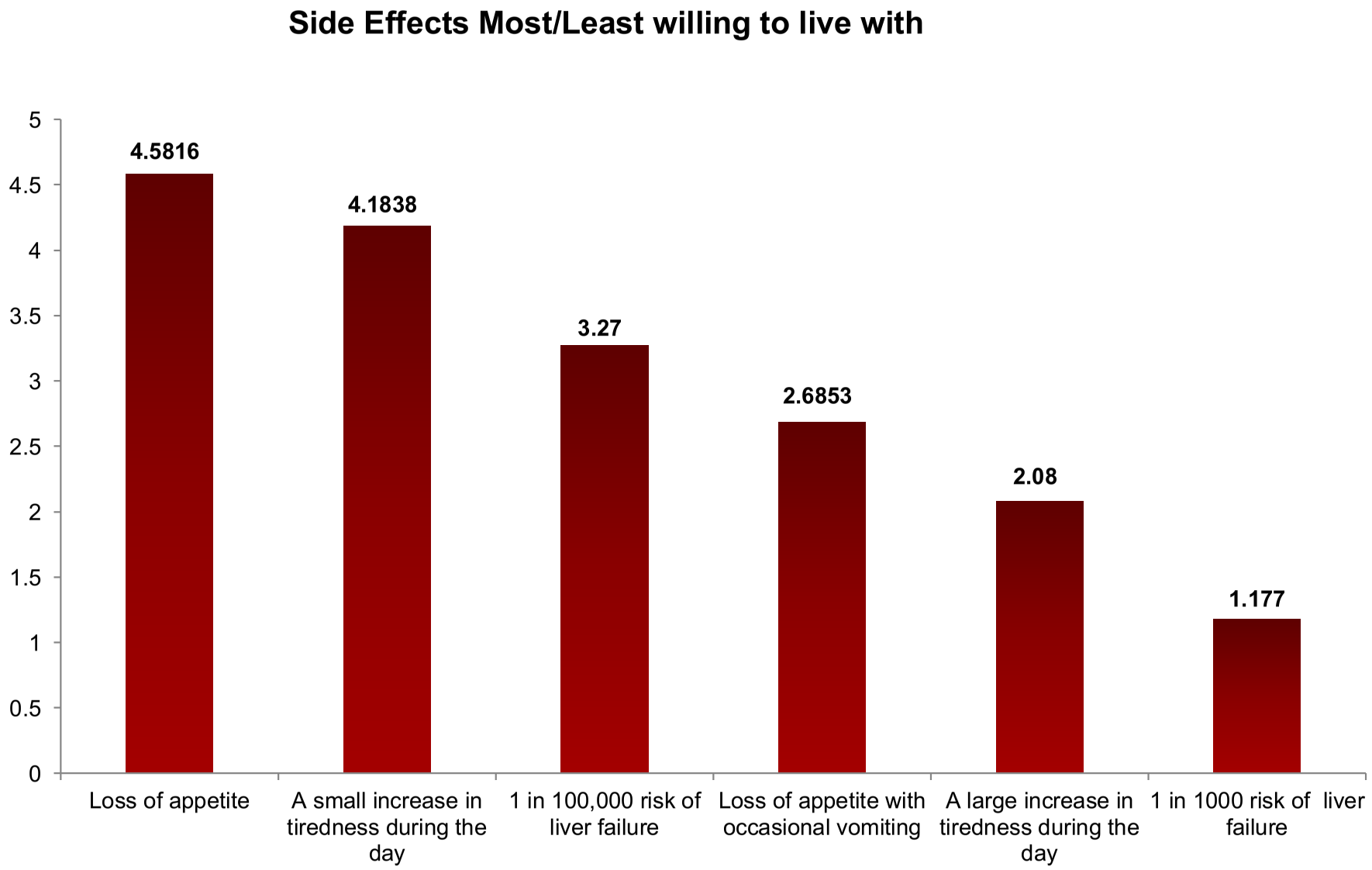
Risk Tolerance Profile

Overall Rank Ordering of Side Effects/Risks



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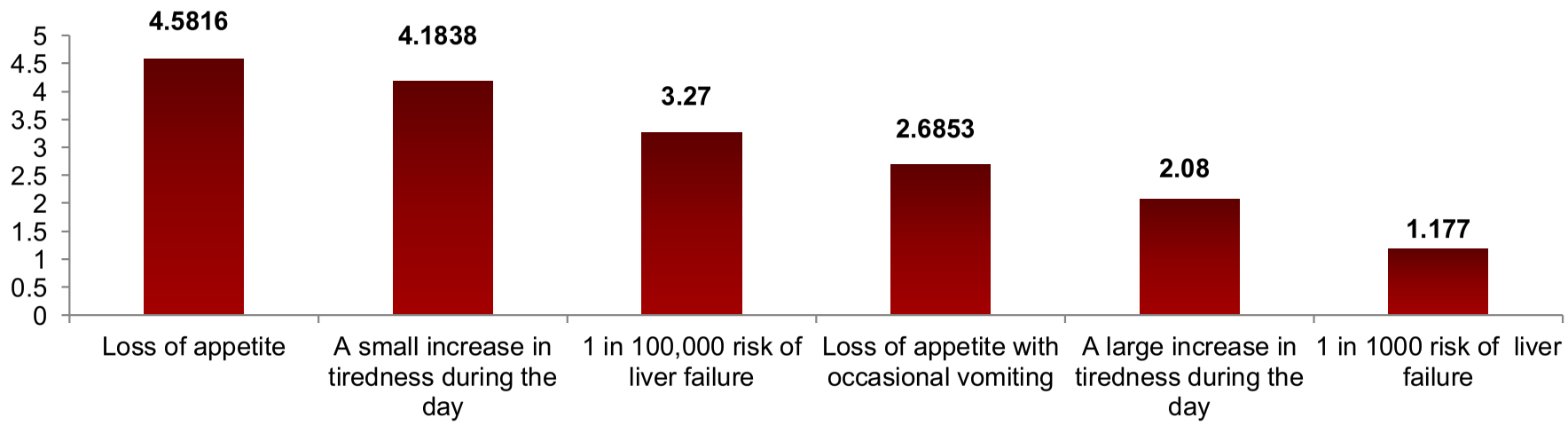
Overall Rank Ordering of Side Effects/Risks



1. Loss of appetite and a small increase in daytime tiredness are the most tolerated risks
2. DM1 sufferers in our study view 1 in 100,000 liver failure risk as the next most tolerable side effect
3. The least tolerable risk of all is a 1 in 1000 liver failure risk although when controlled for factors such as the respondent's overall risk profile, this was somewhat more tolerable (next slide)

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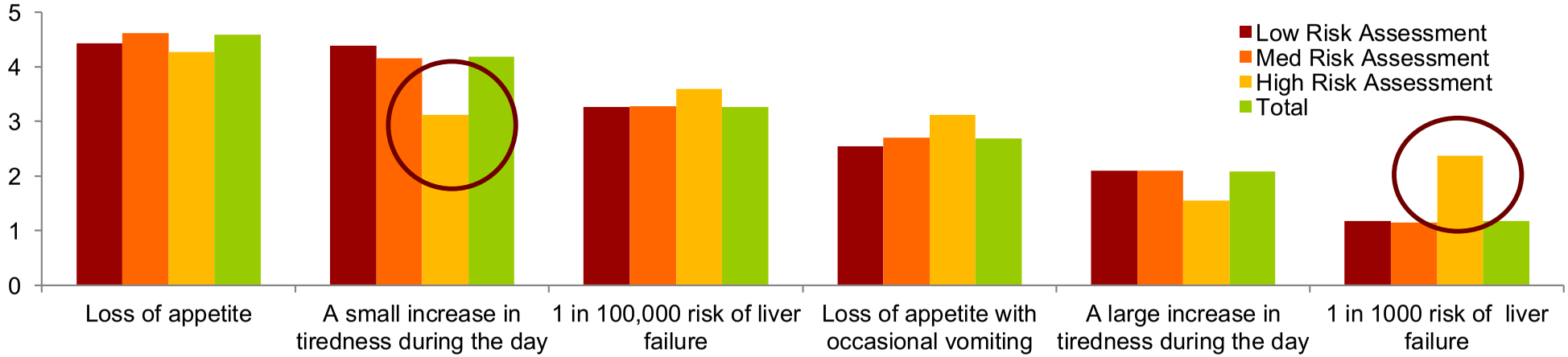
Impact of risk taking propensity on risk tolerance rankings



Low Risk Assessment	**4.4326**	**4.3818**	**3.2632**	**2.5455**	**2.1018**	**1.1747**
Med Risk Assessment	**4.613**	**4.1639**	**3.2723**	**2.6973**	**2.1032**	**1.1476**
High Risk Assessment	**4.2692**	**3.1154**	**3.6**	**3.125**	**1.5556**	**2.375**
Total	**4.5816**	**4.1838**	**3.27**	**2.6853**	**2.08**	**1.177**

- DM1 sufferers who were more risk tolerant(self-rated) were much more tolerant than average of risk of liver failure
- Risk tolerant DM1 sufferers were conversely less likely to tolerate daytime tiredness, perhaps indicating a lower willingness to have their lifestyles curtailed

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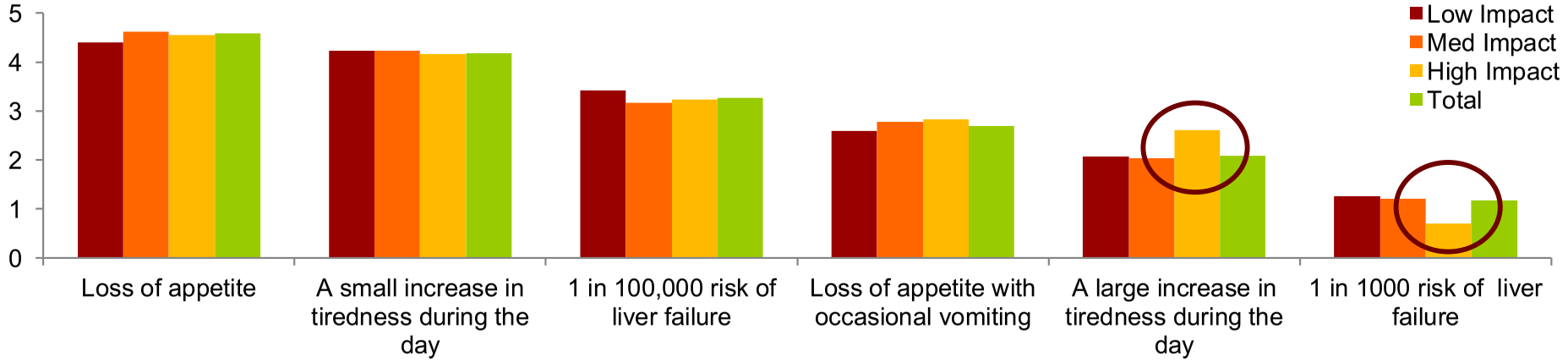
Impact of severity of symptoms on risk tolerance
(Based on University of Rochester's MDH1 short form severity scale)



Low Impact	**4.3994**	**4.2332**	**3.4223**	**2.5877**	**2.0641**	**1.2537**
Med Impact	**4.6084**	**4.2358**	**3.1677**	**2.7771**	**2.0308**	**1.2108**
High Impact	**4.5469**	**4.1642**	**3.2308**	**2.8209**	**2.6066**	**0.7059**
Total	**4.5816**	**4.1838**	**3.27**	**2.6853**	**2.08**	**1.177**

- DM1 sufferers in our study who had a high severity of symptoms (self-rated) were less tolerant of 1 in 1000 liver failure risk
- Those impacted with high severity of symptoms were also more willing to tolerate a large increase in tiredness through the day

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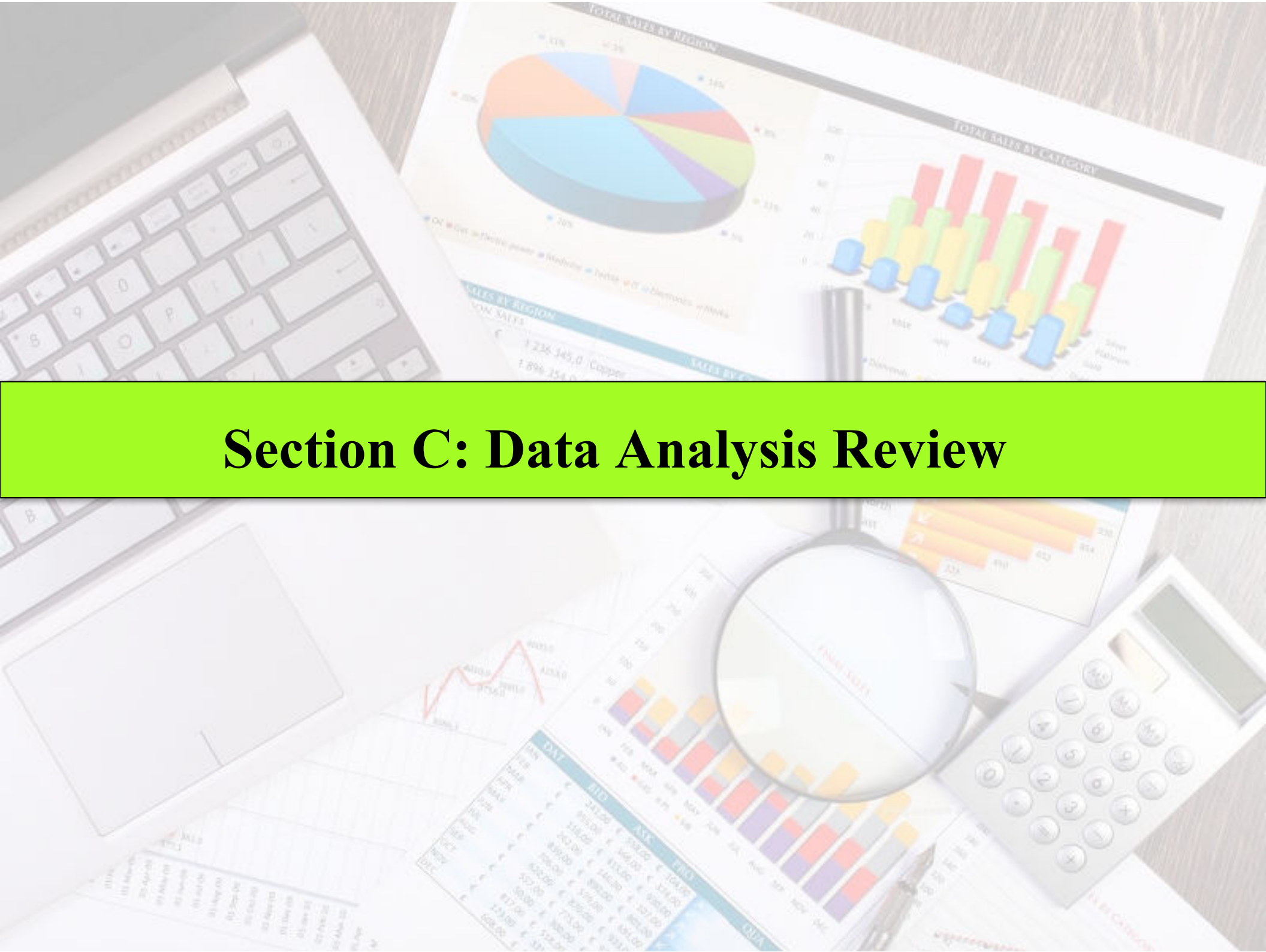

Section C: Data Analysis Review

Best/Worst Scaling Results for Total Sample

Experiment Design Setup

- Each benefit was set up as a separate treatment against which a list of potential side effects was tested

- The result was 8 separate treatments tested against 6 side effects

- Each treatment was then reiterated several times per the Max-Diff formula:
  - 3K/k where K=total number of risks and k=number of risks displayed at a time

- To avoid "order bias", the order in which items were presented to each survey respondent was randomized

Treatment/Risks Table

Treatments (Benefits)	Risks
Improves Muscle Strength	Loss of appetite is experienced by most people
Prevents Further Loss of Muscle Strength	Causes a small increase in tiredness during the day in most people
Slows the Loss of Muscle Strength	1 in 100,000 risk of liver failure
Eliminates Tiredness During the Day	Loss of appetite with occasional vomiting is experienced by most people
Reduces Tiredness During the Day	Causes a large increase in tiredness during the day in most people
Reduces Myotonia	1 in 1,000 risk of liver failure
Prevents Myotonia from Getting Worse	
Slows the Worsening of Myotonia	

Example of Best-Worst Question

TREATMENT 1 - IMPROVES MUSCLE STRENGTH

"Muscle Strength" describes the ability of your muscles to move against resistance in performing day to day activities. For example, muscle strength affects your ability to walk, rise from a seated position, go up or down stairs and lift or hold objects.

Every treatment or therapy will have potential side effects or risks. Click the **best** and **worst** side effect or risk.
By "**Best**" side effect or risk we mean the side effect or risk *you* are **most willing** to live with.
By "**Worst**" side effect or risk we mean the side effect or risk *you* are **least willing** to live with.
(Please choose one "**Best Risk**" ***and*** one "**Worst Risk**" in order to proceed) *

Best Risk	Side Effect of Treatment	Worst Risk
○	1 in 1,000 risk of liver failure	○
○	Loss of appetite is experienced by most people	○
○	Causes a small increase in tiredness during the day in most people	○
○	Loss of appetite with occasional vomiting is experienced by most people	○
○	Causes a large increase in tiredness during the day in most people	○

1 of 4 sets

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Treatment 1-Improves Muscle Strength

TREATMENT 1 – IMPROVES MUSCLE STRENGTH

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**4.3587**
2	Causes a small increase in tiredness during the day in most people	**4.349**
3	1 in 100,000 risk of liver failure	**3.0815**
4	Loss of appetite with occasional vomiting is experienced by most people	**2.6156**
5	Causes a large increase in tiredness during the day in most people	**2.2483**
6	1 in 1,000 risk of liver failure	**1.3385**

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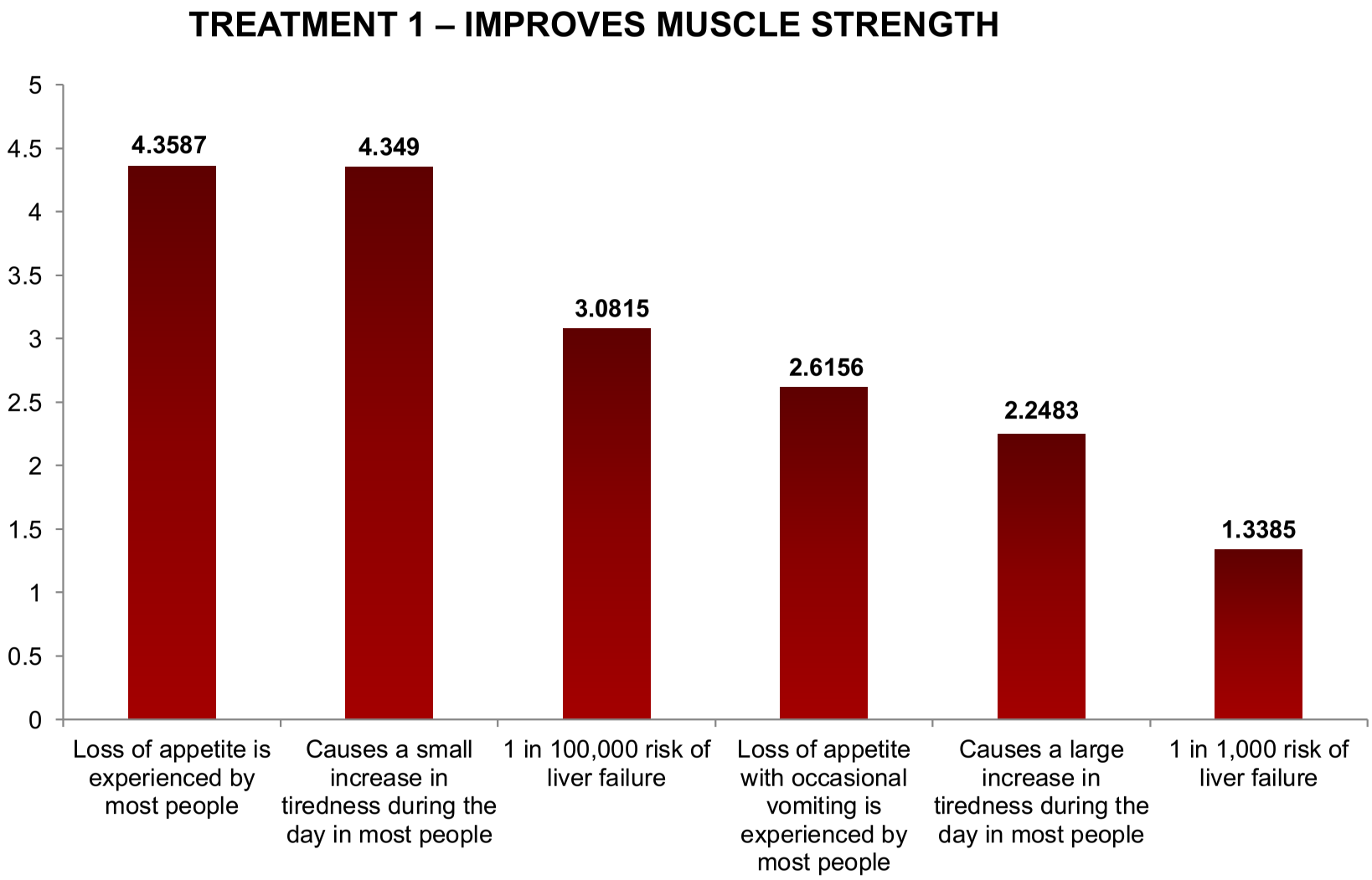
Treatment 1-Improves Muscle Strength



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Treatment 2: Prevents Further Loss of Muscle Strength

TREATMENT 2 - PREVENTS FURTHER LOSS OF MUSCLE STRENGTH

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**4.4464**
2	Causes a small increase in tiredness during the day in most people	**4.3854**
3	1 in 100,000 risk of liver failure	**3.1291**
4	Loss of appetite with occasional vomiting is experienced by most people	**2.5605**
5	Causes a large increase in tiredness during the day in most people	**2.2659**
6	1 in 1000 risk of liver failure	**1.2027**

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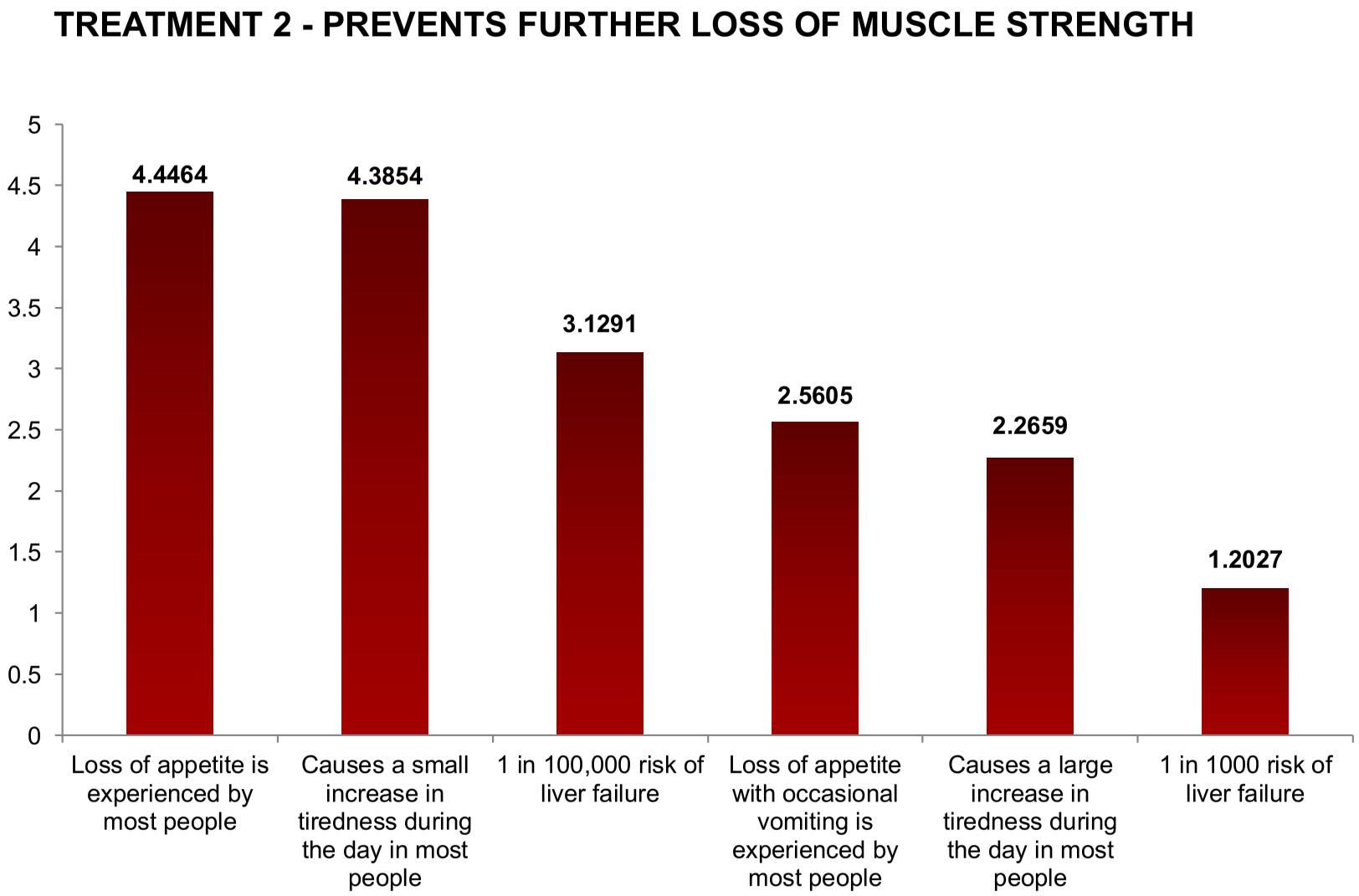
Treatment 2: Prevents Further Loss of Muscle Strength



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Treatment 3: Slows the Loss of Muscle Strength

TREATMENT 3 – SLOWS THE LOSS OF MUSCLE STRENGTH

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**4.4933**
2	Causes a small increase in tiredness during the day in most people	**4.3527**
3	1 in 100,000 risk of liver failure	**3.1816**
4	Loss of appetite with occasional vomiting is experienced by most people	**2.6061**
5	Causes a large increase in tiredness during the day in most people	**2.2373**
6	1 in 1000 risk of liver failure	**1.1707**

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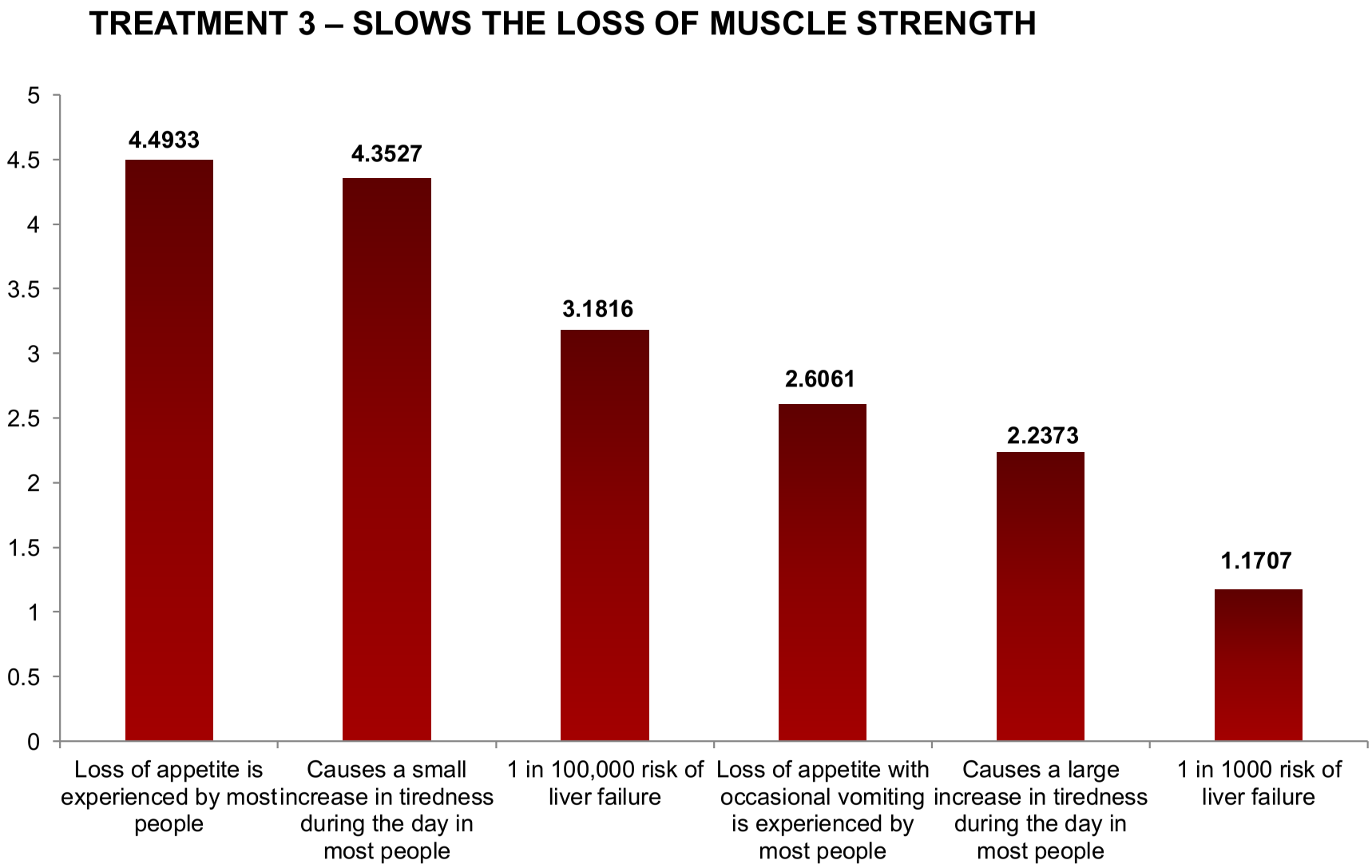
Treatment 3: Slows the Loss of Muscle Strength



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Treatment 4: Eliminates Tiredness During the Day

TREATMENT 4 – ELIMINATES TIREDNESS DURING THE DAY

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**3.5768**
2	1 in 100,000 risk of liver failure	**2.2686**
3	Loss of appetite with occasional vomiting is experienced by most people	**1.7687**
4	1 in 1000 risk of liver failure	**0.4428**

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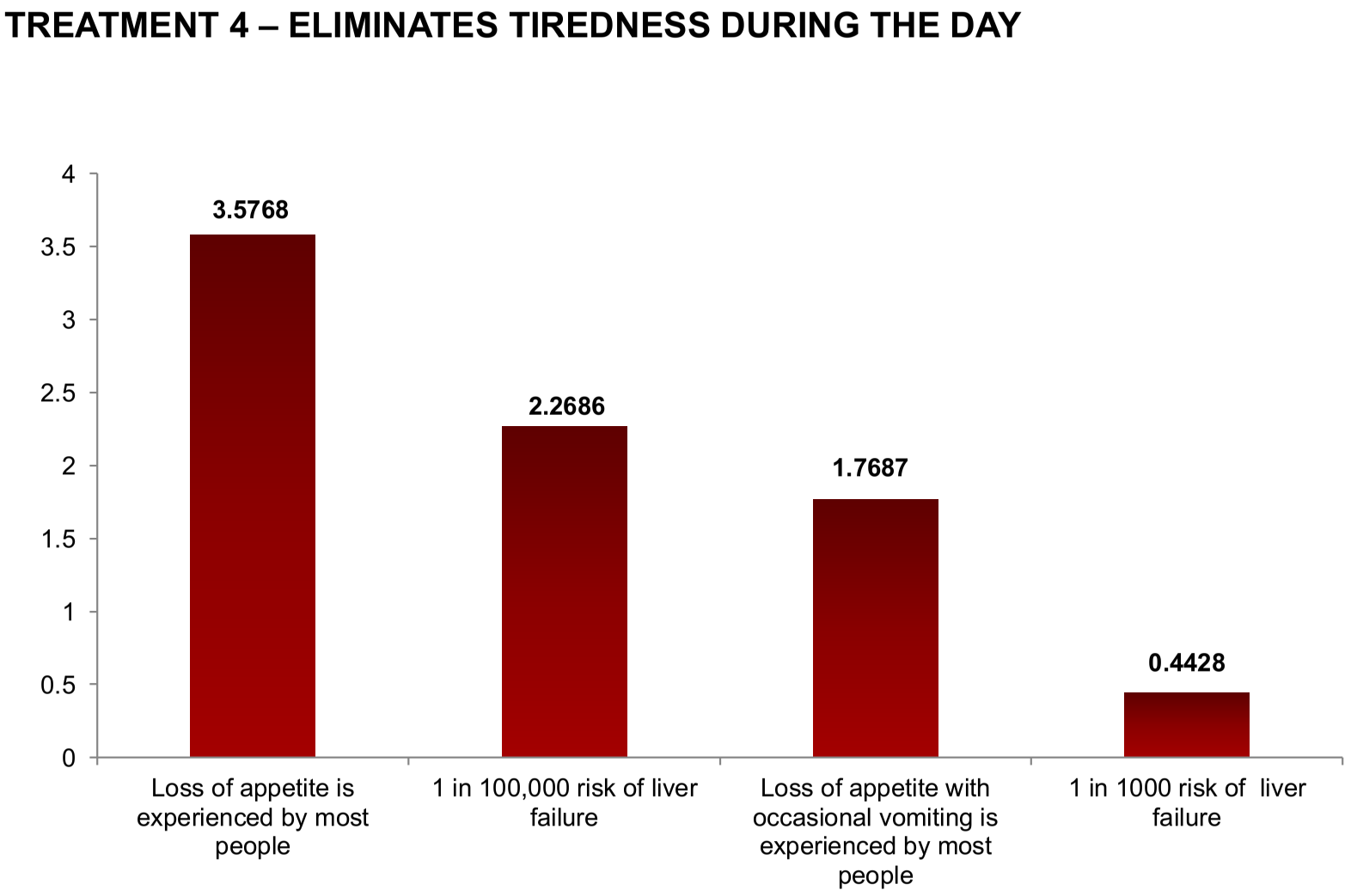
Treatment 4: Eliminates Tiredness During the Day



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Treatment 5: Reduces Tiredness During the Day

TREATMENT 5 – REDUCES TIREDNESS DURING THE DAY

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**3.5796**
2	1 in 100,000 risk of liver failure	**2.2335**
3	Loss of appetite with occasional vomiting is experienced by most people	**1.7621**
4	1 in 1000 risk of liver failure	**0.4747**

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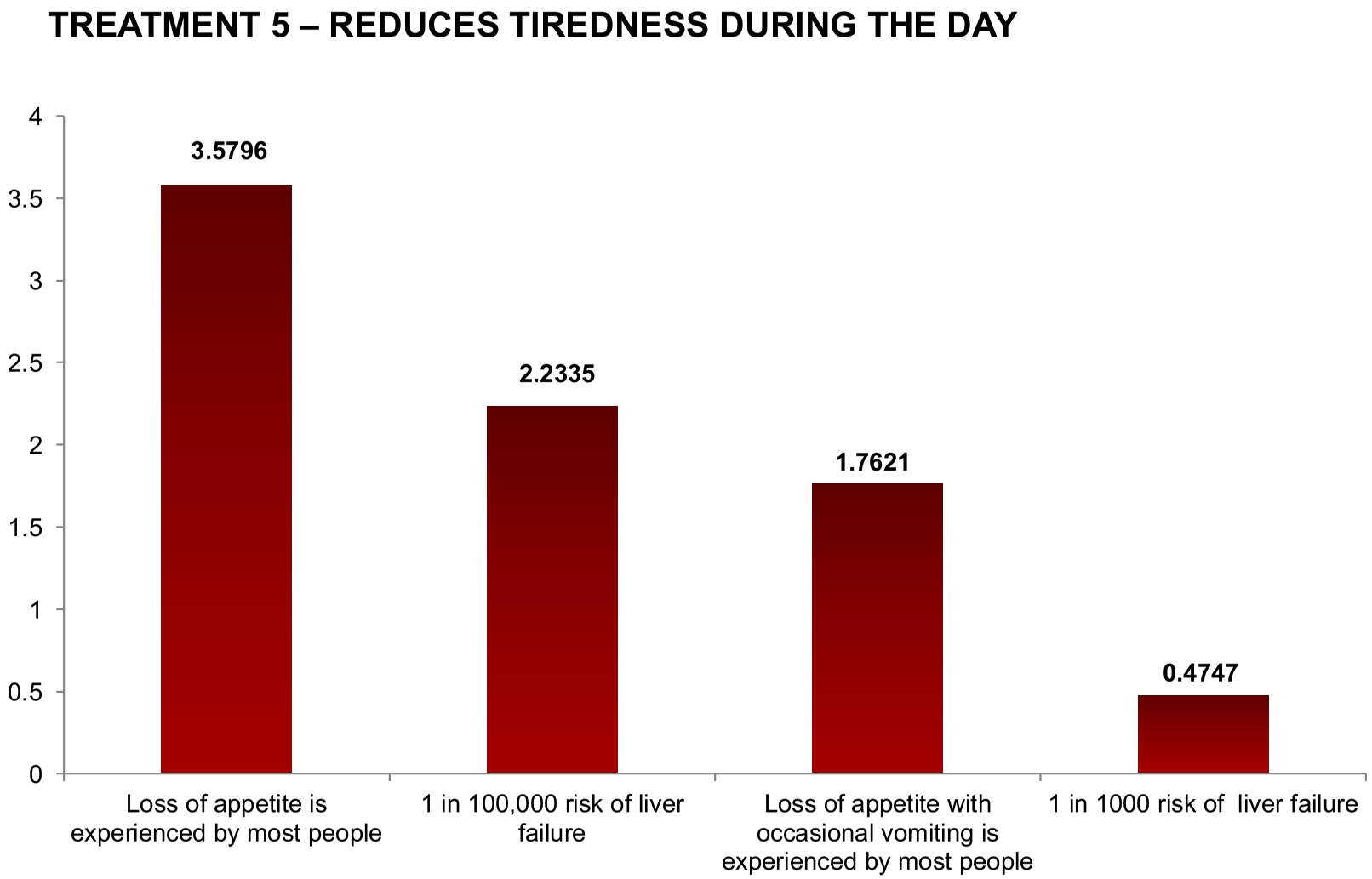
Treatment 5: Reduces Tiredness During the Day



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Treatment 6: Reduces Myotonia

TREATMENT 6 – REDUCES MYOTONIA

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**4.5998**
2	Causes a small increase in tiredness during the day in most people	**4.2649**
3	1 in 100,000 risk of liver failure	**3.202**
4	Loss of appetite with occasional vomiting is experienced by most people	**2.5915**
5	Causes a large increase in tiredness during the day in most people	**2.2534**
6	1 in 1000 risk of liver failure	**1.1262**

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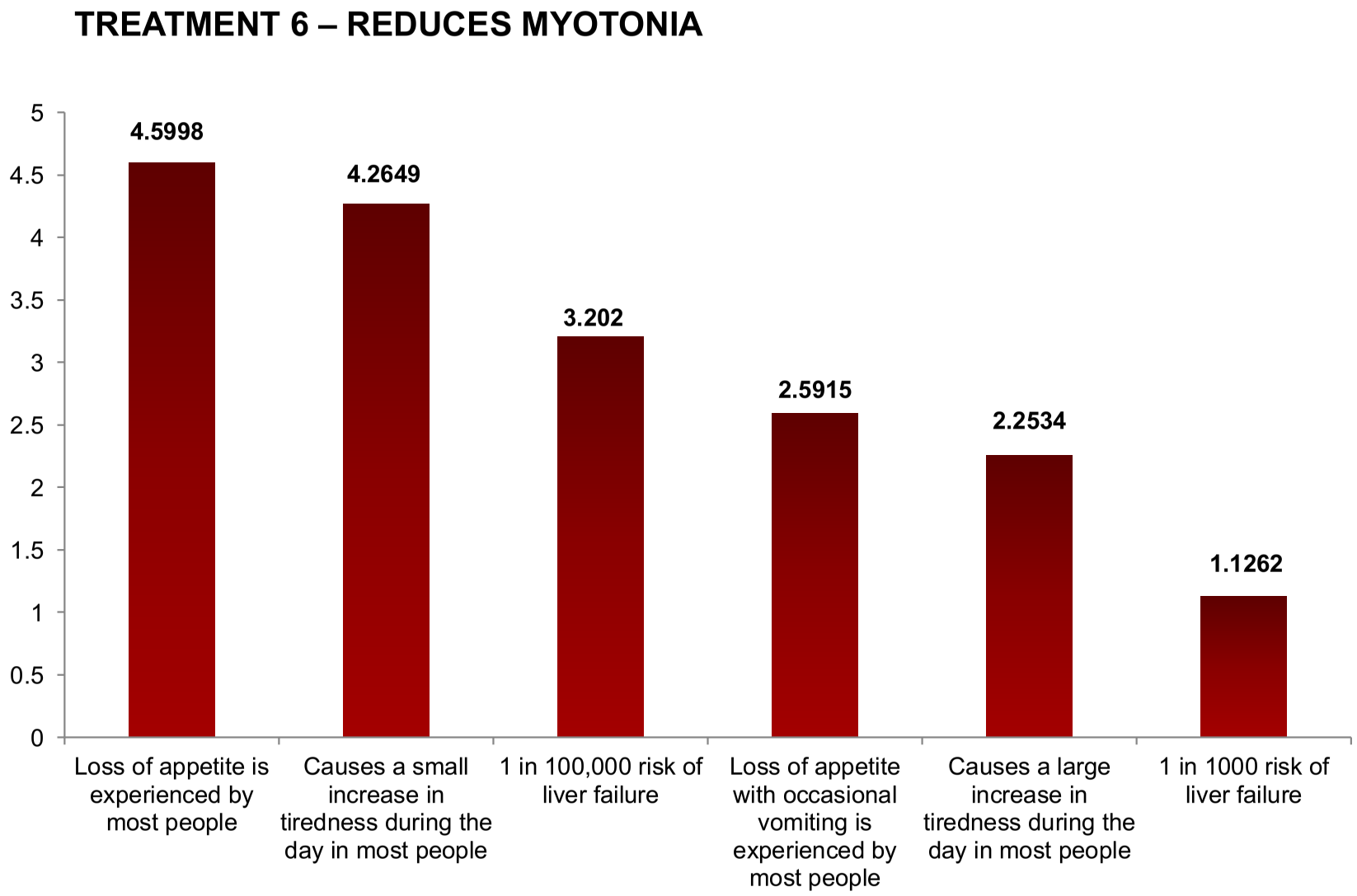
Treatment 6: Reduces Myotonia



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Treatment 7: Prevents Myotonia from Getting Worse

TREATMENT 7 – PREVENTS MYOTONIA FROM GETTING WORSE

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**4.6283**
2	Causes a small increase in tiredness during the day in most people	**4.2114**
3	1 in 100,000 risk of liver failure	**3.2002**
4	Loss of appetite with occasional vomiting is experienced by most people	**2.633**
5	Causes a large increase in tiredness during the day in most people	**2.2081**
6	1 in 1000 risk of liver failure	**1.133**

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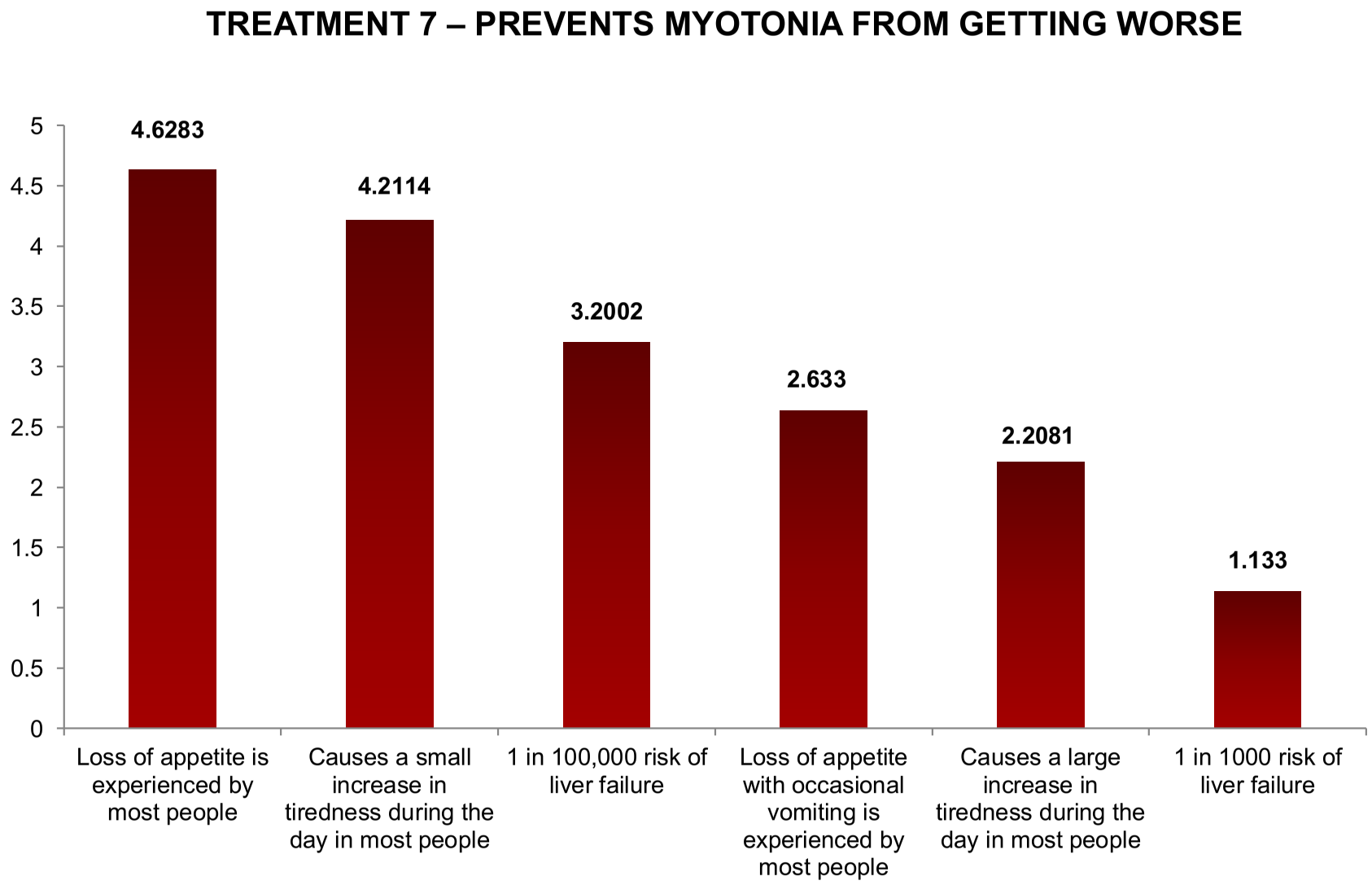
Treatment 7: Prevents Myotonia from Getting Worse



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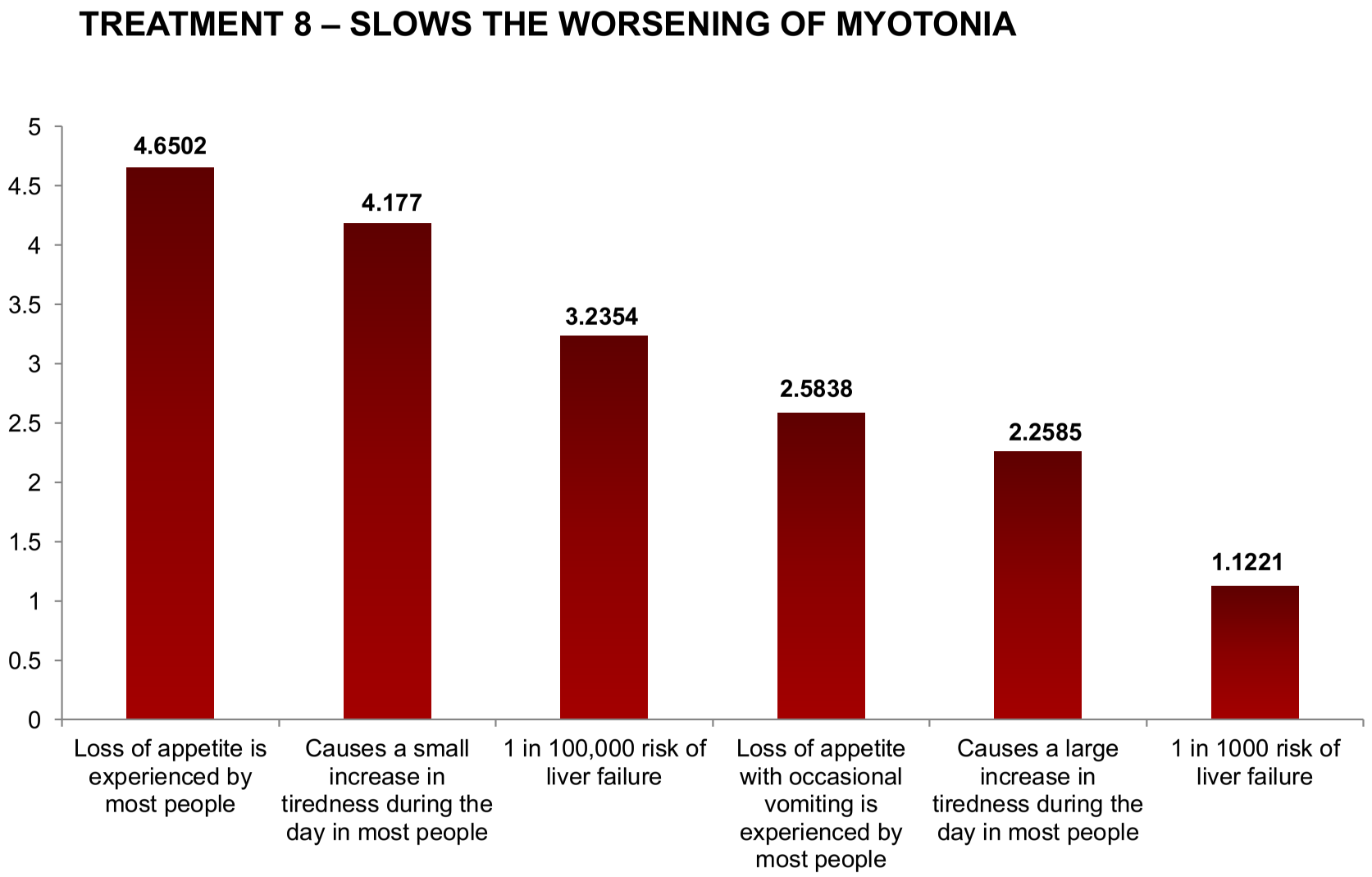
Treatment 8: Slows the Worsening of Myotonia

TREATMENT 8 – SLOWS THE WORSENING OF MYOTONIA

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**4.6502**
2	Causes a small increase in tiredness during the day in most people	**4.177**
3	1 in 100,000 risk of liver failure	**3.2354**
4	Loss of appetite with occasional vomiting is experienced by most people	**2.5838**
5	Causes a large increase in tiredness during the day in most people	**2.2585**
6	1 in 1000 risk of liver failure	**1.1221**

n=267

Treatment 8: Slows the Worsening of Myotonia



n=267

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Overall Rank Ordering of Side Effects/Risks

Side Effects Most/Least willing to live with

Rank	Attribute	Bayesian Average
1	Loss of appetite is experienced by most people	**4.5816**
2	Causes a small increase in tiredness during the day in most people	**4.1838**
3	1 in 100,000 risk of liver failure	**3.27**
4	Loss of appetite with occasional vomiting is experienced by most people	**2.6853**
5	Causes a large increase in tiredness during the day in most people	**2.08**
6	1 in 1000 risk of liver failure	**1.177**

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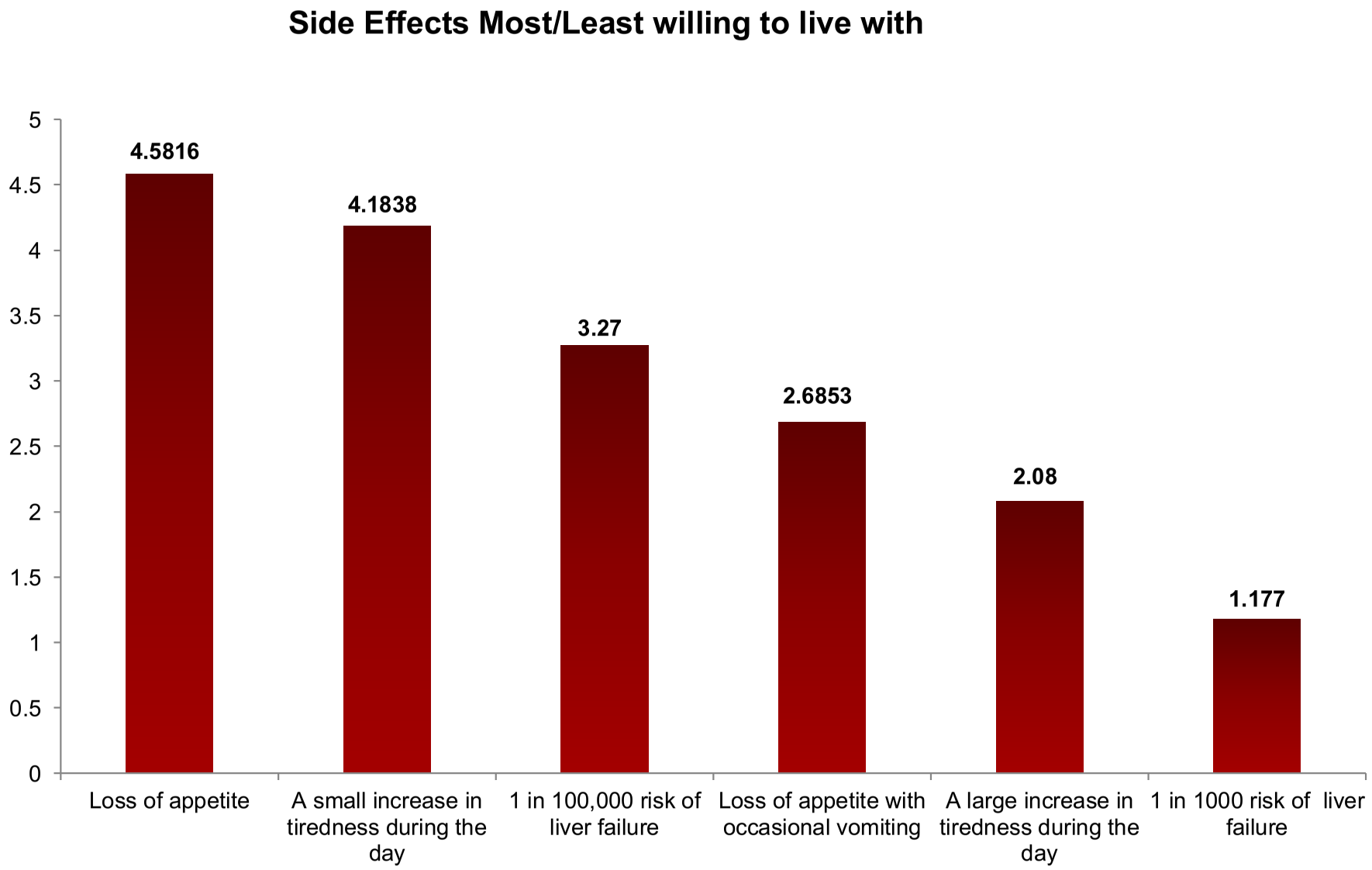
n=267

Overall Rank Ordering of Side Effects/Risks



n=267

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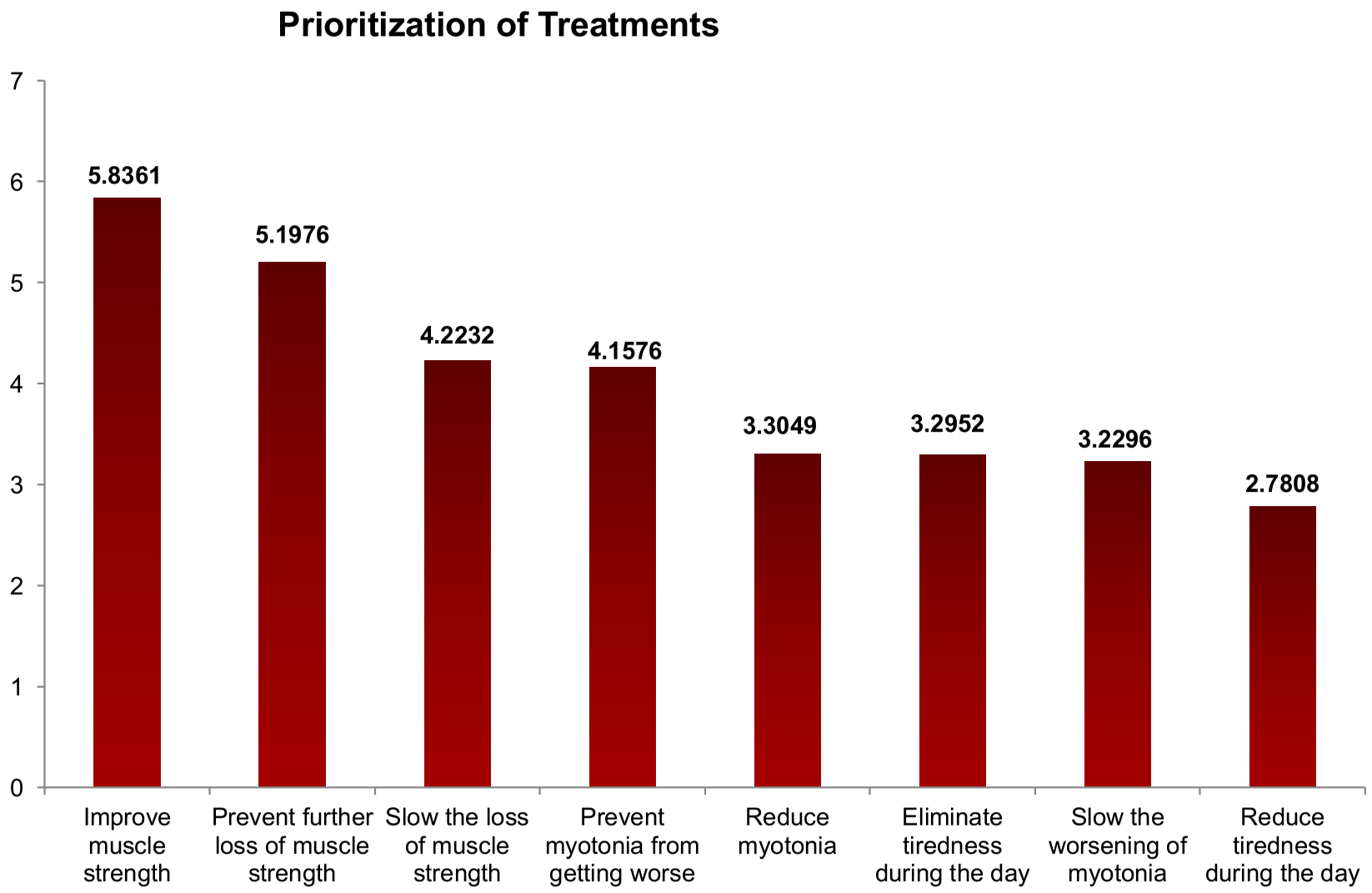
Overall Rank Ordering of Treatments or Benefits

Prioritization of Treatments

Rank	Attribute	Bayesian Average
1	Improve muscle strength	**5.8361**
2	Prevent further loss of muscle strength	**5.1976**
3	Slow the loss of muscle strength	**4.2232**
4	Prevent myotonia from getting worse ["stiffness" or inability to release an object	**4.1576**
5	Reduce myotonia ["stiffness" or inability to release an object]	**3.3049**
6	Eliminate tiredness during the day	**3.2952**
7	Slow the worsening of myotonia ["stiffness" or inability to release an object]	**3.2296**
8	Reduce tiredness during the day	**2.7808**

n=267

Overall Rank Ordering of Treatments or Benefits



n=267

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Key Takeaways

- Survey respondents exhibited a highly consistent pattern for risk tolerance for different benefits or treatments
- Loss of appetite and small increases in daytime tiredness are consistently the top two risks survey respondents are most willing to tolerate
- 1 in 1000 risk of liver failure is consistently the least tolerable risk

Cross-tabulations

Purpose of Cross-Tabulations

- To examine the effects of respondent characteristics on the prioritization data obtained, we asked the following classification questions:
  - Severity of symptoms (using a validated survey instrument, MDHI Short Form, developed by University of Rochester and Dr. Chad Heatwole)
  - Respondent's risk taking profile
  - Respondent's comfort level with numbers or numeracy skill (as one of the risks, liver failure risk, was stated as a numerical probabilities
- This section explores the effects of these variables on the overall results

MDHI Short Form Survey Instrument (severity of symptoms)

How much does the following impact your life now? [Please check the ***one*** box that applies to you for each item]

	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
Limitations with your mobility or walking	☐	☐	☐	☐	☐	☐
Problems with your hands or arms	☐	☐	☐	☐	☐	☐
Inability to do activities	☐	☐	☐	☐	☐	☐
Fatigue	☐	☐	☐	☐	☐	☐
Pain	☐	☐	☐	☐	☐	☐
Gastrointestinal issues	☐	☐	☐	☐	☐	☐
Problems with your vision	☐	☐	☐	☐	☐	☐
Communication difficulties	☐	☐	☐	☐	☐	☐
Impaired sleep or daytime sleepiness	☐	☐	☐	☐	☐	☐
Emotional issues	☐	☐	☐	☐	☐	☐
Difficulty thinking	☐	☐	☐	☐	☐	☐
Decreased satisfaction in social situations	☐	☐	☐	☐	☐	☐
Decreased performance in social situations	☐	☐	☐	☐	☐	☐
Myotonia	☐	☐	☐	☐	☐	☐
Breathing difficulties	☐	☐	☐	☐	☐	☐
Choking or swallowing issues	☐	☐	☐	☐	☐	☐
Hearing difficulties	☐	☐	☐	☐	☐	☐

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Risk Taking Attitude Question

For each of the following, please choose the number that best reflects how strongly you agree with that statement. "1" = Strongly Disagree and "6" = Strongly Agree.

	1-Strongly Disagree	2	3	4	5	6-Strongly Agree
I enjoy taking risks	○	○	○	○	○	○
I try to avoid situations that have uncertain outcomes	○	○	○	○	○	○
Taking risks does not bother me if the gains involved are high	○	○	○	○	○	○
I consider security an important element in every aspect of my life	○	○	○	○	○	○
People have told me that I seem to enjoy taking chances	○	○	○	○	○	○
I rarely, if ever, take risks when there is another alternative	○	○	○	○	○	○

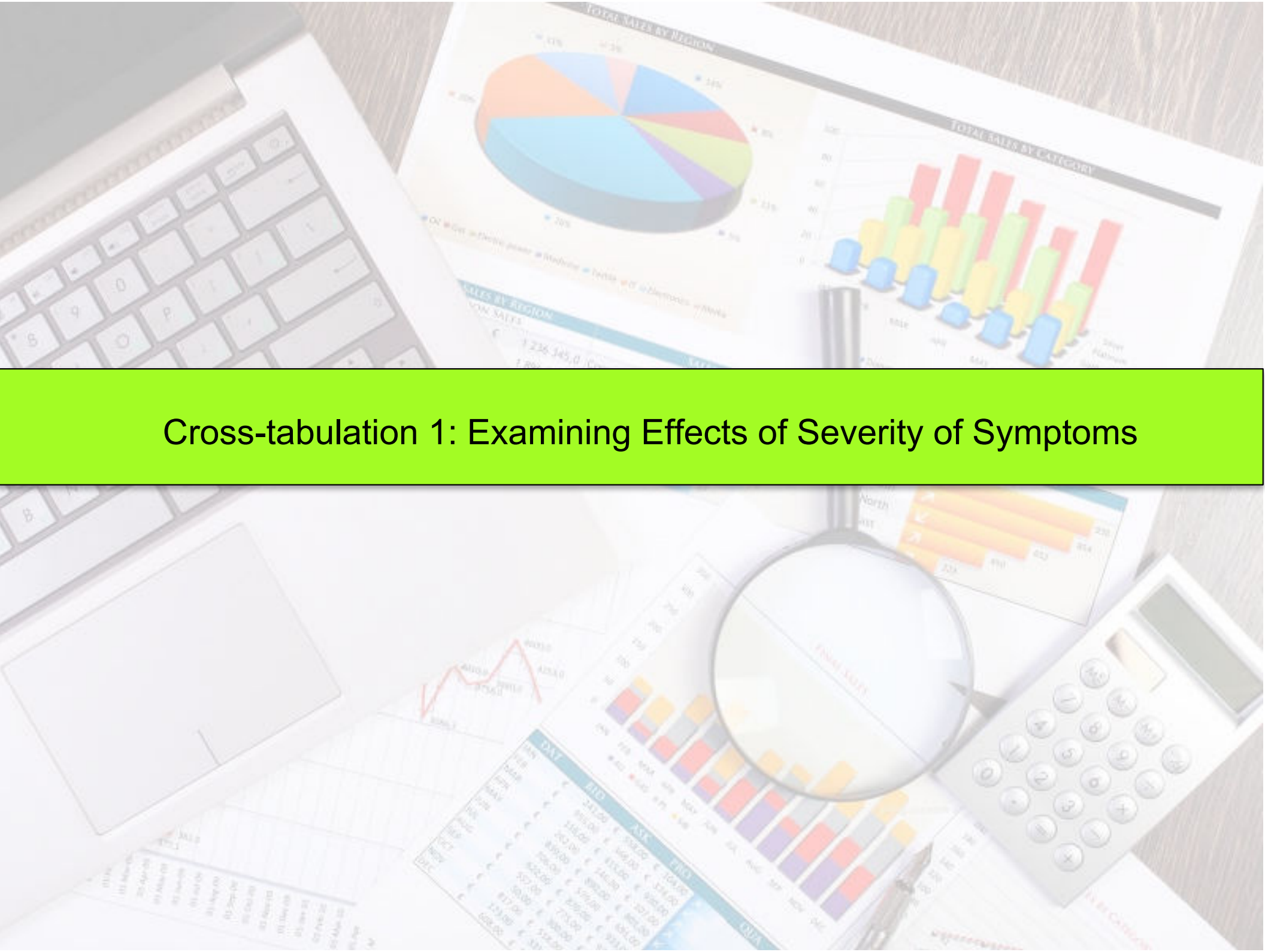
Numeracy Skill Question

For each of the following questions, please choose the number that best reflects how good you are at doing the following things:

	1-Not good at all	2	3	4	5	6-Excellent
How good are you at working with fractions?	○	○	○	○	○	○
How good are you at figuring out how much a shirt will cost if it is 25% off?	○	○	○	○	○	○

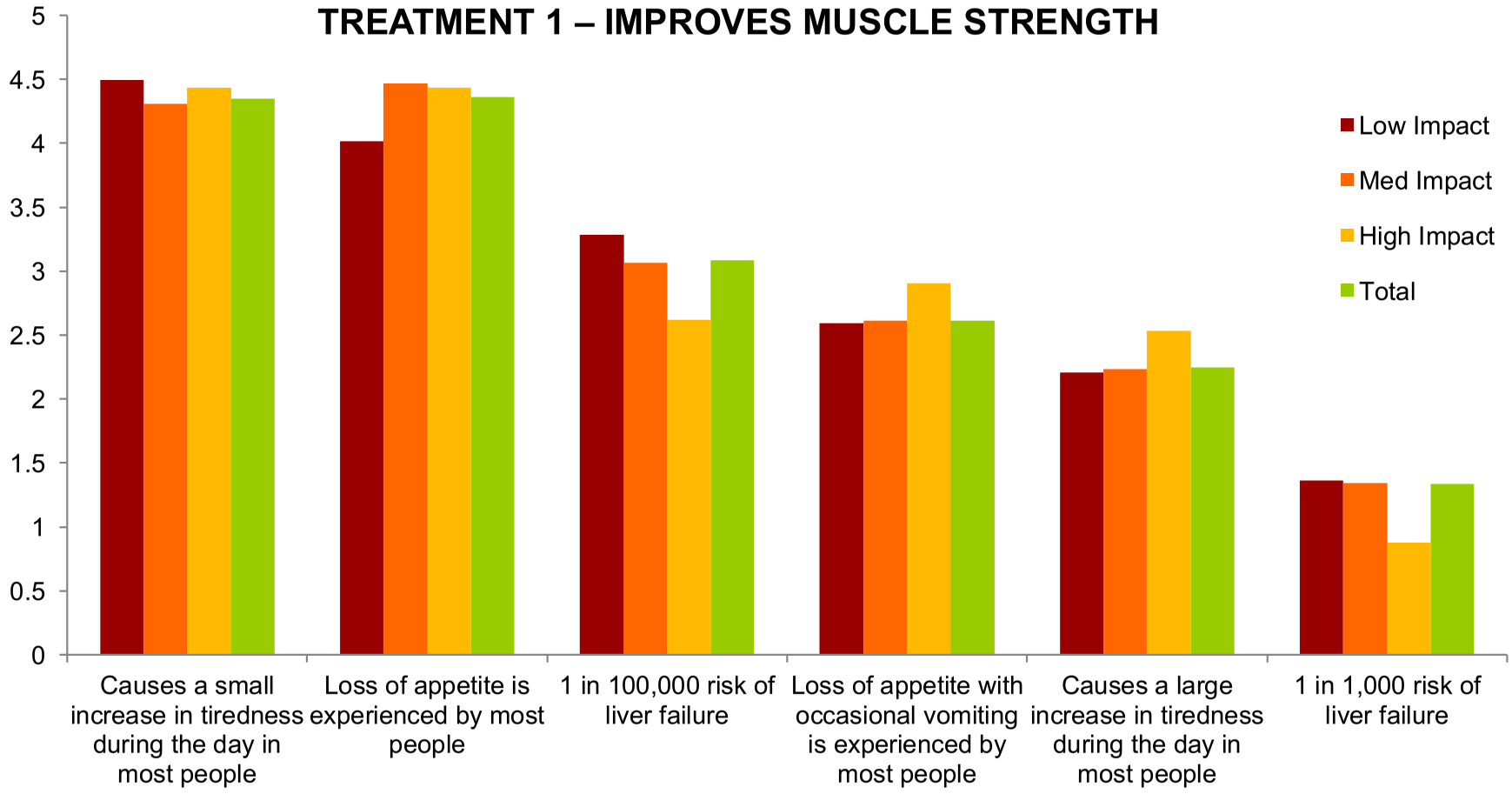
For the following question, please choose the number that best reflects how often you find the following useful:

	1-Never	2	3	4	5	6-Very often
How often do you find numerical information to be useful?	○	○	○	○	○	○



Cross-tabulation 1: Examining Effects of Severity of Symptoms

Impact of Severity of Symptoms: Treatment 1



n=267

Low Impact	**4.4914**	**4.0174**	**3.2866**	**2.5953**	**2.2072**	**1.3652**
Med Impact	**4.3063**	**4.4667**	**3.0638**	**2.6156**	**2.2338**	**1.3455**
High Impact	**4.4366**	**4.4328**	**2.619**	**2.9032**	**2.5313**	**0.8769**
Total	**4.349**	**4.3587**	**3.0815**	**2.6156**	**2.2483**	**1.3385**

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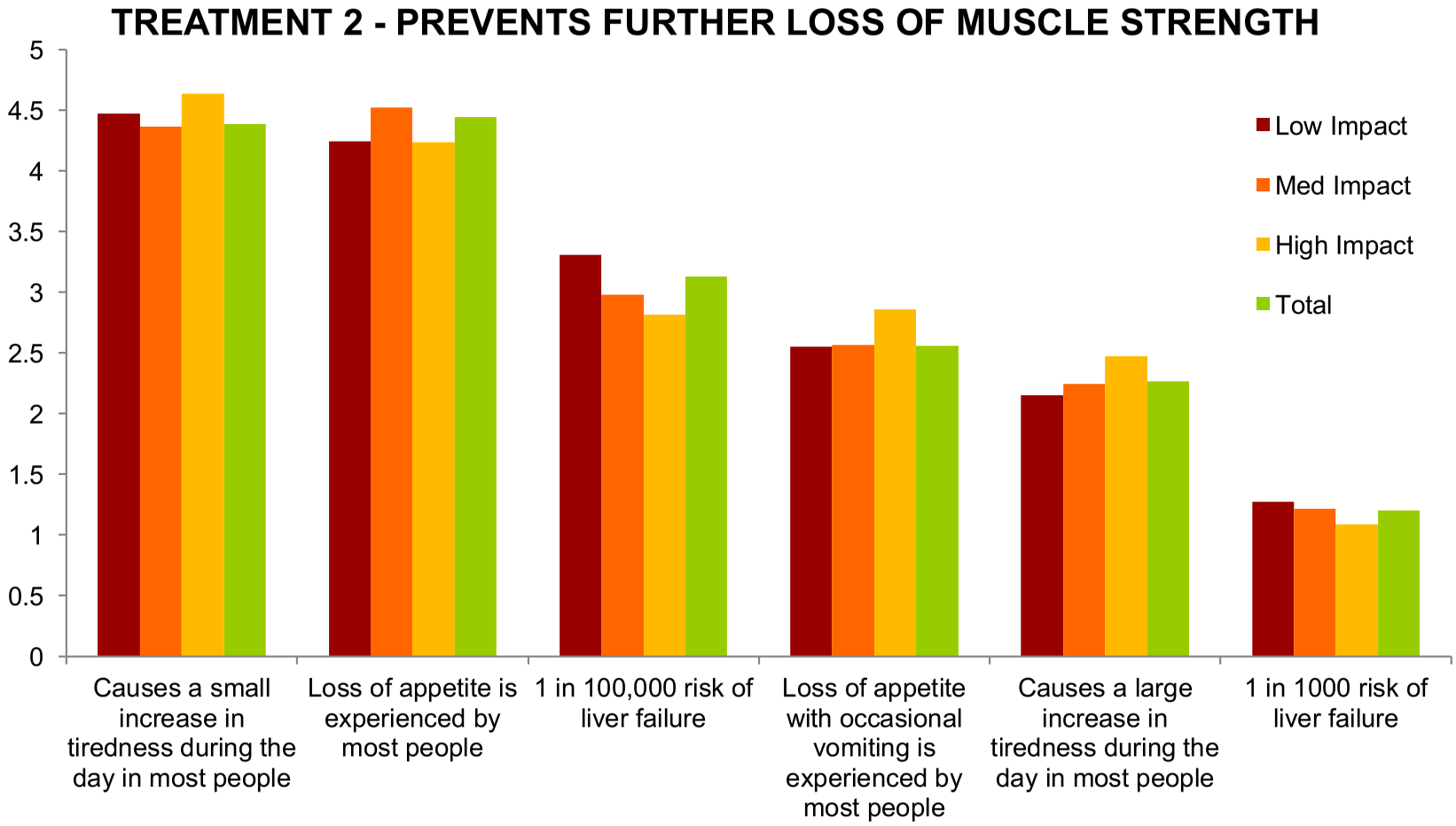
Impact of Severity of Symptoms: Treatment 2



n=267

Low Impact	**4.4694**	**4.2463**	**3.3061**	**2.5491**	**2.1527**	**1.2768**
Med Impact	**4.3662**	**4.5223**	**2.9813**	**2.5701**	**2.2454**	**1.2152**
High Impact	**4.6406**	**4.2381**	**2.8182**	**2.8615**	**2.4706**	**1.0909**
Total	**4.3854**	**4.4464**	**3.1291**	**2.5605**	**2.2659**	**1.2027**

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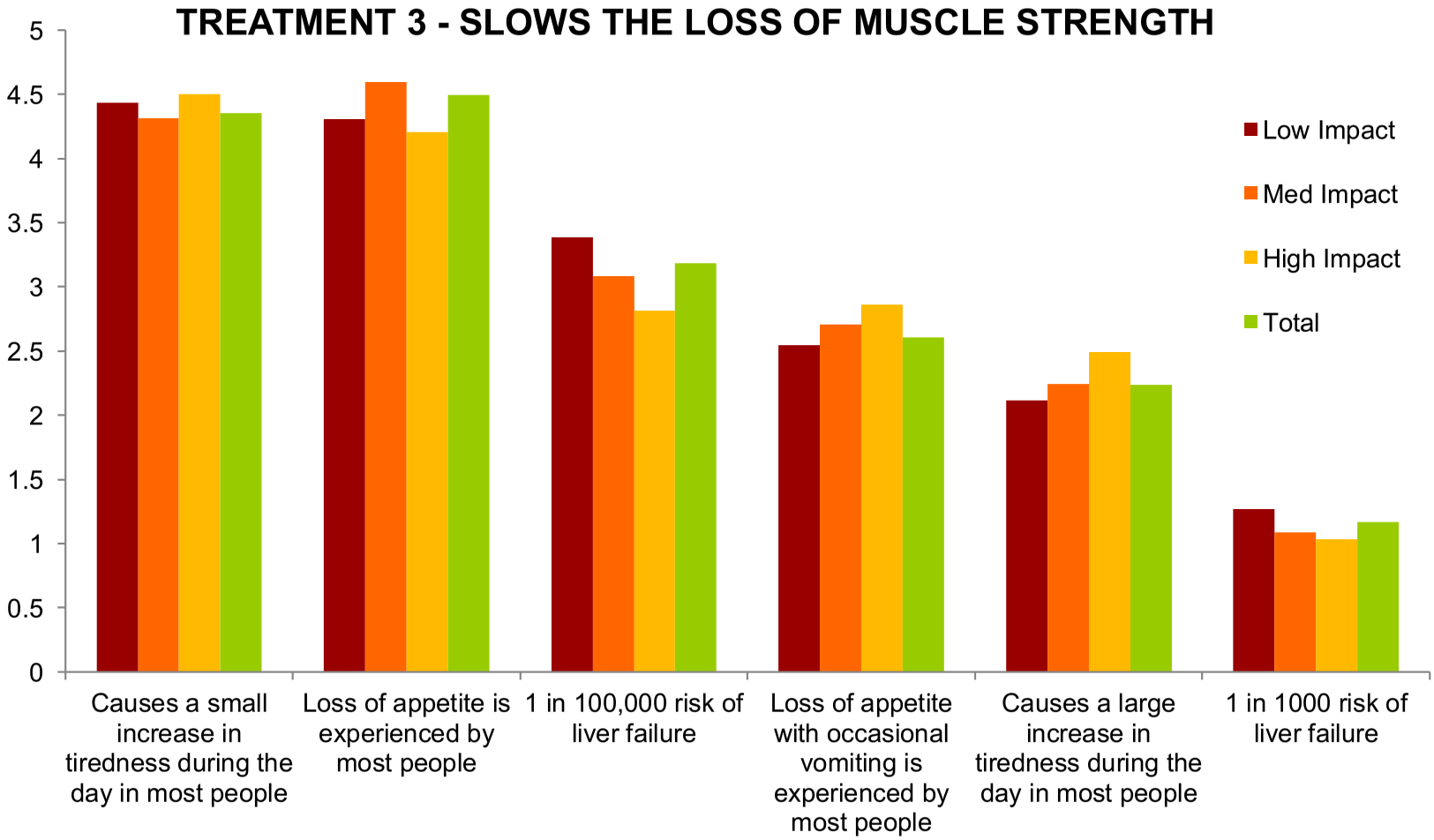
Impact of Severity of Symptoms: Treatment 3



n=267

Low Impact	**4.4371**	**4.307**	**3.3871**	**2.5457**	**2.1187**	**1.2672**
Med Impact	**4.3113**	**4.5926**	**3.0818**	**2.7075**	**2.2432**	**1.0867**
High Impact	**4.5**	**4.209**	**2.8154**	**2.8615**	**2.4923**	**1.0313**
Total	**4.3527**	**4.4933**	**3.1816**	**2.6061**	**2.2373**	**1.1707**

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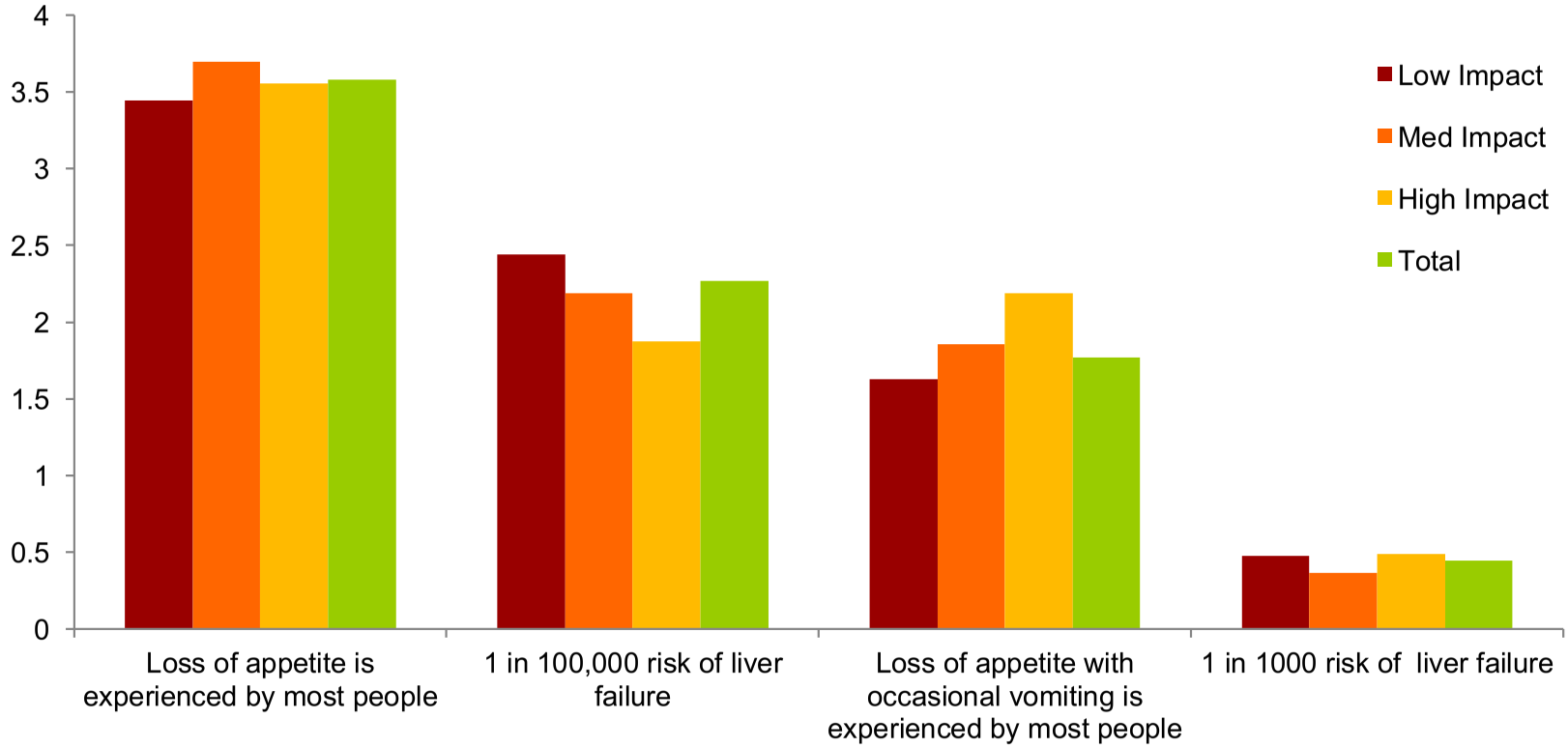
Impact of Severity of Symptoms: Treatment 4

TREATMENT 4 - ELIMINATES TIREDNESS DURING THE DAY



n=267

Low Impact	**3.4437**	**2.4414**	**1.6254**	**0.4733**
Med Impact	**3.694**	**2.1891**	**1.8547**	**0.3636**
High Impact	**3.5556**	**1.871**	**2.1852**	**0.4912**
Total	**3.5768**	**2.2686**	**1.7687**	**0.4428**

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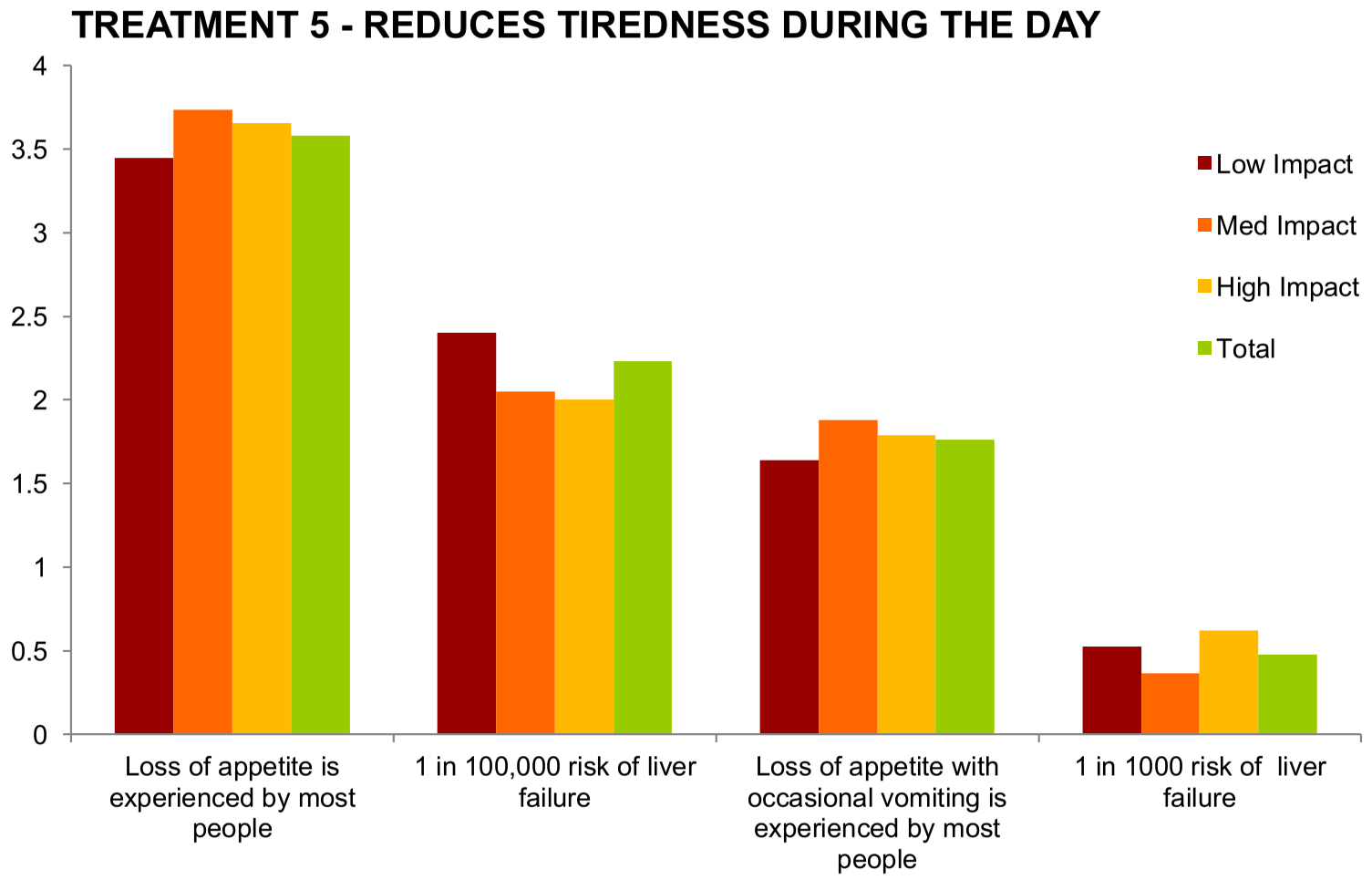
Impact of Severity of Symptoms: Treatment 5



n=267

Low Impact	**3.449**	**2.4038**	**1.6376**	**0.5249**
Med Impact	**3.7367**	**2.0505**	**1.8811**	**0.3636**
High Impact	**3.6552**	**2**	**1.7895**	**0.623**
Total	**3.5796**	**2.2335**	**1.7621**	**0.4747**

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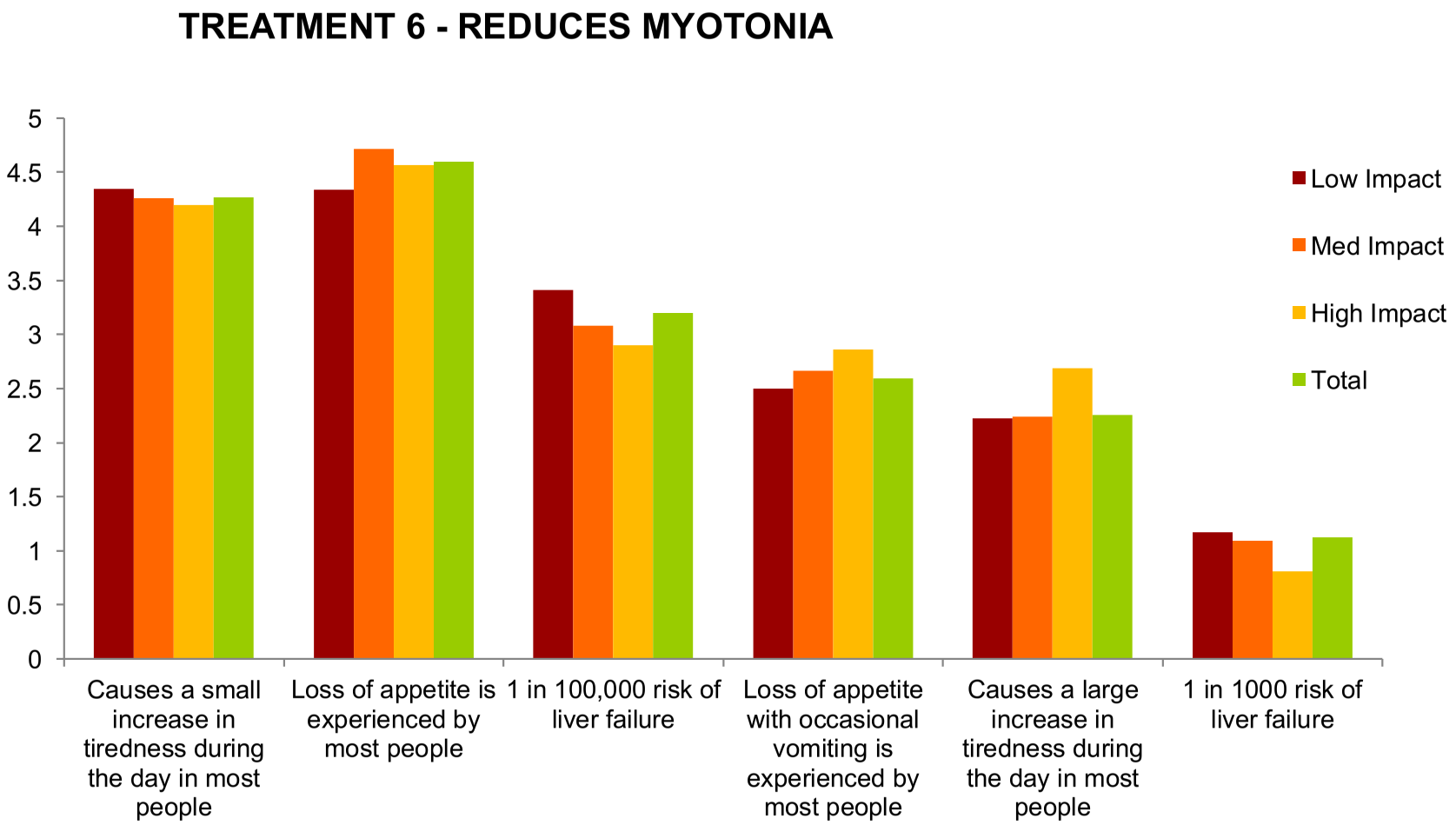
Impact of Severity of Symptoms: Treatment 6



n=267

Low Impact	**4.3482**	**4.3372**	**3.4129**	**2.5015**	**2.2209**	**1.1701**
Med Impact	**4.2613**	**4.7196**	**3.0772**	**2.6647**	**2.2406**	**1.0893**
High Impact	**4.2**	**4.5672**	**2.9016**	**2.8615**	**2.6866**	**0.806**
Total	**4.2649**	**4.5998**	**3.202**	**2.5915**	**2.2534**	**1.1262**

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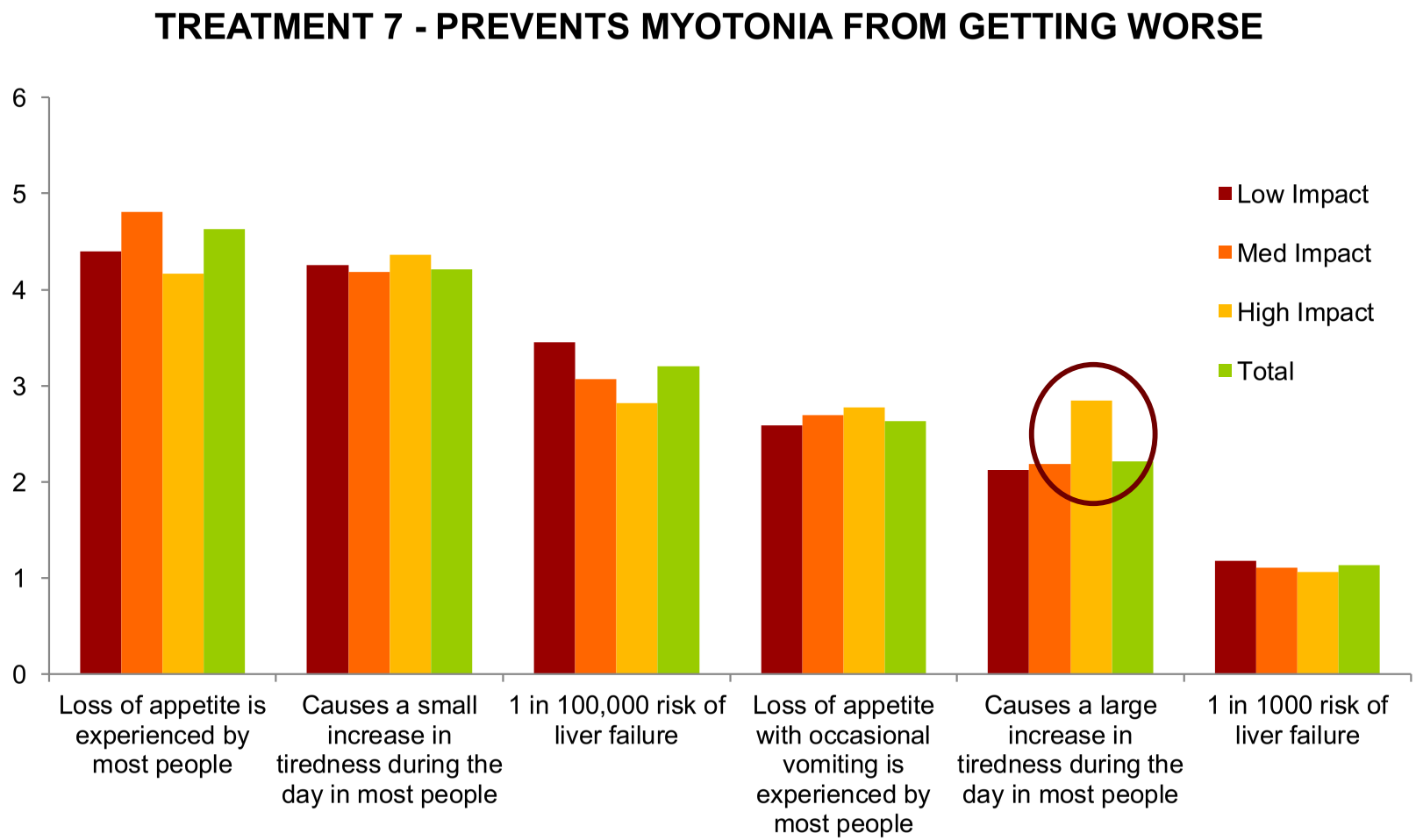
Impact of Severity of Symptoms: Treatment 7



n=267

Low Impact	**4.4012**	**4.2581**	**3.4496**	**2.5838**	**2.1243**	**1.1802**
Med Impact	**4.8037**	**4.1815**	**3.064**	**2.6935**	**2.1884**	**1.1043**
High Impact	**4.1642**	**4.3636**	**2.8182**	**2.7727**	**2.8475**	**1.0588**
Total	**4.6283**	**4.2114**	**3.2002**	**2.633**	**2.2081**	**1.133**

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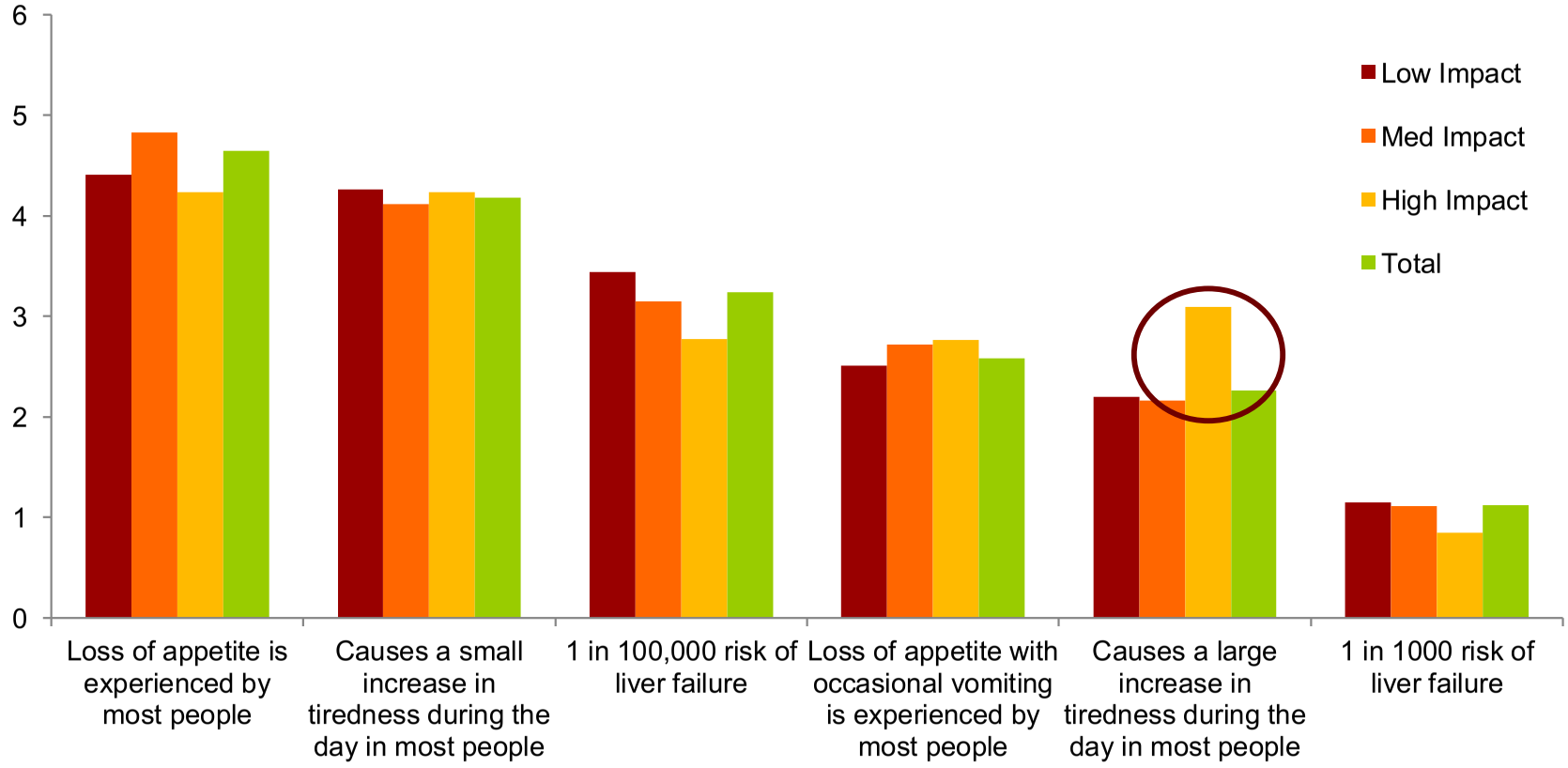
Impact of Severity of Symptoms: Treatment 8

TREATMENT 8 - SLOWS THE WORSENING OF MYOTONIA



n=267

Low Impact	**4.4092**	**4.2581**	**3.4399**	**2.5085**	**2.1951**	**1.1525**
Med Impact	**4.8318**	**4.1156**	**3.1468**	**2.7156**	**2.1641**	**1.1138**
High Impact	**4.2381**	**4.2353**	**2.7761**	**2.7692**	**3.0923**	**0.8438**
Total	**4.6502**	**4.177**	**3.2354**	**2.5838**	**2.2585**	**1.1221**

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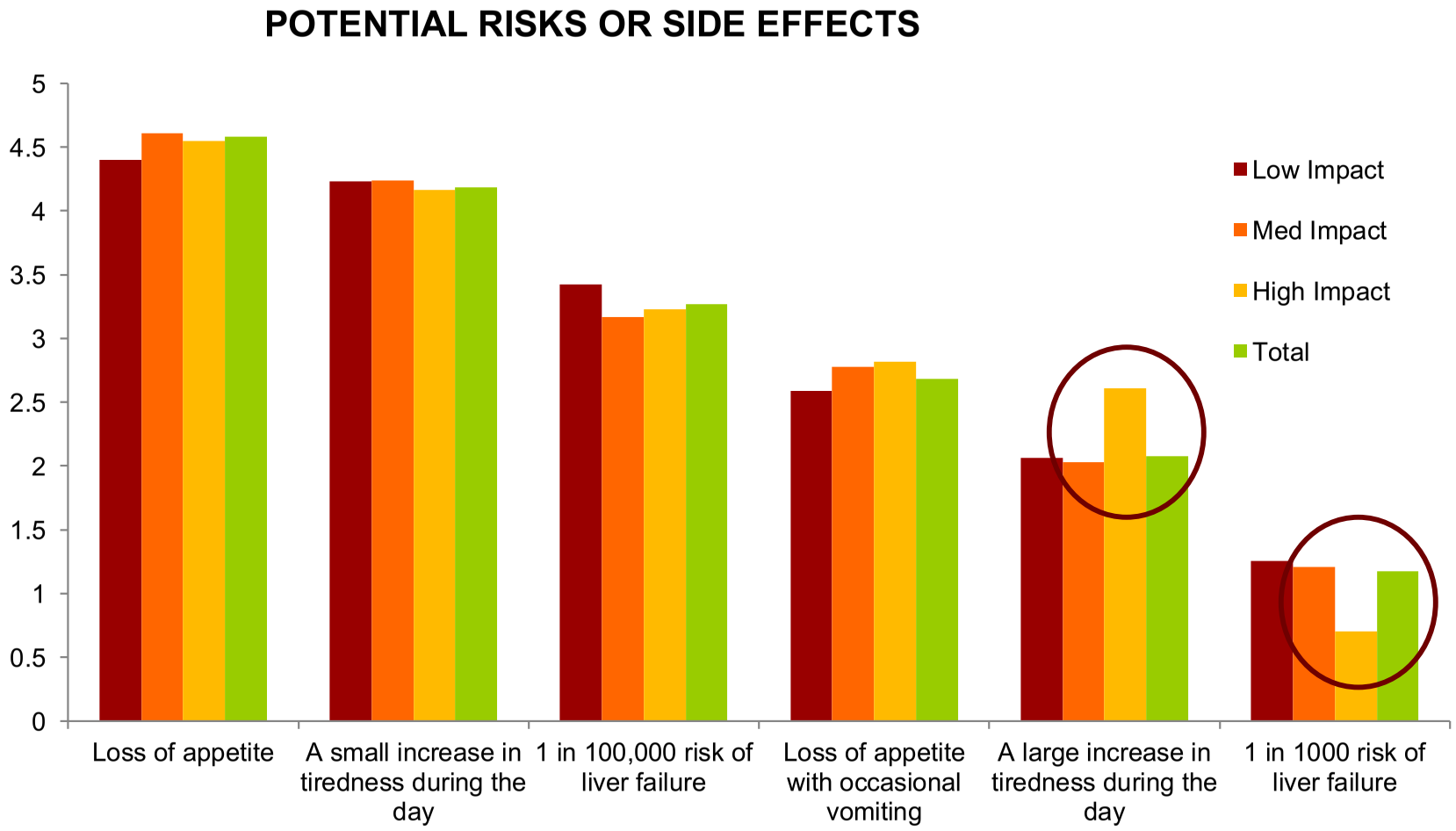
Impact of Severity of Symptoms: POTENTIAL RISKS OR SIDE EFFECTS



n=267

Low Impact	**4.3994**	**4.2332**	**3.4223**	**2.5877**	**2.0641**	**1.2537**
Med Impact	**4.6084**	**4.2358**	**3.1677**	**2.7771**	**2.0308**	**1.2108**
High Impact	**4.5469**	**4.1642**	**3.2308**	**2.8209**	**2.6066**	**0.7059**
Total	**4.5816**	**4.1838**	**3.27**	**2.6853**	**2.08**	**1.177**

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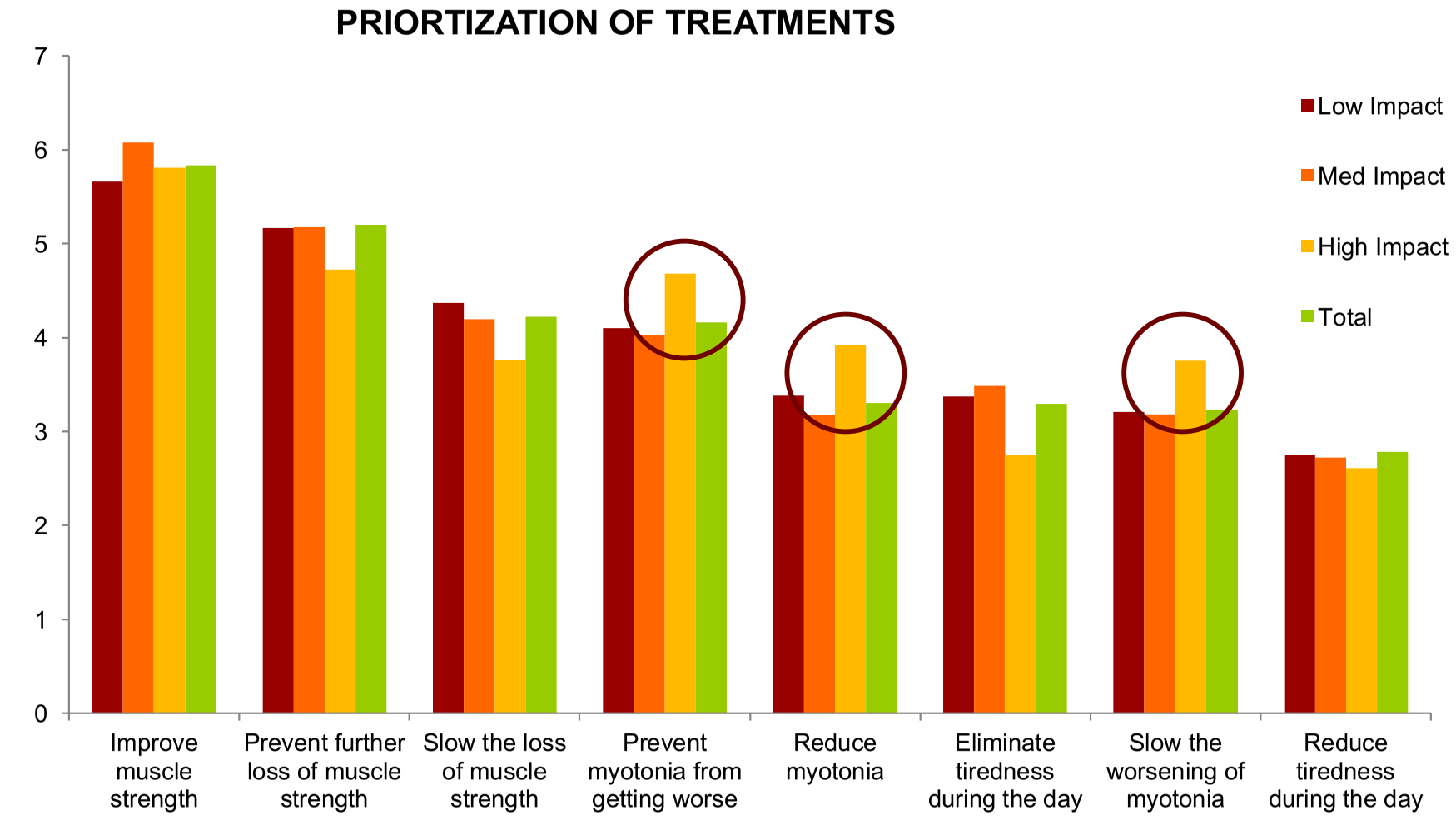
Impact of Severity of Symptoms: PRIORTIZATION OF TREATMENTS



n=267

Low Impact	**5.6604**	**5.168**	**4.3692**	**4.0964**	**3.3846**	**3.3684**	**3.203**	**2.749**
Med Impact	**6.0741**	**5.1784**	**4.1959**	**4.0328**	**3.1741**	**3.4859**	**3.177**	**2.7213**
High Impact	**5.8039**	**4.72**	**3.76**	**4.6809**	**3.9184**	**2.7451**	**3.7551**	**2.6122**
Total	**5.8361**	**5.1976**	**4.2232**	**4.1576**	**3.3049**	**3.2952**	**3.2296**	**2.7808**

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Key Takeaways

- DM1 sufferers in our study who had a high severity of symptoms (self-rated) were less tolerant of 1 in 1000 liver failure risk
- Those impacted with high severity of symptoms were also more willing to tolerate a large increase in tiredness through the day
- Those impacted with high severity of symptoms put far more emphasis on all three myotonia options, preventing, reducing or slowing myotonia.

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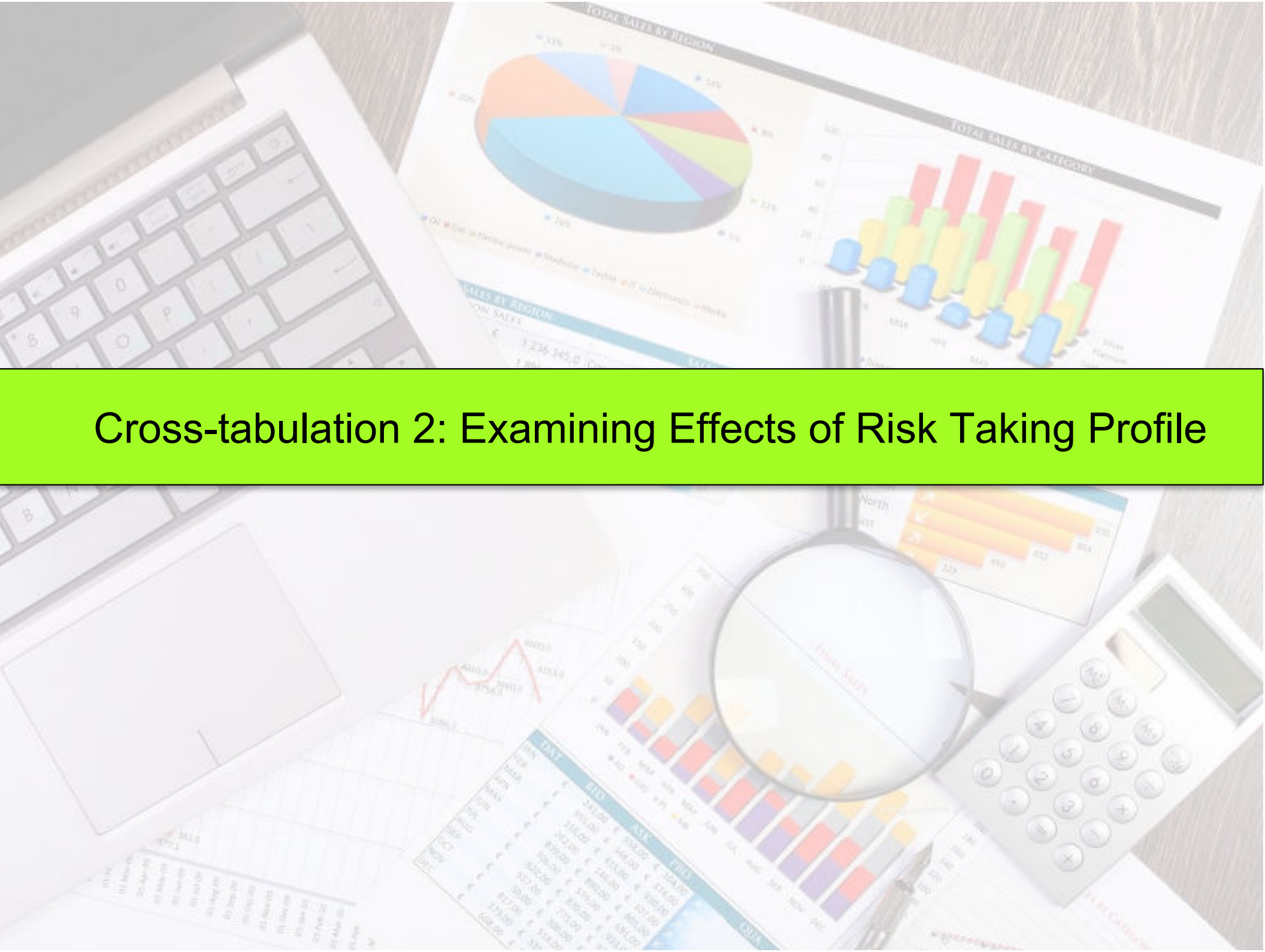
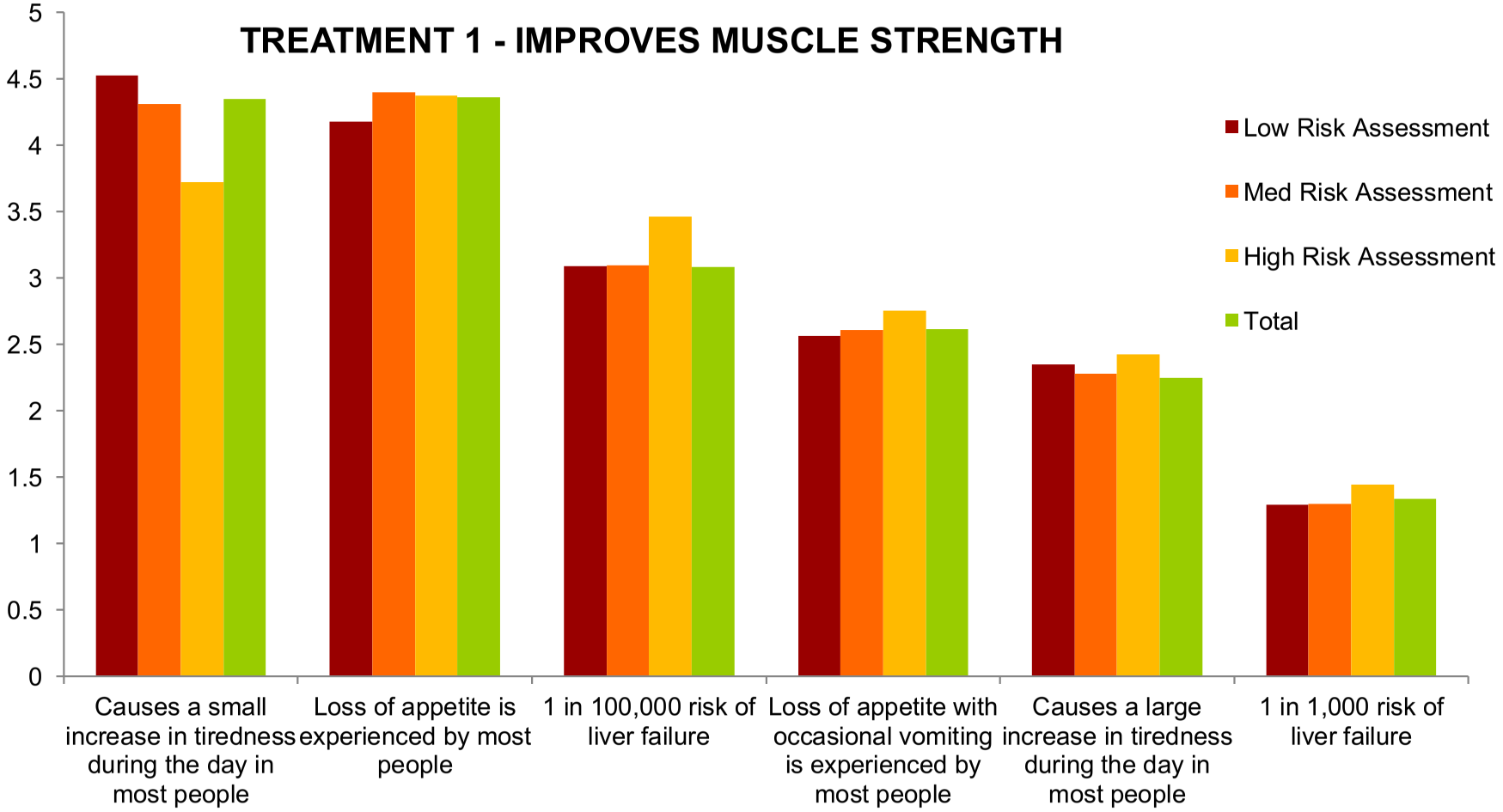


Cross-tabulation 2: Examining Effects of Risk Taking Profile

Impact of Risk Taking Profile: Treatment 1



n=267

Low Risk Assessment	**4.526**	**4.1786**	**3.0909**	**2.561**	**2.3471**	**1.2907**
Med Risk Assessment	**4.3089**	**4.3973**	**3.0955**	**2.6063**	**2.2787**	**1.2966**
High Risk Assessment	**3.72**	**4.375**	**3.4615**	**2.75**	**2.4231**	**1.4444**
Total	**4.349**	**4.3587**	**3.0815**	**2.6156**	**2.2483**	**1.3385**

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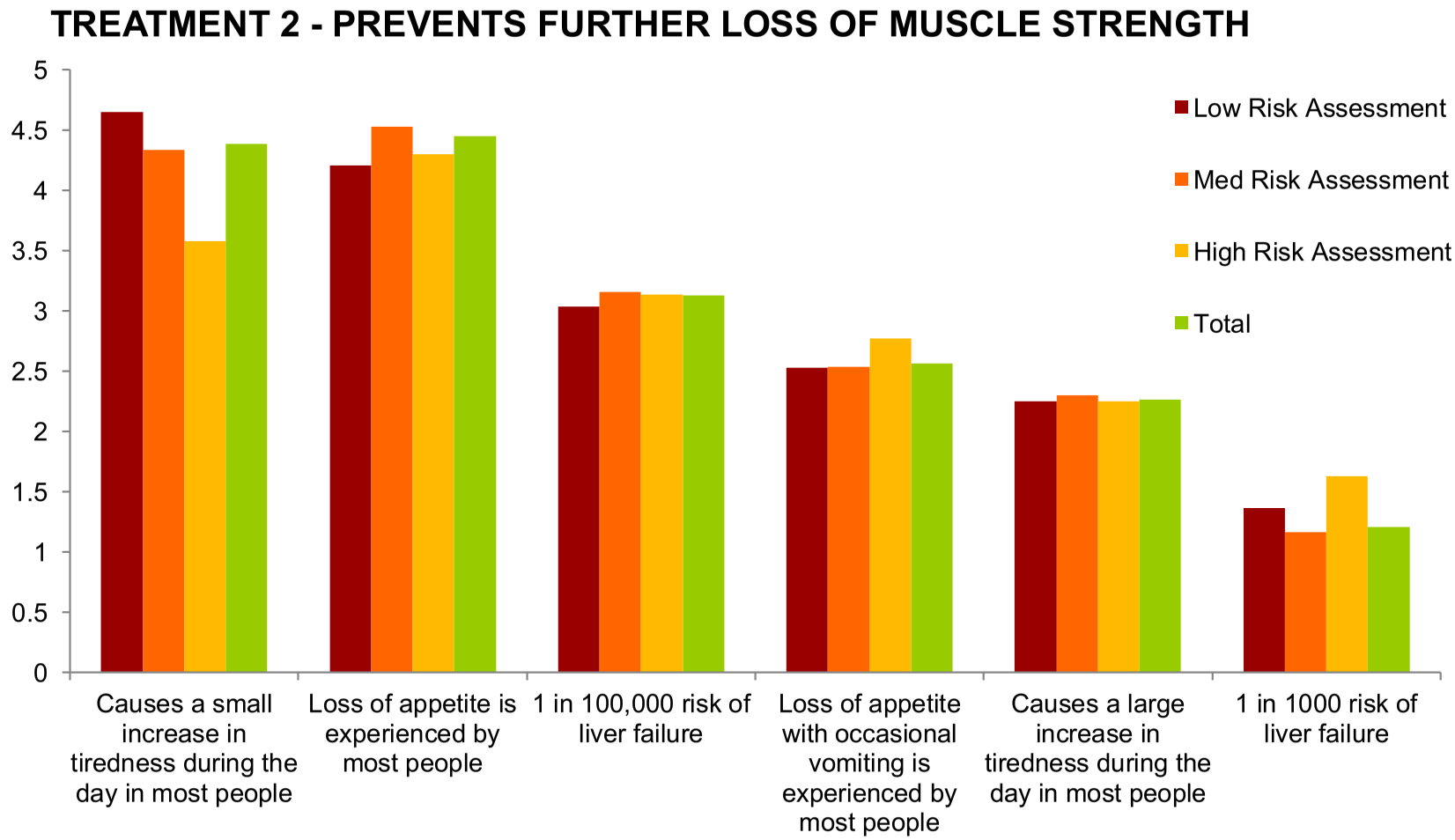
Impact of Risk Taking Profile: Treatment 2



n=267

Low Risk Assessment	**4.6446**	**4.2071**	**3.0357**	**2.5235**	**2.25**	**1.3653**
Med Risk Assessment	**4.3303**	**4.5271**	**3.1543**	**2.534**	**2.296**	**1.1608**
High Risk Assessment	**3.5769**	**4.3**	**3.1364**	**2.7692**	**2.25**	**1.625**
Total	**4.3854**	**4.4464**	**3.1291**	**2.5605**	**2.2659**	**1.2027**

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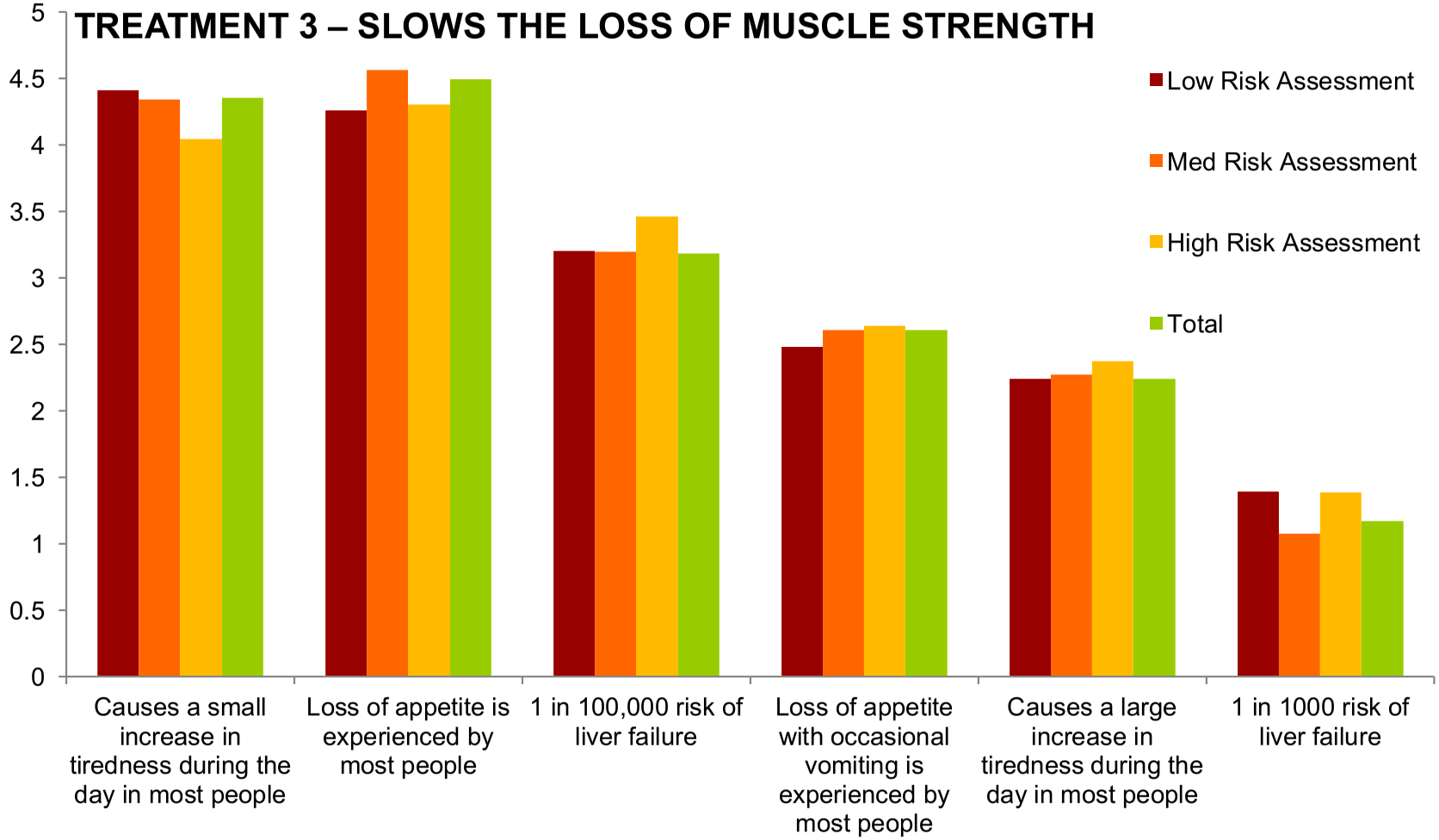
Impact of Risk Taking Profile: Treatment 3



n=267

Low Risk Assessment	**4.4107**	**4.2586**	**3.2025**	**2.4821**	**2.2367**	**1.3941**
Med Risk Assessment	**4.341**	**4.5656**	**3.1958**	**2.6063**	**2.2704**	**1.0727**
High Risk Assessment	**4.0435**	**4.3043**	**3.4615**	**2.64**	**2.375**	**1.3846**
Total	**4.3527**	**4.4933**	**3.1816**	**2.6061**	**2.2373**	**1.1707**

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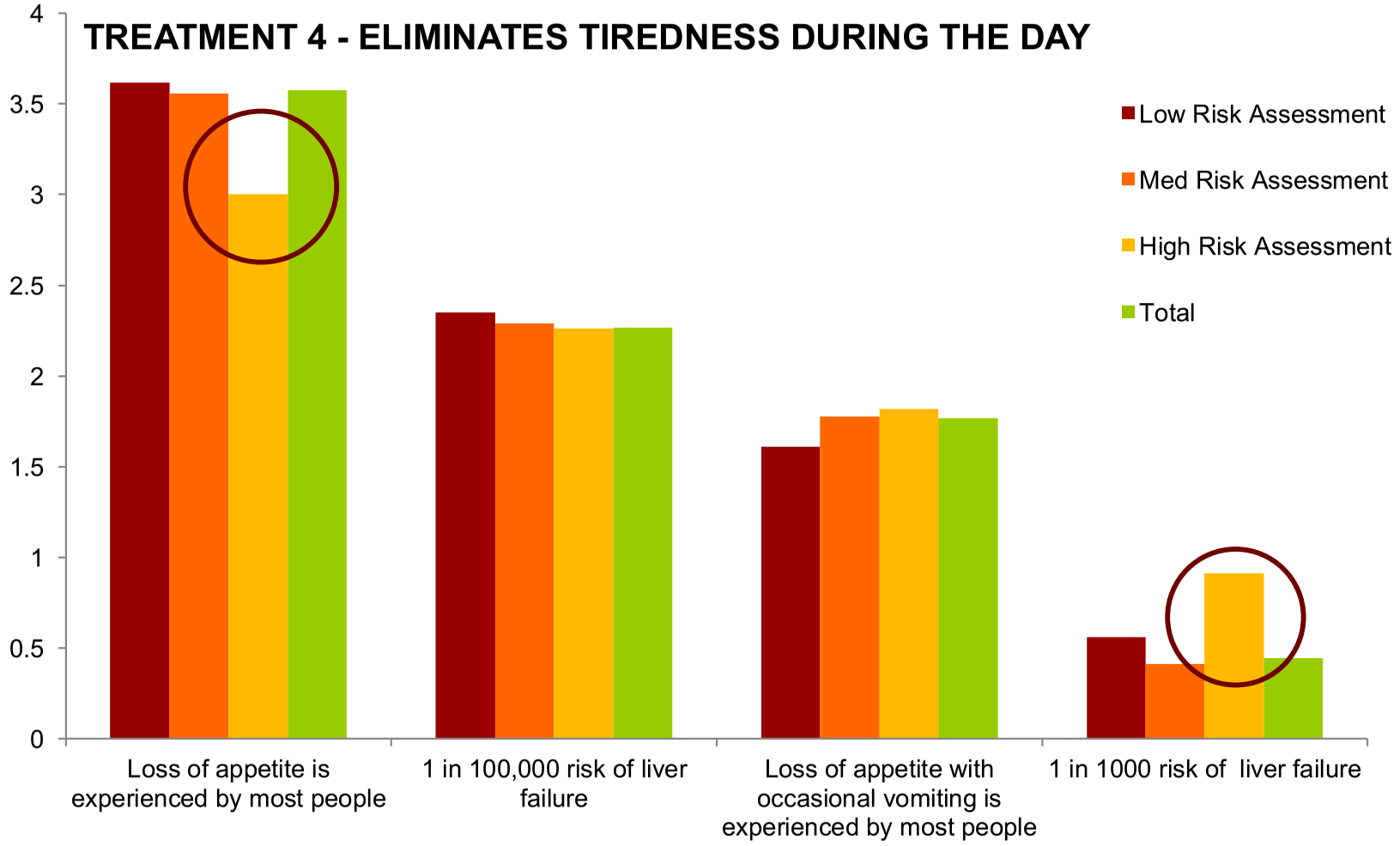
Impact of Risk Taking Profile: Treatment 4



n=267

Low Risk Assessment	**3.619**	**2.3521**	**1.6084**	**0.559**
Med Risk Assessment	**3.559**	**2.2897**	**1.7758**	**0.4109**
High Risk Assessment	**3**	**2.2609**	**1.8182**	**0.9091**
Total	**3.5768**	**2.2686**	**1.7687**	**0.4428**

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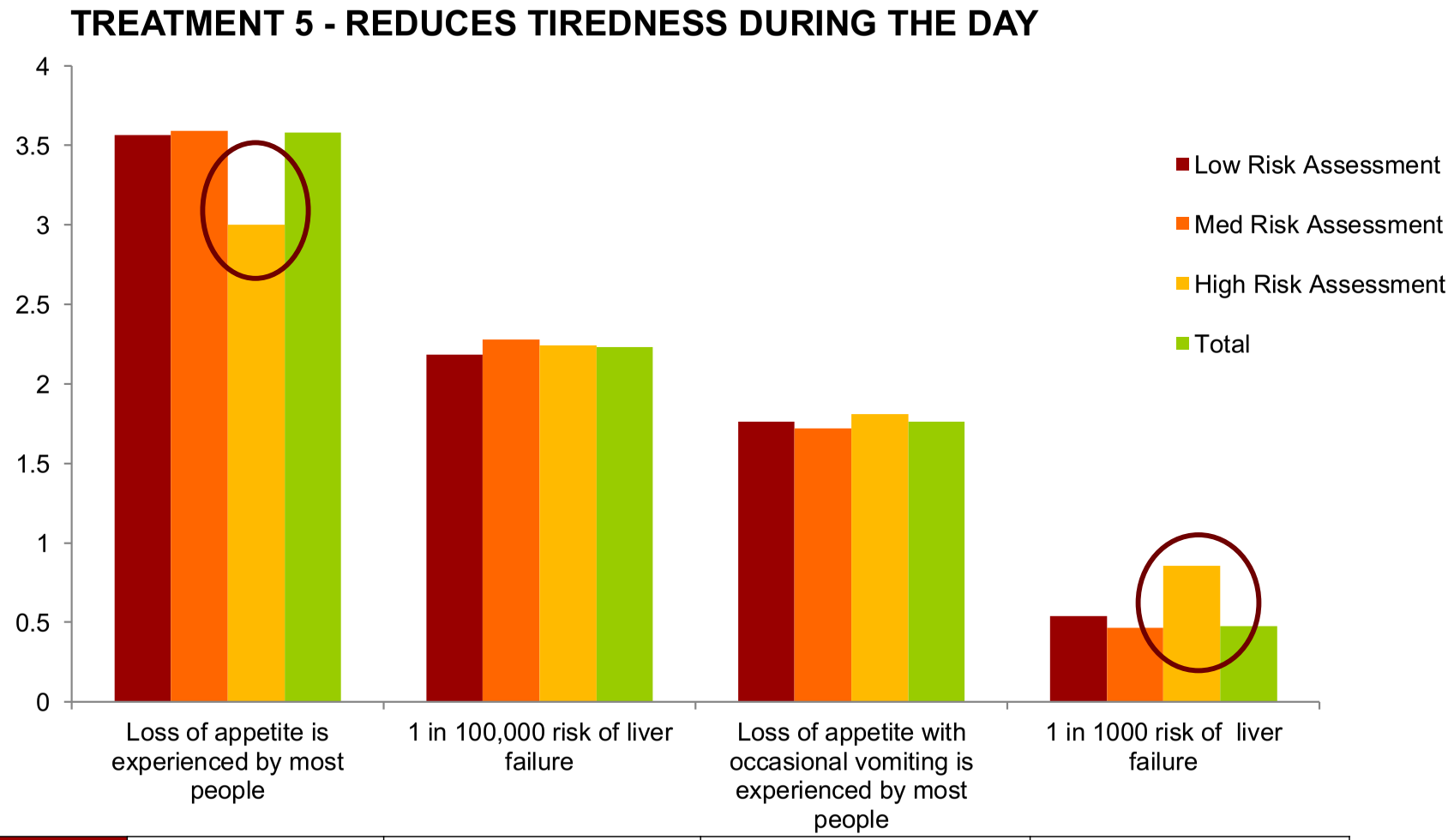
Impact of Risk Taking Profile: Treatment 5



n=267

Low Risk Assessment	**3.5664**	**2.1854**	**1.7616**	**0.5405**
Med Risk Assessment	**3.5896**	**2.2779**	**1.7221**	**0.4639**
High Risk Assessment	**3**	**2.24**	**1.8095**	**0.8571**
Total	**3.5796**	**2.2335**	**1.7621**	**0.4747**

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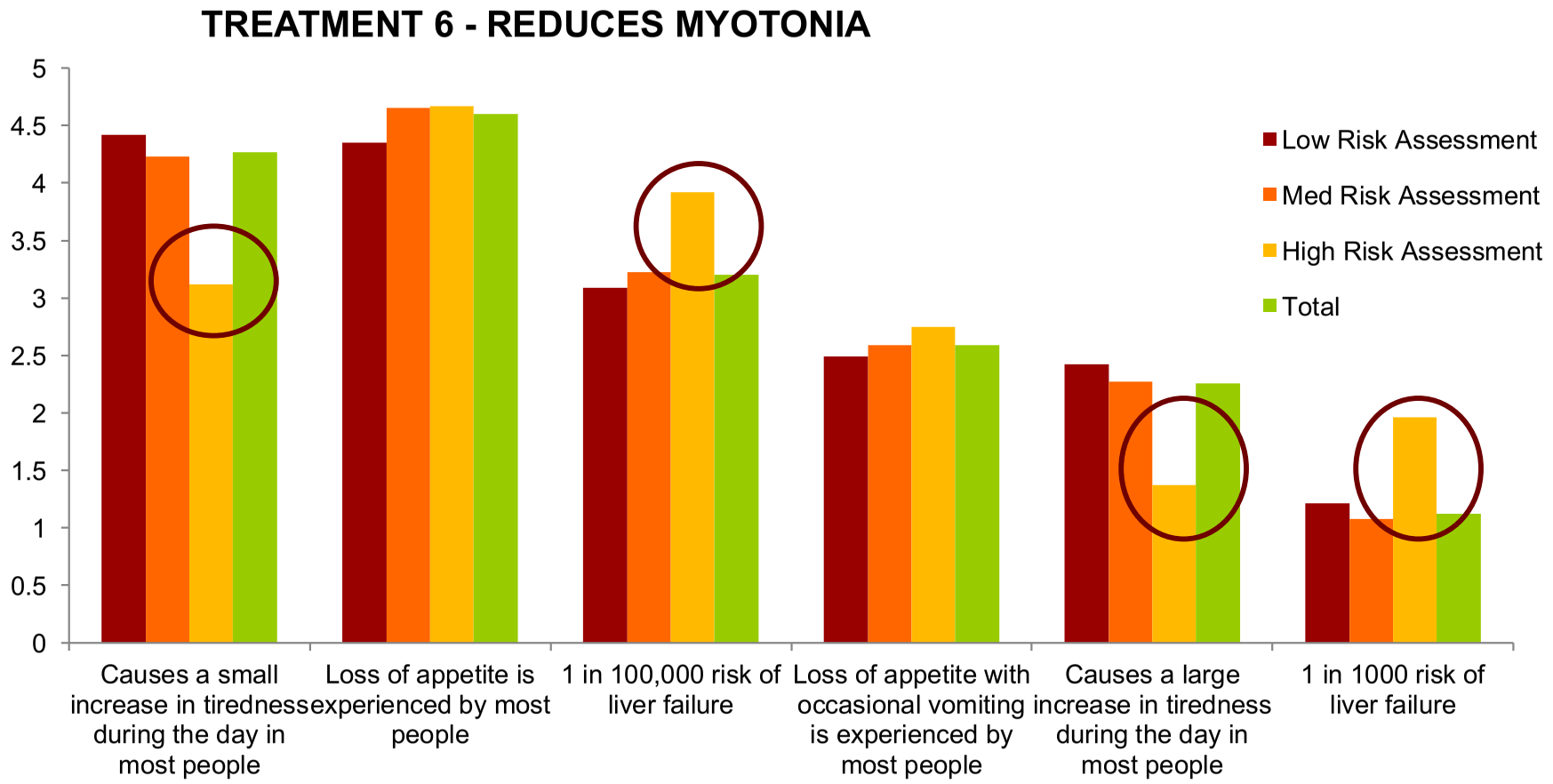
Impact of Risk Taking Profile: Treatment 6



n=267

Low Risk Assessment	**4.4192**	**4.3509**	**3.0888**	**2.4912**	**2.4217**	**1.2143**
Med Risk Assessment	**4.2316**	**4.6555**	**3.2262**	**2.5881**	**2.2749**	**1.0784**
High Risk Assessment	**3.12**	**4.6667**	**3.9231**	**2.75**	**1.375**	**1.9615**
Total	**4.2649**	**4.5998**	**3.202**	**2.5915**	**2.2534**	**1.1262**

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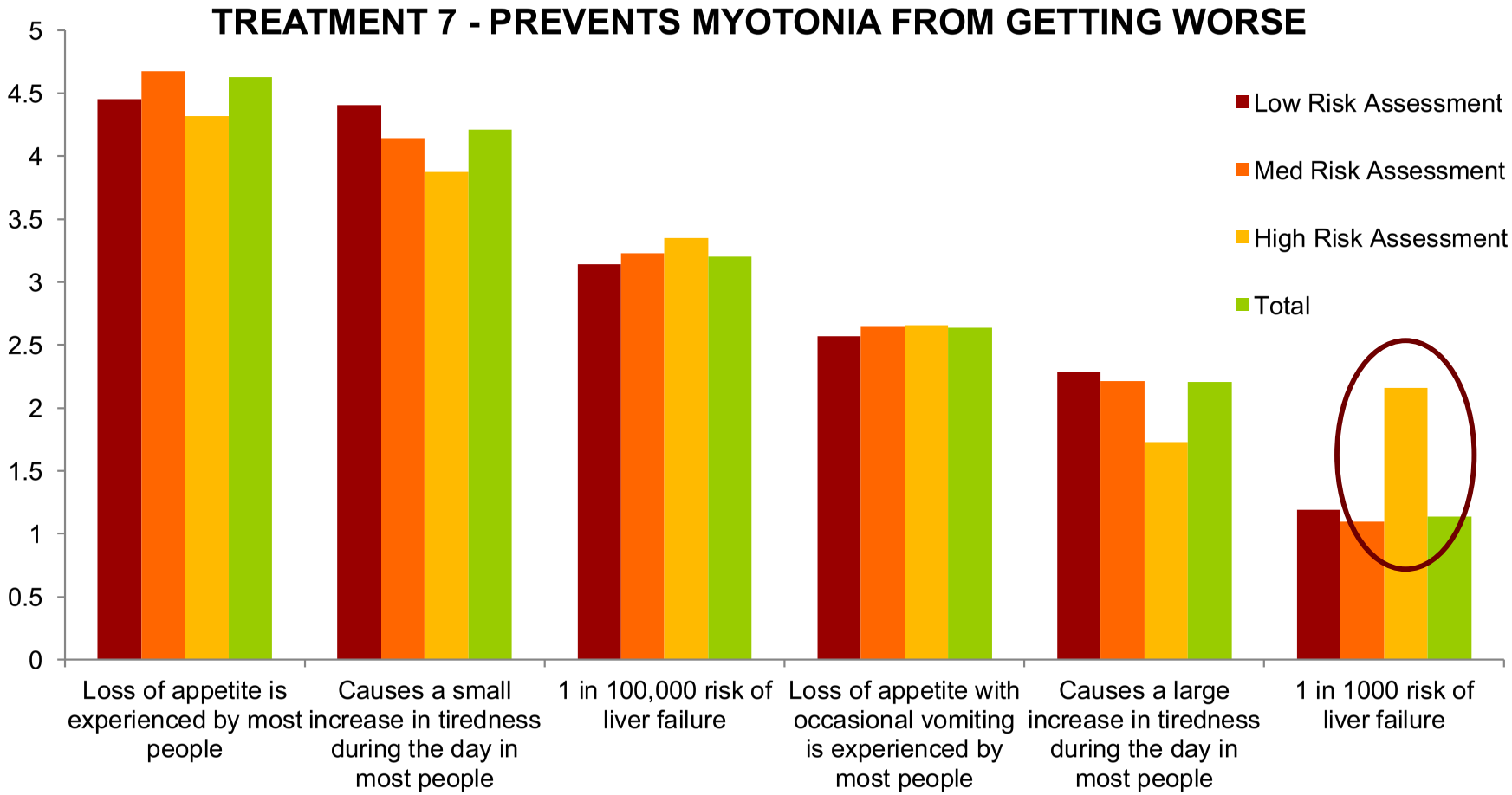
Impact of Risk Taking Profile: Treatment 7



n=267

Low Risk Assessment	**4.4551**	**4.4024**	**3.1437**	**2.5663**	**2.2849**	**1.193**
Med Risk Assessment	**4.6748**	**4.1441**	**3.2308**	**2.6441**	**2.215**	**1.0959**
High Risk Assessment	**4.32**	**3.875**	**3.3462**	**2.6538**	**1.7308**	**2.16**
Total	**4.6283**	**4.2114**	**3.2002**	**2.633**	**2.2081**	**1.133**

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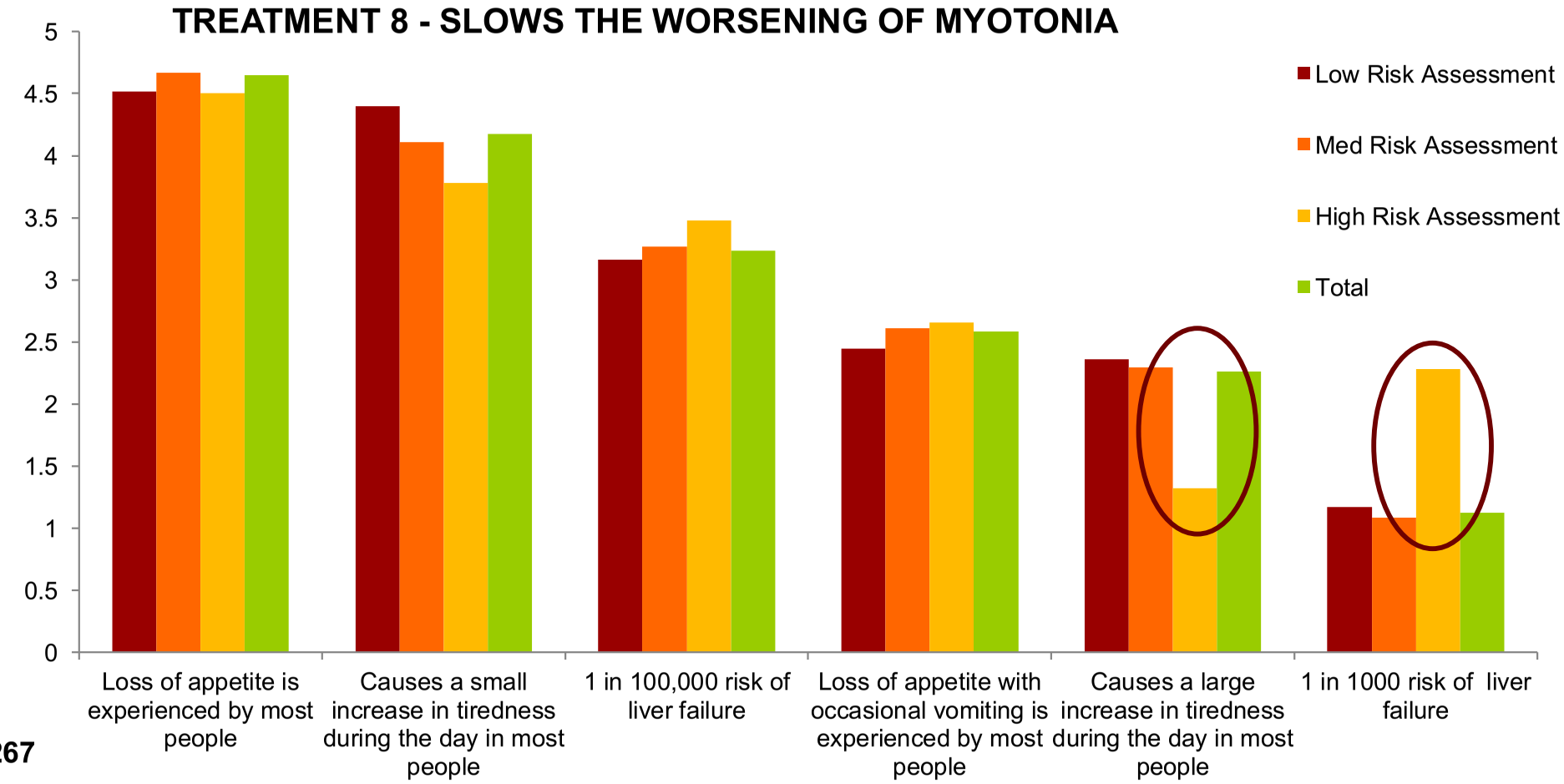
Impact of Risk Taking Profile: Treatment 8



n=267

Low Risk Assessment	**4.5176**	**4.4**	**3.1617**	**2.4483**	**2.3598**	**1.1686**
Med Risk Assessment	**4.6672**	**4.1103**	**3.2662**	**2.6071**	**2.2947**	**1.0816**
High Risk Assessment	**4.5**	**3.7778**	**3.48**	**2.6538**	**1.32**	**2.28**
Total	**4.6502**	**4.177**	**3.2354**	**2.5838**	**2.2585**	**1.1221**

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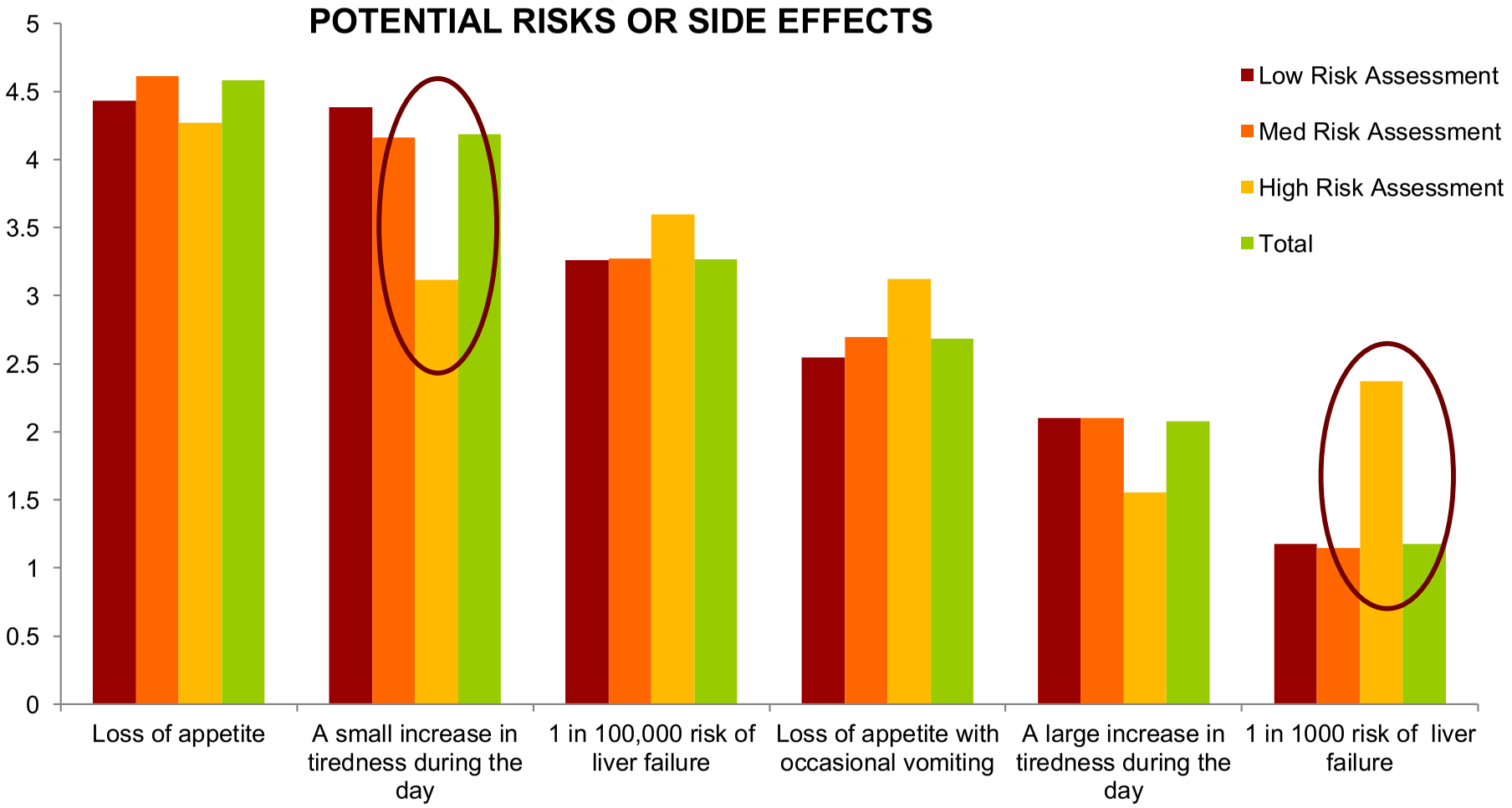
Impact of Risk Taking Profile: POTENTIAL RISKS OR SIDE EFFECTS



n=267

Low Risk Assessment	4.4326	4.3818	3.2632	2.5455	2.1018	1.1747
Med Risk Assessment	4.613	4.1639	3.2723	2.6973	2.1032	1.1476
High Risk Assessment	4.2692	3.1154	3.6	3.125	1.5556	2.375
Total	4.5816	4.1838	3.27	2.6853	2.08	1.177

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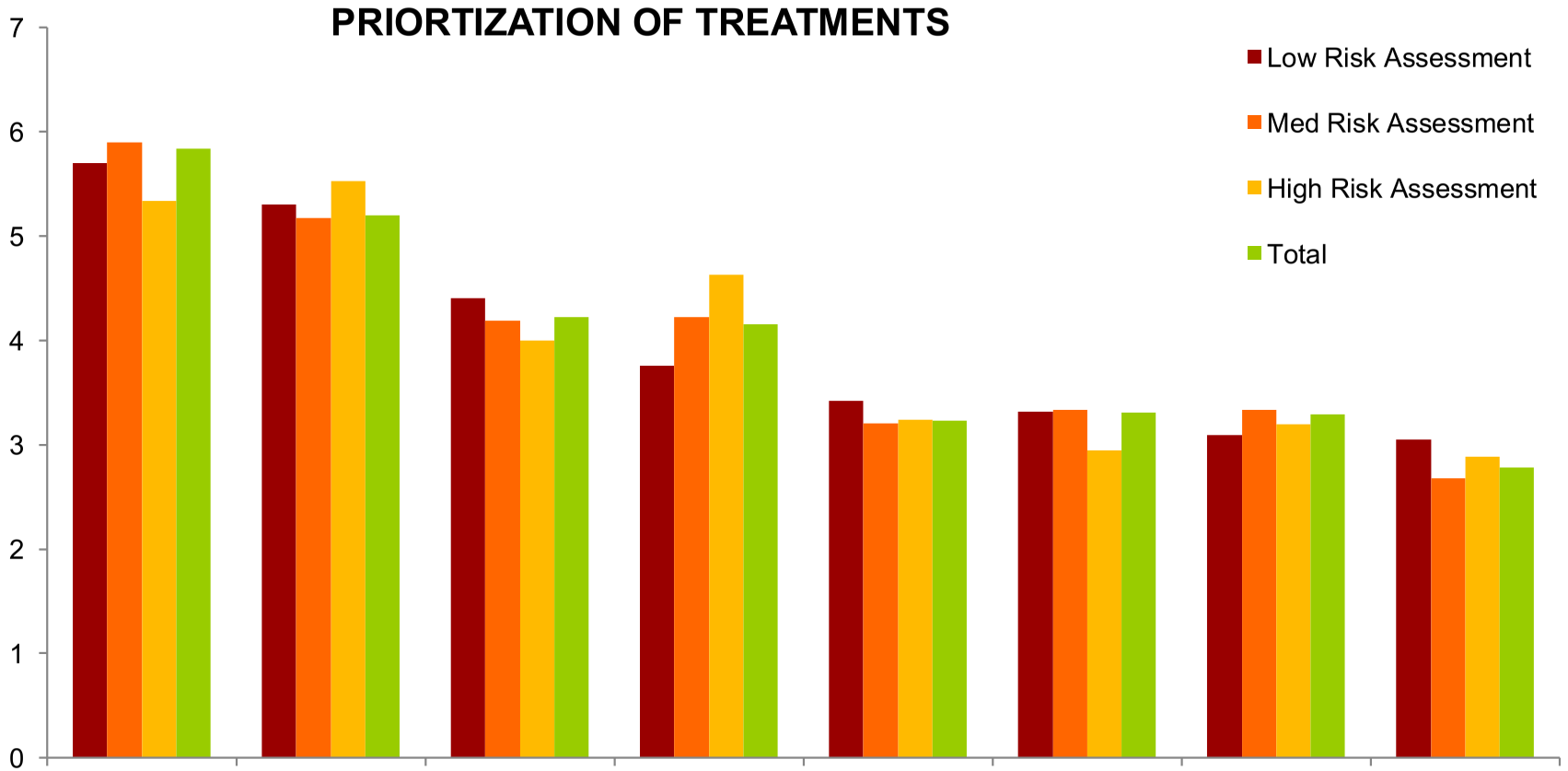
Impact of Risk Taking Profile: PRIORTIZATION OF TREATMENTS



n=267

Low Risk Assessment	**5.7008**	**5.3008**	**4.4063**	**3.7538**	**3.4194**	**3.3178**	**3.0968**	**3.0534**
Med Risk Assessment	**5.896**	**5.1765**	**4.1924**	**4.2276**	**3.2016**	**3.3307**	**3.332**	**2.6774**
High Risk Assessment	**5.3333**	**5.5238**	**4**	**4.6316**	**3.2381**	**2.9474**	**3.2**	**2.8889**
Total	**5.8361**	**5.1976**	**4.2232**	**4.1576**	**3.2296**	**3.3049**	**3.2952**	**2.7808**

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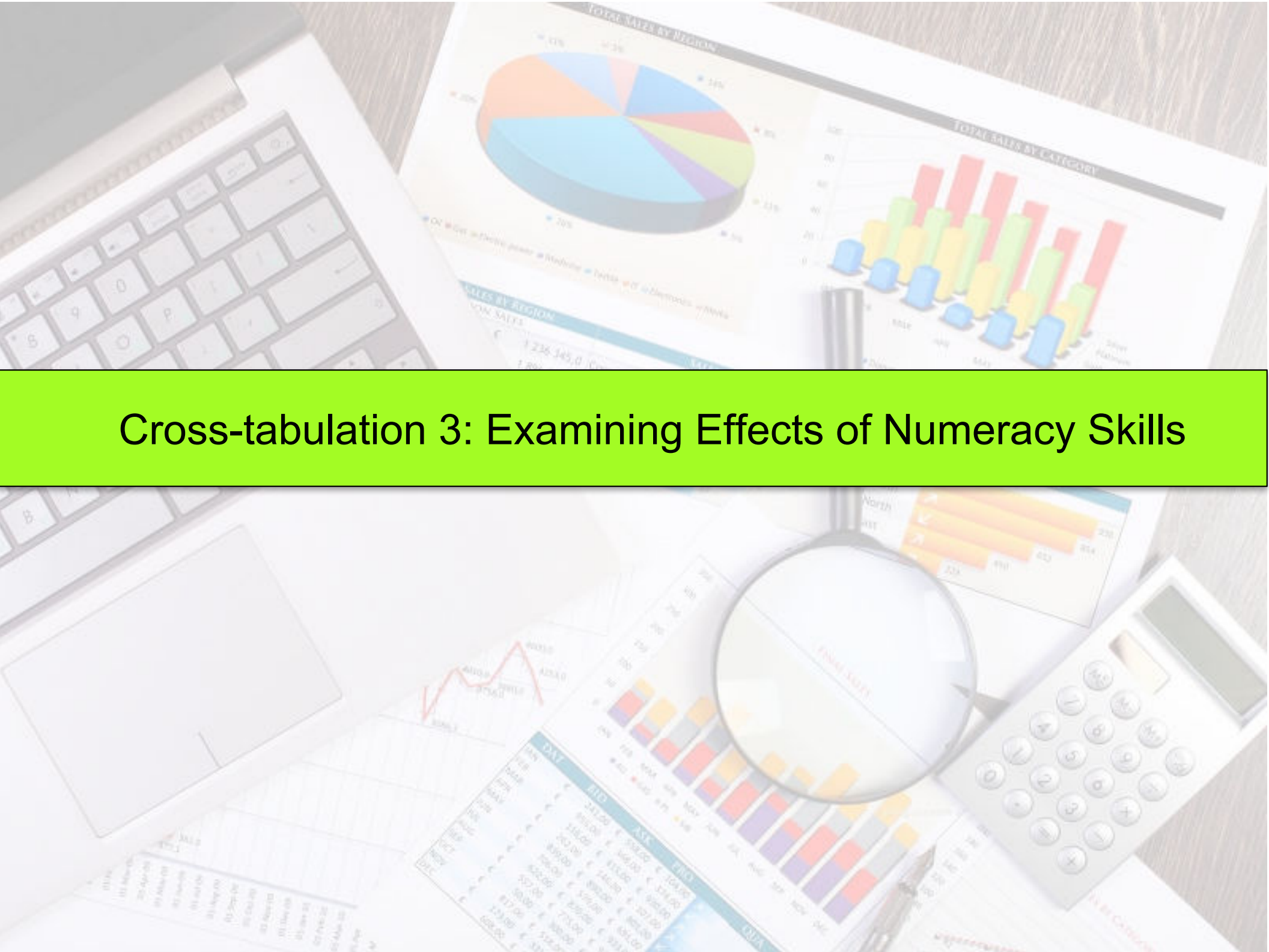
Key Takeaways

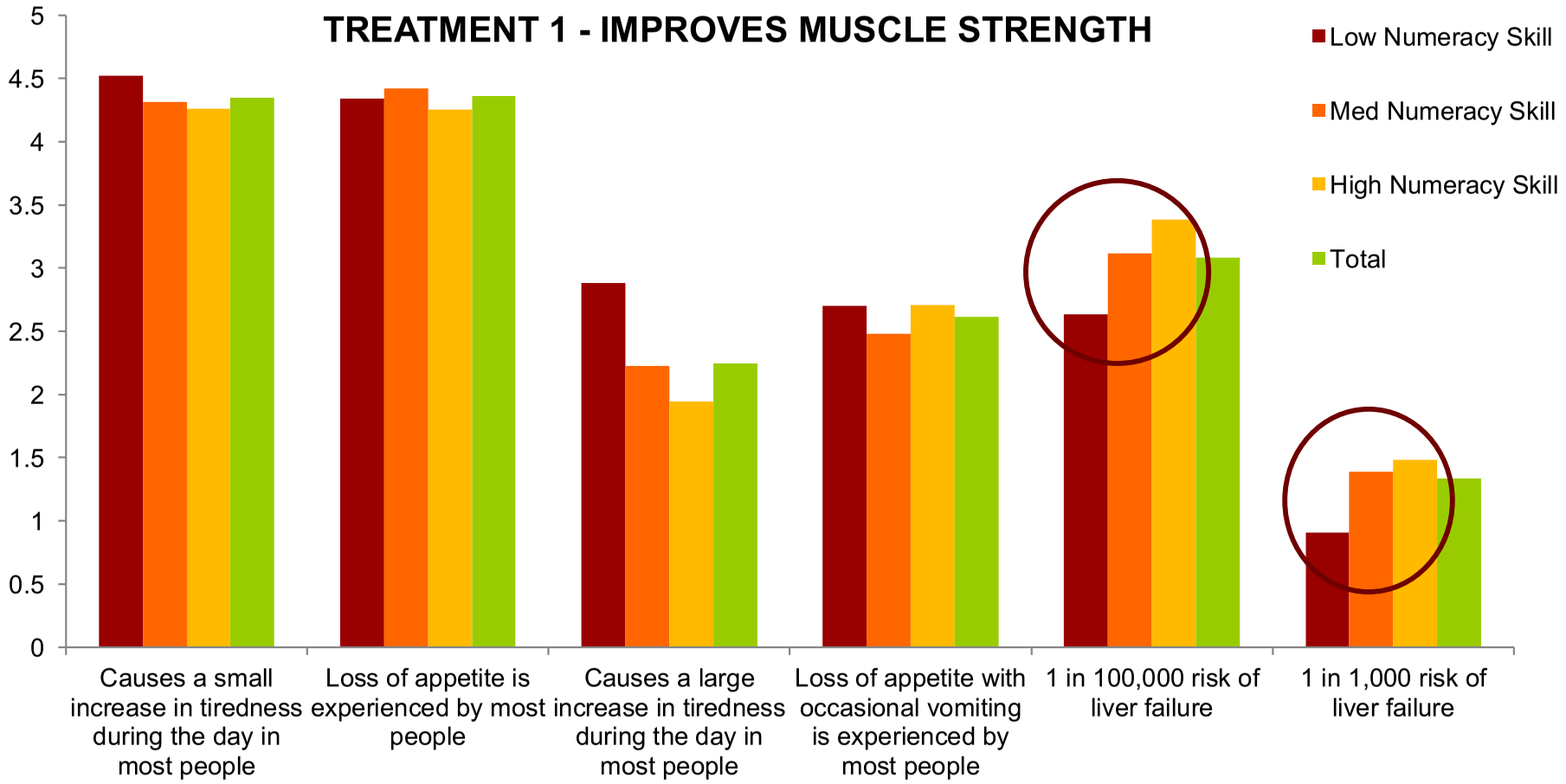
- DM1 sufferers who were more risk tolerant(self-rated) were much more tolerant than average of risk of liver failure

- Risk tolerant DM1 sufferers were conversely less likely to tolerate daytime tiredness, perhaps indicating a lower willingness to have their lifestyles curtailed



Cross-tabulation 3: Examining Effects of Numeracy Skills

Impact of Numeracy Skill: Treatment 1



n=267

Low Numeracy Skill	**4.5254**	**4.3448**	**2.8814**	**2.7**	**2.6313**	**0.9086**
Med Numeracy Skill	**4.3176**	**4.4239**	**2.2248**	**2.482**	**3.1169**	**1.3899**
High Numeracy Skill	**4.259**	**4.257**	**1.9448**	**2.7061**	**3.3828**	**1.4801**
Total	**4.349**	**4.3587**	**2.2483**	**2.6156**	**3.0815**	**1.3385**

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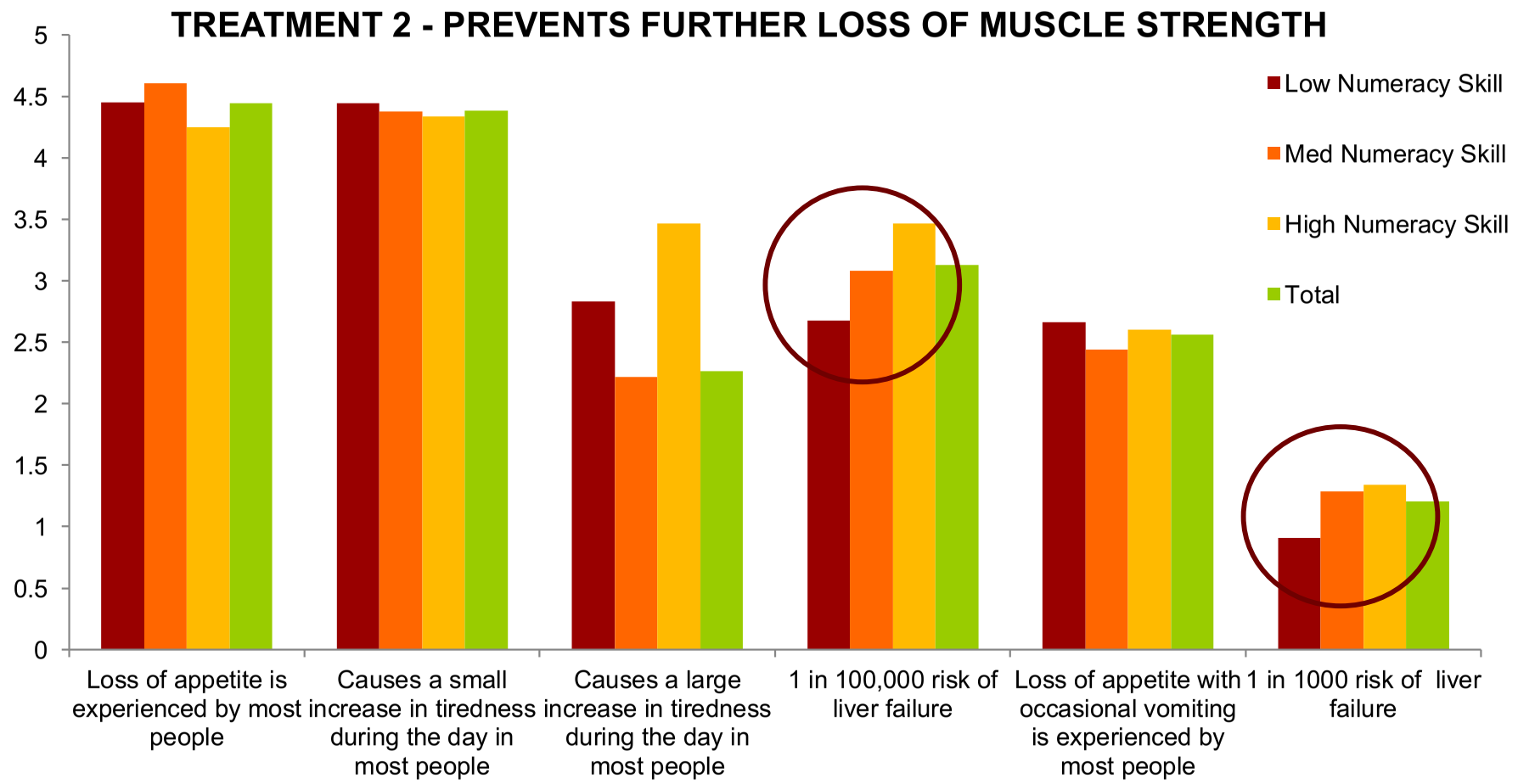
Impact of Numeracy Skill: Treatment 2



n=267

Low Numeracy Skill	**4.4483**	**4.4407**	**2.8295**	**2.6761**	**2.661**	**0.907**
Med Numeracy Skill	**4.605**	**4.3743**	**2.2203**	**3.0787**	**2.4403**	**1.2846**
High Numeracy Skill	**4.2491**	**4.3344**	**3.4631**	**3.4631**	**2.6047**	**1.3389**
Total	**4.4464**	**4.3854**	**2.2659**	**3.1291**	**2.5605**	**1.2027**

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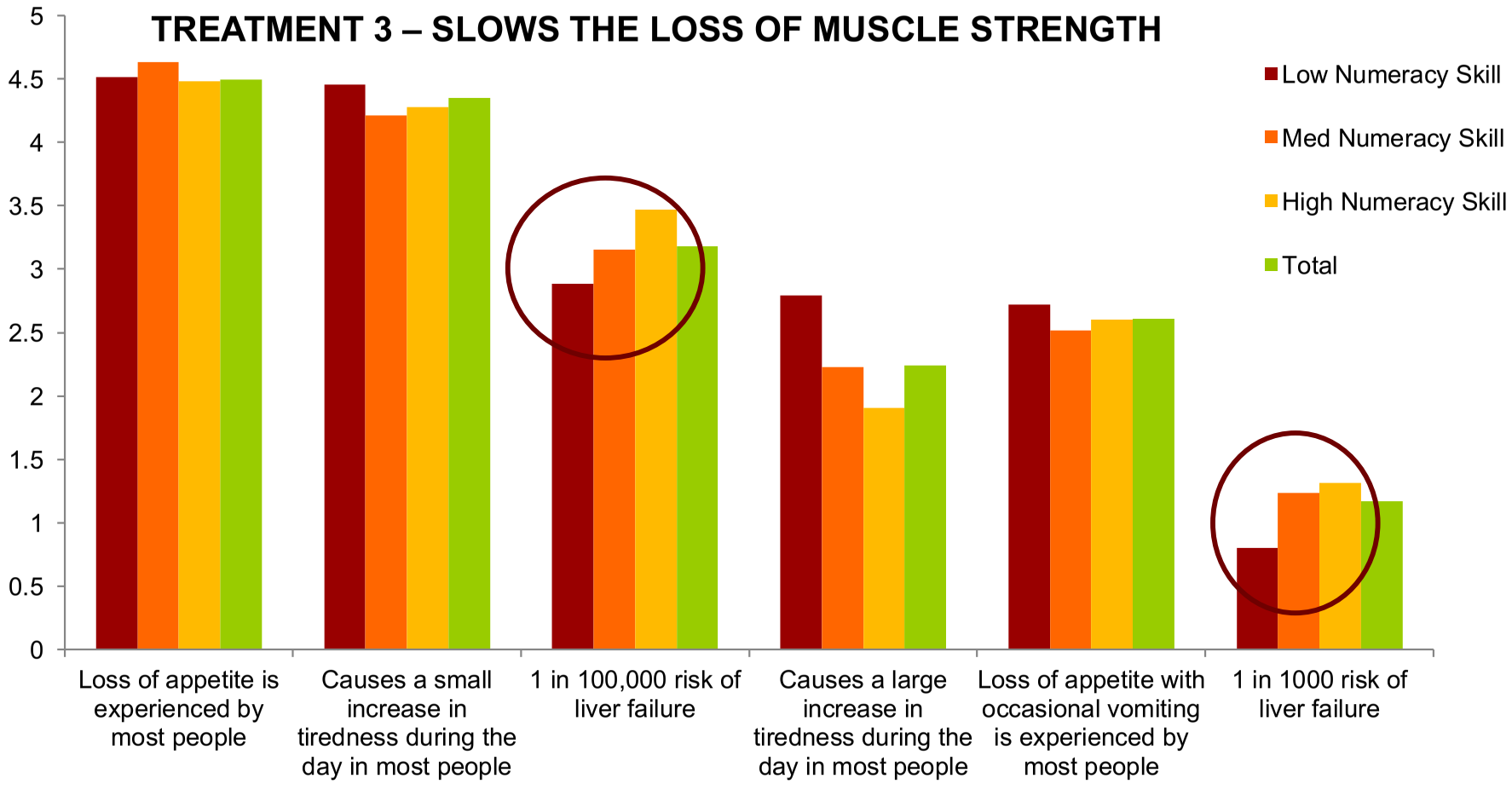
Impact of Numeracy Skill : Treatment 3



n=267

Low Numeracy Skill	**4.5176**	**4.4561**	**2.882**	**2.7943**	**2.7176**	**0.8033**
Med Numeracy Skill	**4.6357**	**4.2141**	**3.1571**	**2.2288**	**2.5154**	**1.2353**
High Numeracy Skill	**4.4795**	**4.277**	**3.4704**	**1.9054**	**2.5987**	**1.3131**
Total	**4.4933**	**4.3527**	**3.1816**	**2.2373**	**2.6061**	**1.1707**

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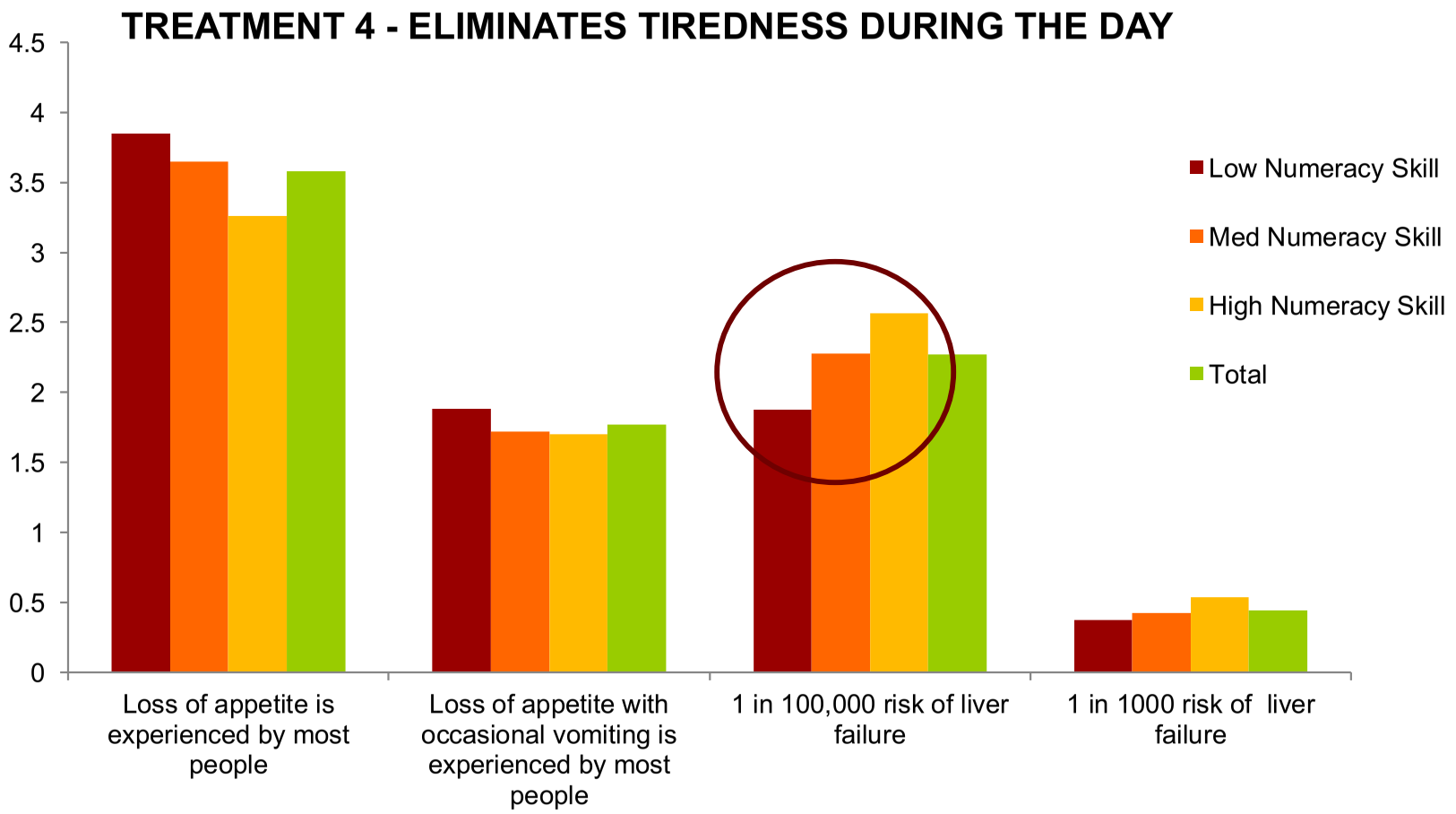
Impact of Numeracy Skill : Treatment 4



n=267

Low Numeracy Skill	**3.8462**	**1.8831**	**1.8792**	**0.3742**
Med Numeracy Skill	**3.6488**	**1.7229**	**2.2746**	**0.4261**
High Numeracy Skill	**3.2578**	**1.6996**	**2.5681**	**0.5373**
Total	**3.5768**	**1.7687**	**2.2686**	**0.4428**

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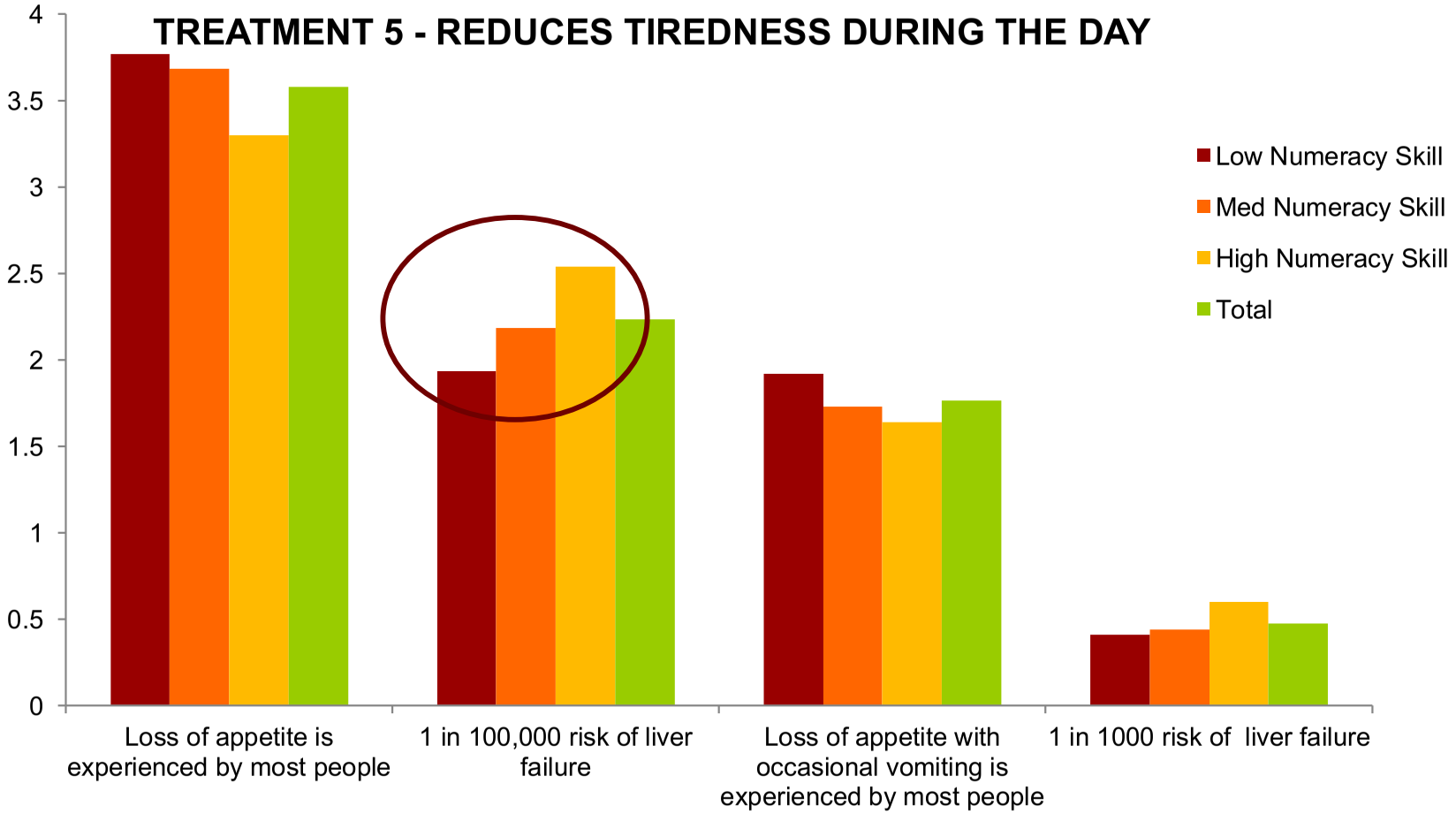
Impact of Numeracy Skill : Treatment 5



n=267

Low Numeracy Skill	**3.7662**	**1.9351**	**1.9195**	**0.4076**
Med Numeracy Skill	**3.6814**	**2.1834**	**1.7299**	**0.4393**
High Numeracy Skill	**3.296**	**2.5405**	**1.6398**	**0.5985**
Total	**3.5796**	**2.2335**	**1.7621**	**0.4747**

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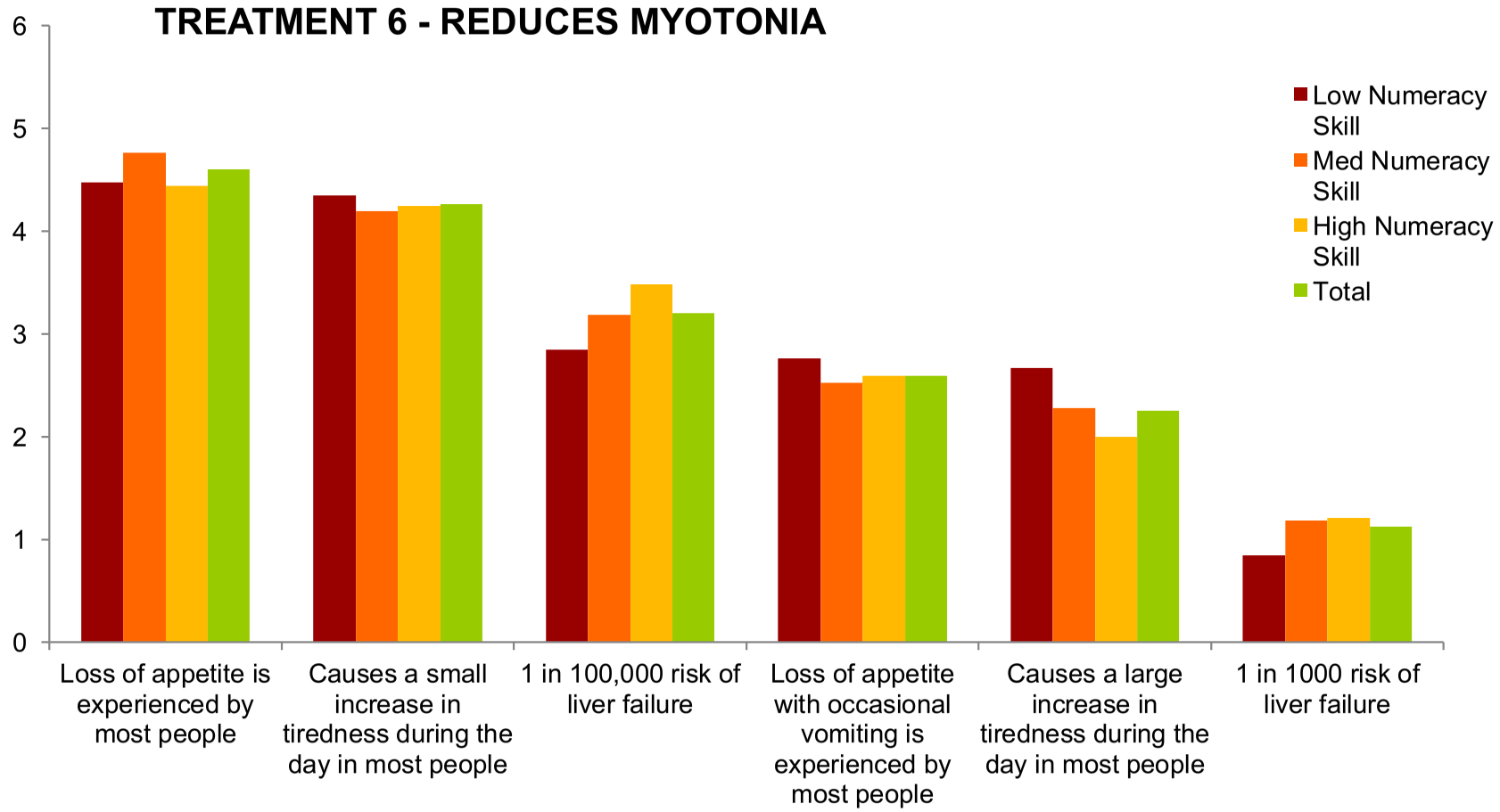
Impact of Numeracy Skill : Treatment 6



Low Numeracy Skill	**4.4746**	**4.3466**	**2.8439**	**2.7614**	**2.6648**	**0.8421**
Med Numeracy Skill	**4.7656**	**4.1938**	**3.1846**	**2.5243**	**2.2769**	**1.1854**
High Numeracy Skill	**4.4392**	**4.2424**	**3.4832**	**2.5872**	**1.9966**	**1.2082**
Total	**4.5998**	**4.2649**	**3.202**	**2.5915**	**2.2534**	**1.1262**

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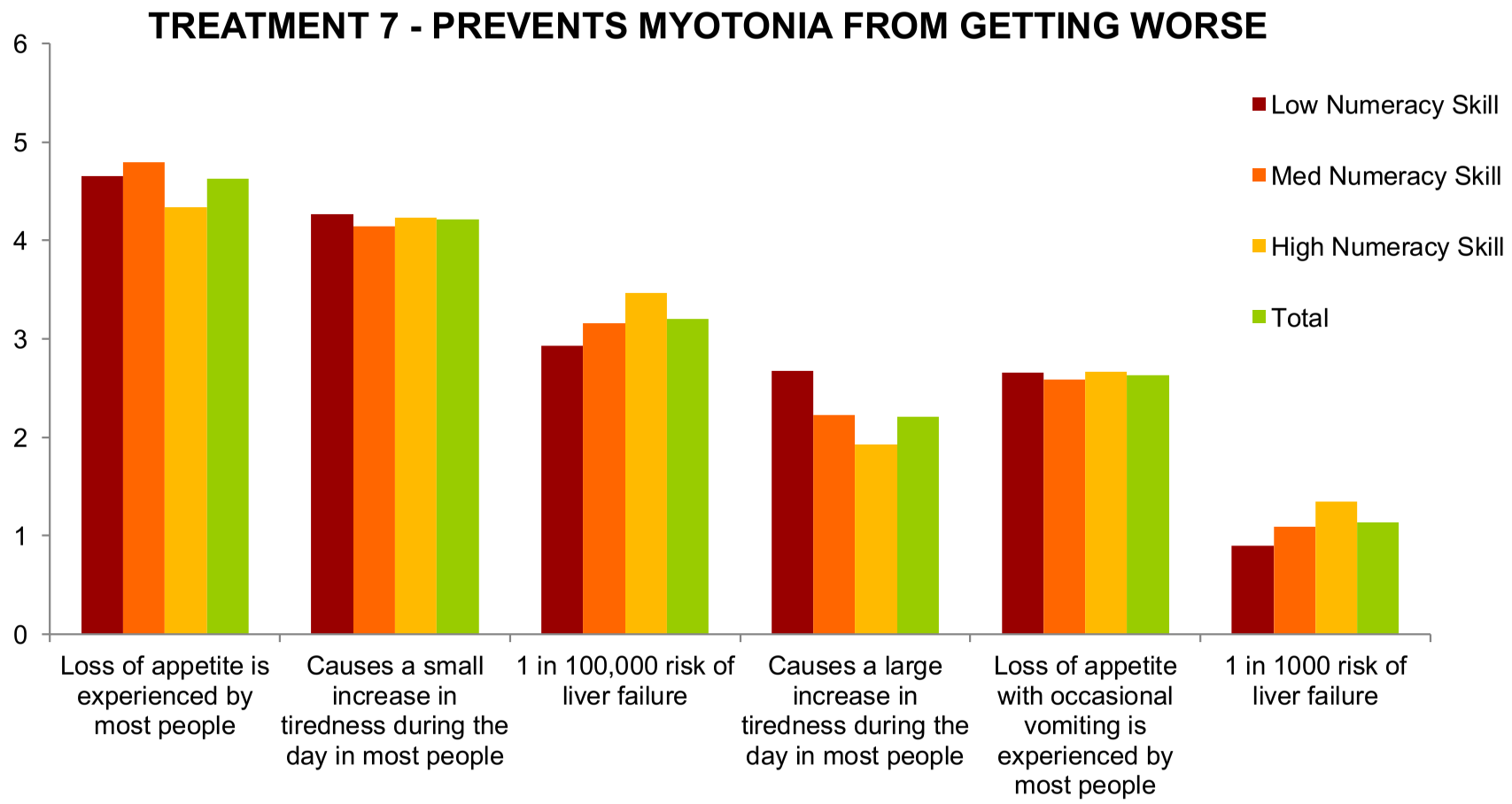
Impact of Numeracy Skill : Treatment 7



n=267

Low Numeracy Skill	**4.657**	**4.2632**	**2.9333**	**2.6743**	**2.661**	**0.8983**
Med Numeracy Skill	**4.7969**	**4.1414**	**3.1583**	**2.229**	**2.5888**	**1.0951**
High Numeracy Skill	**4.338**	**4.2277**	**3.4694**	**1.9293**	**2.669**	**1.3505**
Total	**4.6283**	**4.2114**	**3.2002**	**2.2081**	**2.633**	**1.133**

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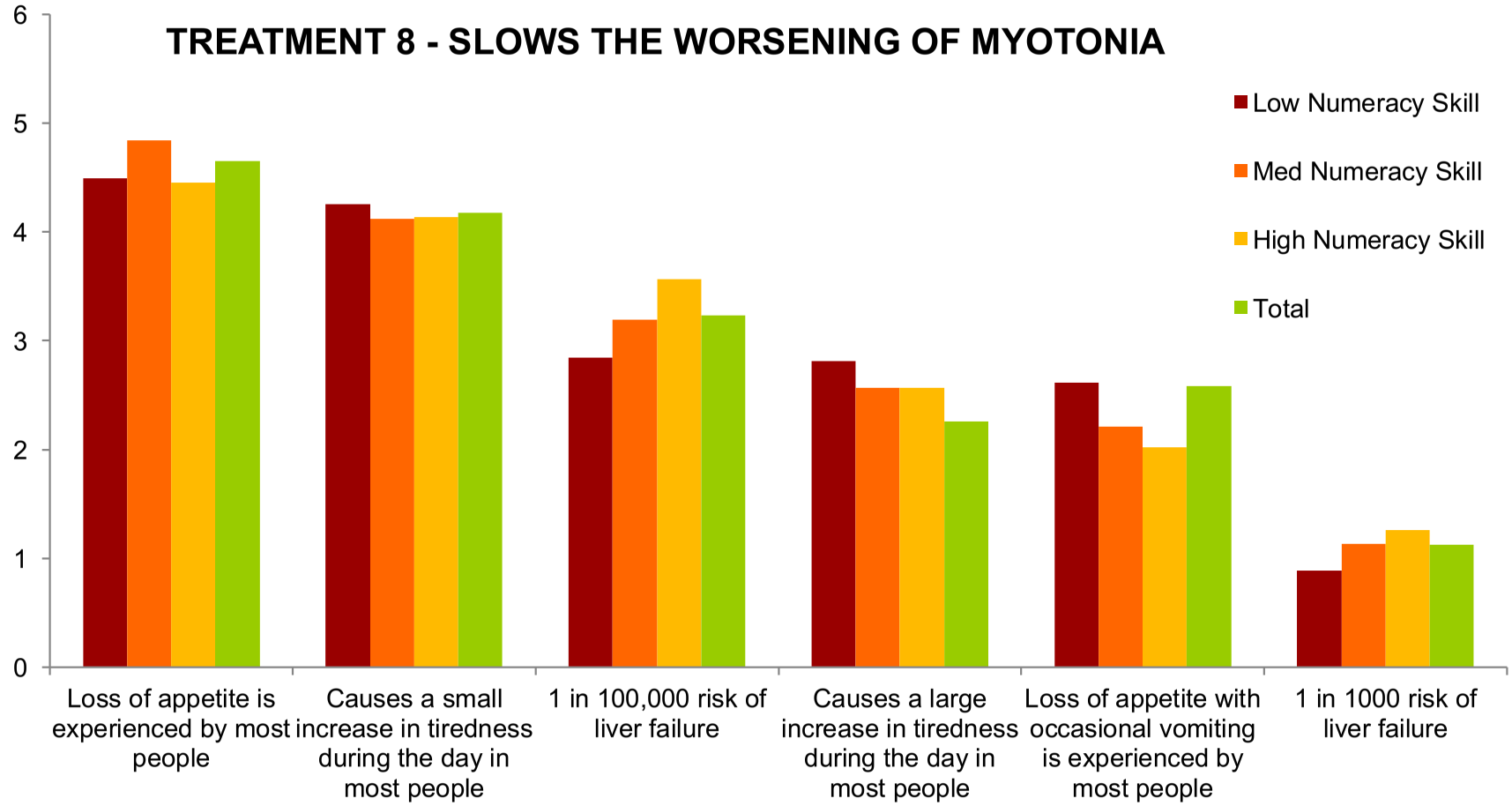
Impact of Numeracy Skill : Treatment 8



n=267

Low Numeracy Skill	**4.4918**	**4.2586**	**2.8421**	**2.8156**	**2.6163**	**0.8844**
Med Numeracy Skill	**4.8402**	**4.1201**	**3.197**	**2.5704**	**2.215**	**1.1372**
High Numeracy Skill	**4.4536**	**4.14**	**3.5631**	**2.5672**	**2.0247**	**1.26**
Total	**4.6502**	**4.177**	**3.2354**	**2.2585**	**2.5838**	**1.1221**

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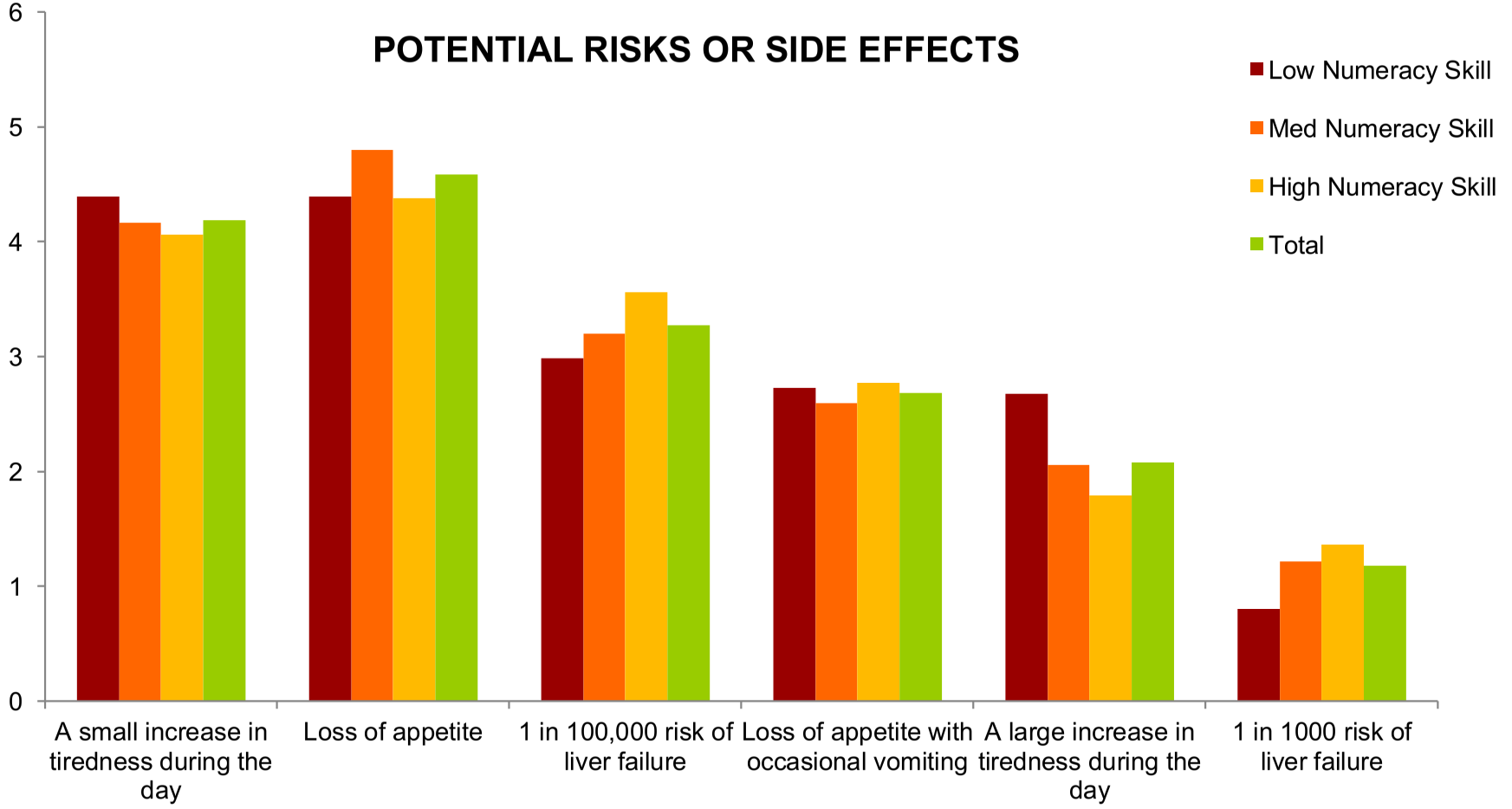
Impact of Numeracy Skill : POTENTIAL RISKS OR SIDE EFFECTS



Low Numeracy Skill	**4.3898**	**4.3898**	**2.9831**	**2.7273**	**2.6786**	**0.8011**
Med Numeracy Skill	**4.1623**	**4.8**	**3.2016**	**2.5944**	**2.0574**	**1.2154**
High Numeracy Skill	**4.06**	**4.3746**	**3.5593**	**2.7692**	**1.7875**	**1.3664**
Total	**4.1838**	**4.5816**	**3.27**	**2.6853**	**2.08**	**1.177**

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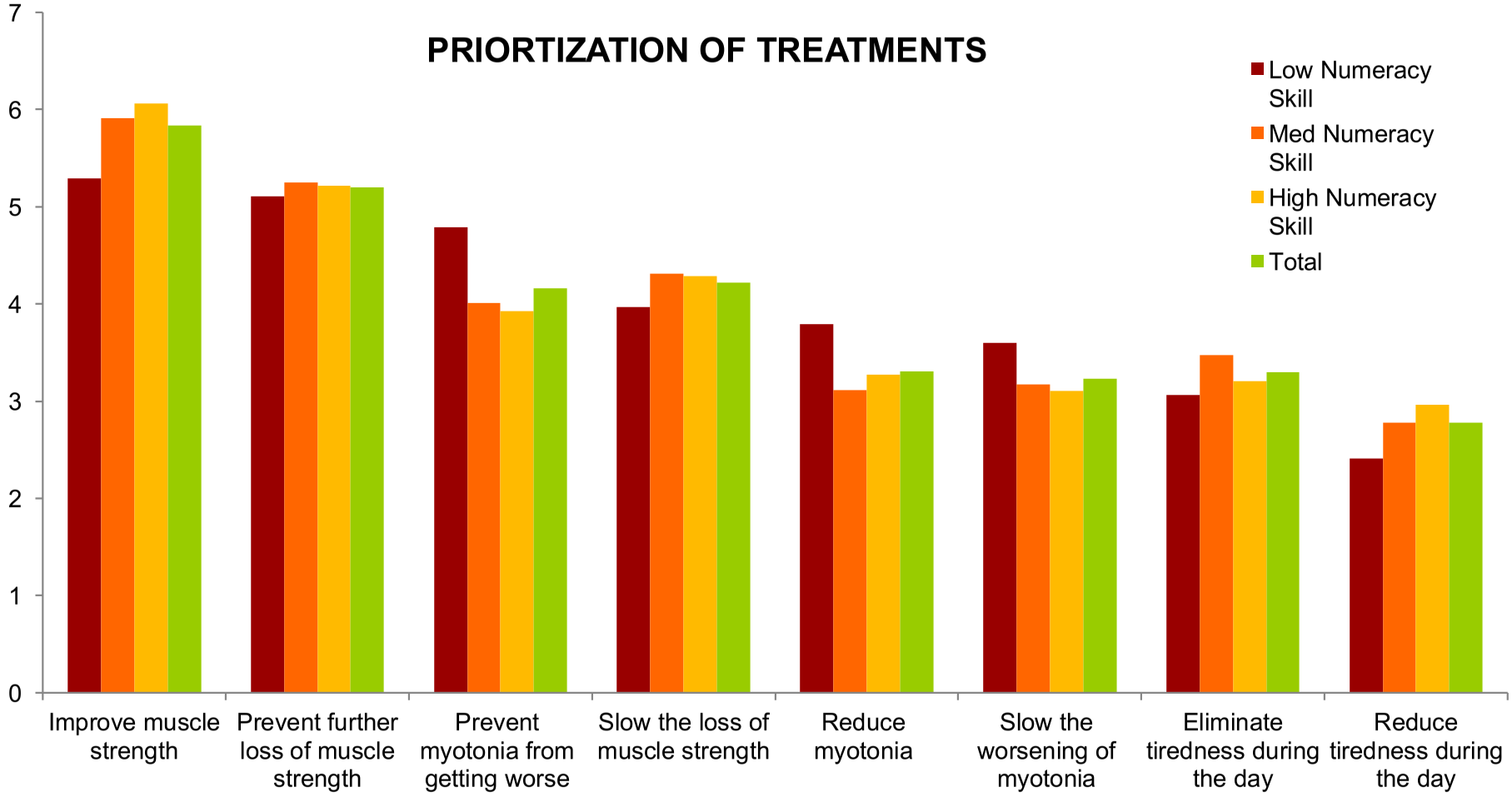
Impact of Numeracy Skill : PRIORTIZATION OF TREATMENTS



Low Numeracy Skill	**5.2932**	**5.1077**	**4.7879**	**3.9695**	**3.791**	**3.6031**	**3.0606**	**2.406**
Med Numeracy Skill	**5.9107**	**5.2475**	**4.0135**	**4.3119**	**3.1171**	**3.1701**	**3.4712**	**2.7766**
High Numeracy Skill	**6.0617**	**5.215**	**3.9256**	**4.2896**	**3.2711**	**3.1073**	**3.2074**	**2.9643**
Total	**5.8361**	**5.1976**	**4.1576**	**4.2232**	**3.3049**	**3.2296**	**3.2952**	**2.7808**

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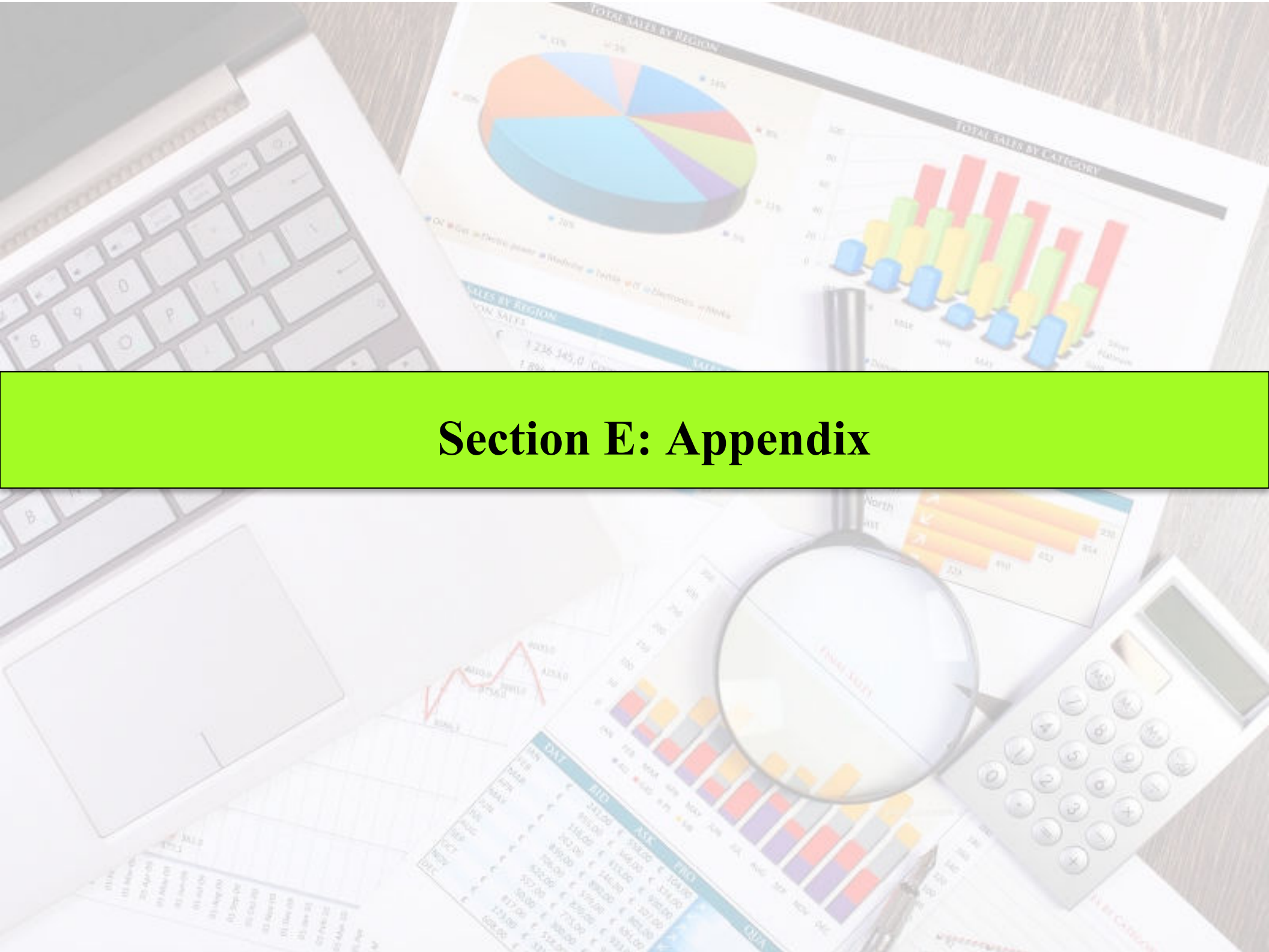
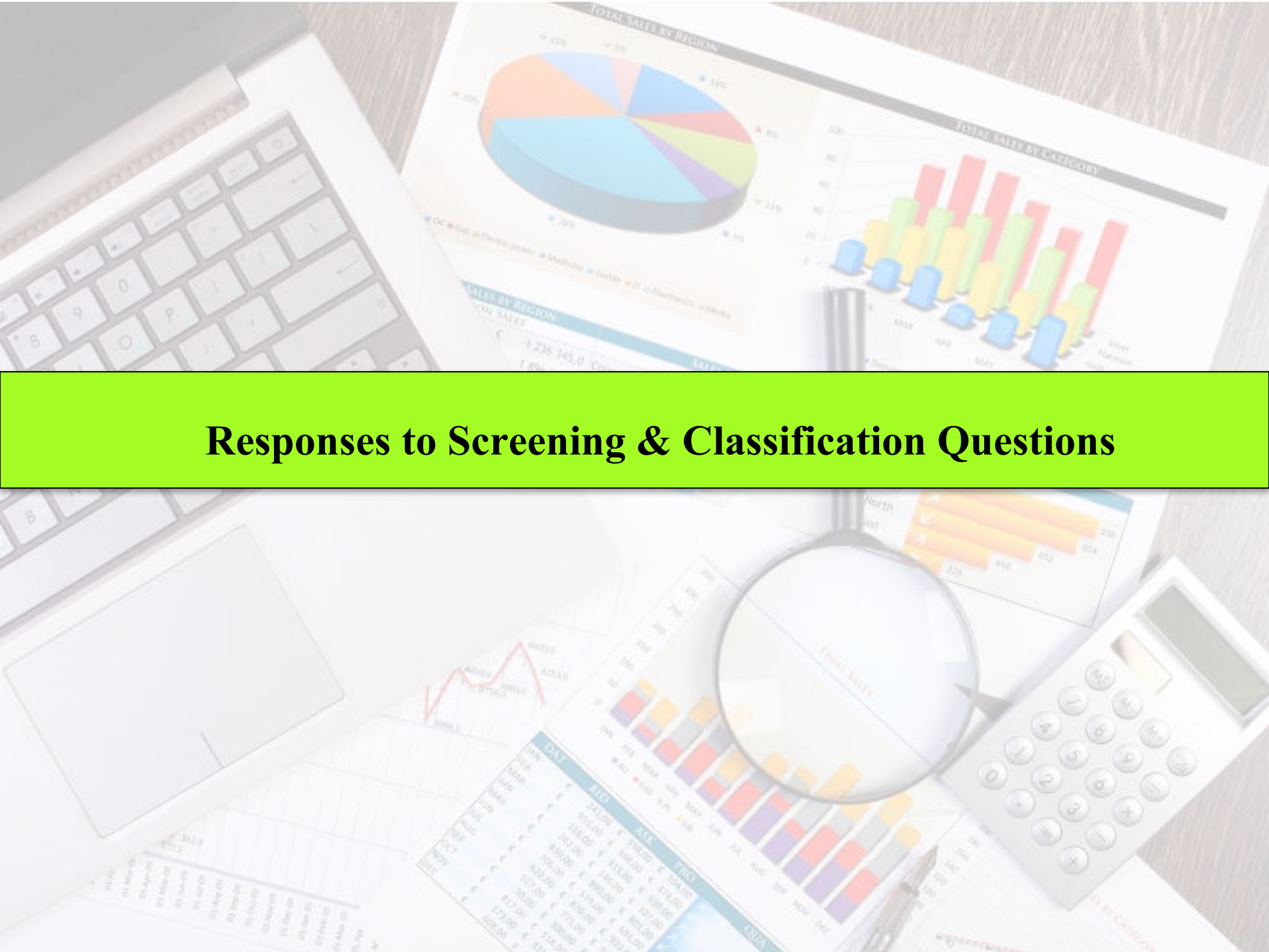
Key Takeaways

- Those who rate their numerical skills low tend to overestimate the risks of the two attributes that contained numerical expressions, namely:
  - I in 100,000 risk of liver failure, and:
  - I in 1,000 risk of liver failure

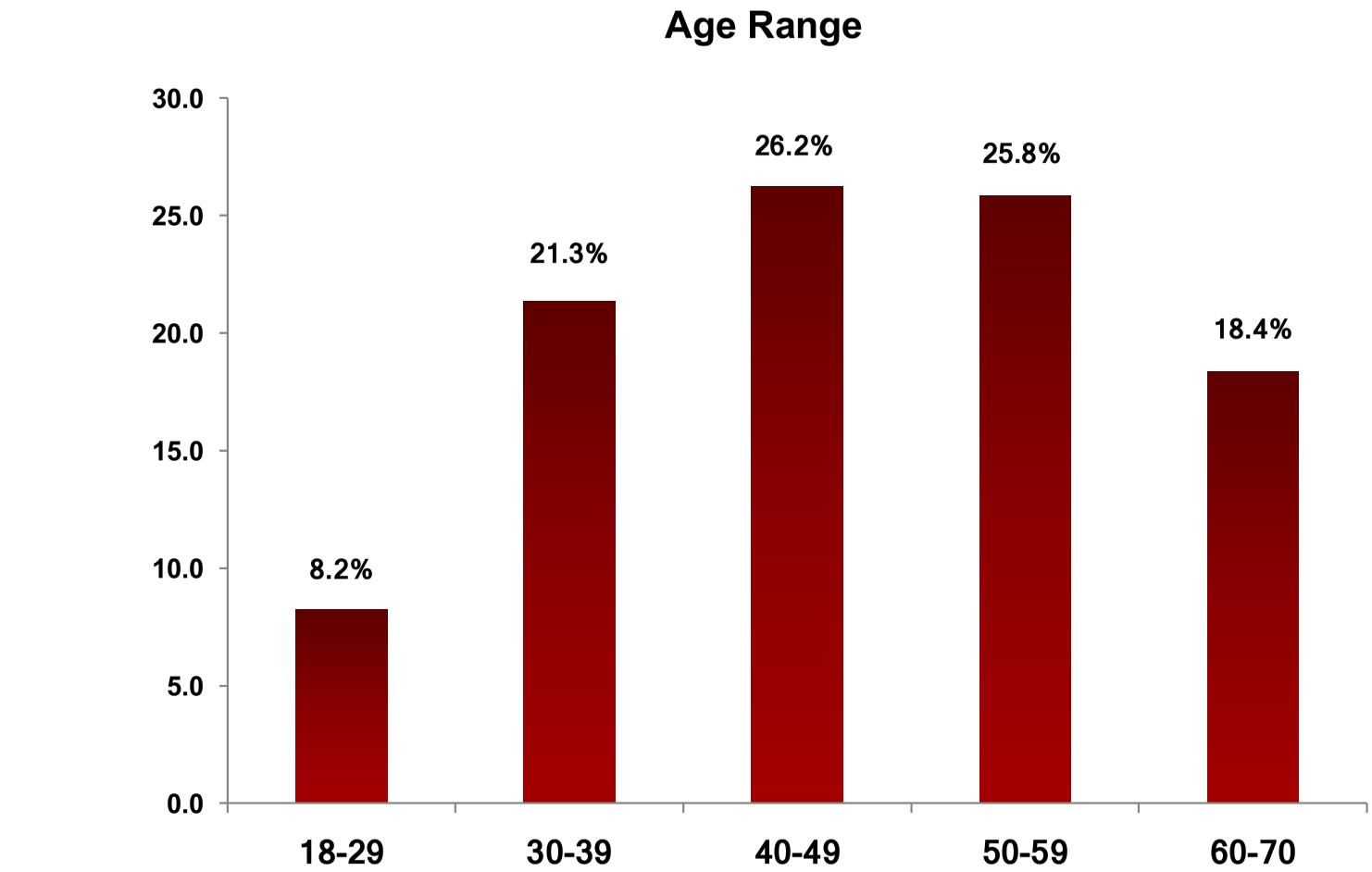


Section E: Appendix



Responses to Screening & Classification Questions

Respondent Age



n=267

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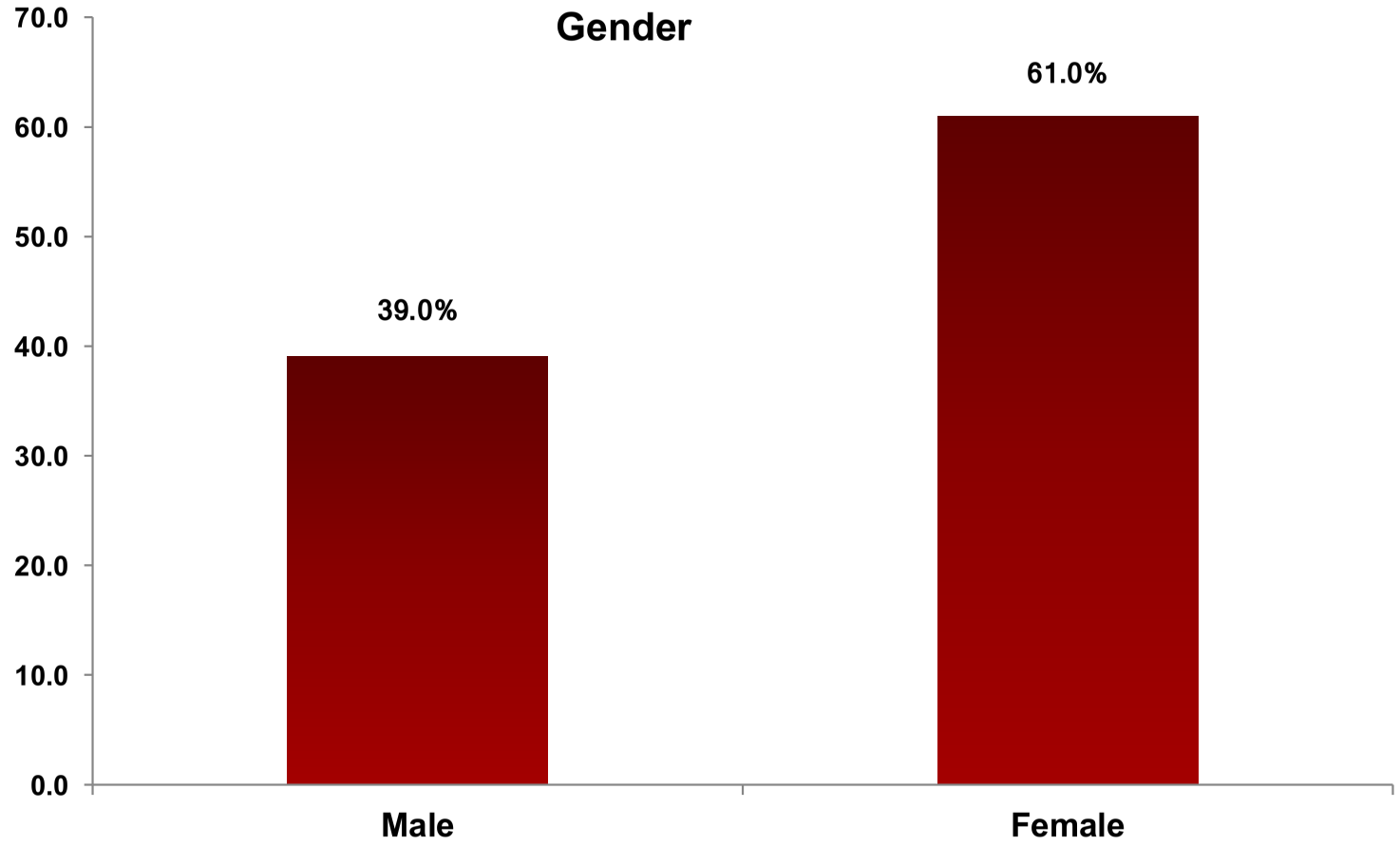
Respondent Gender



n=264

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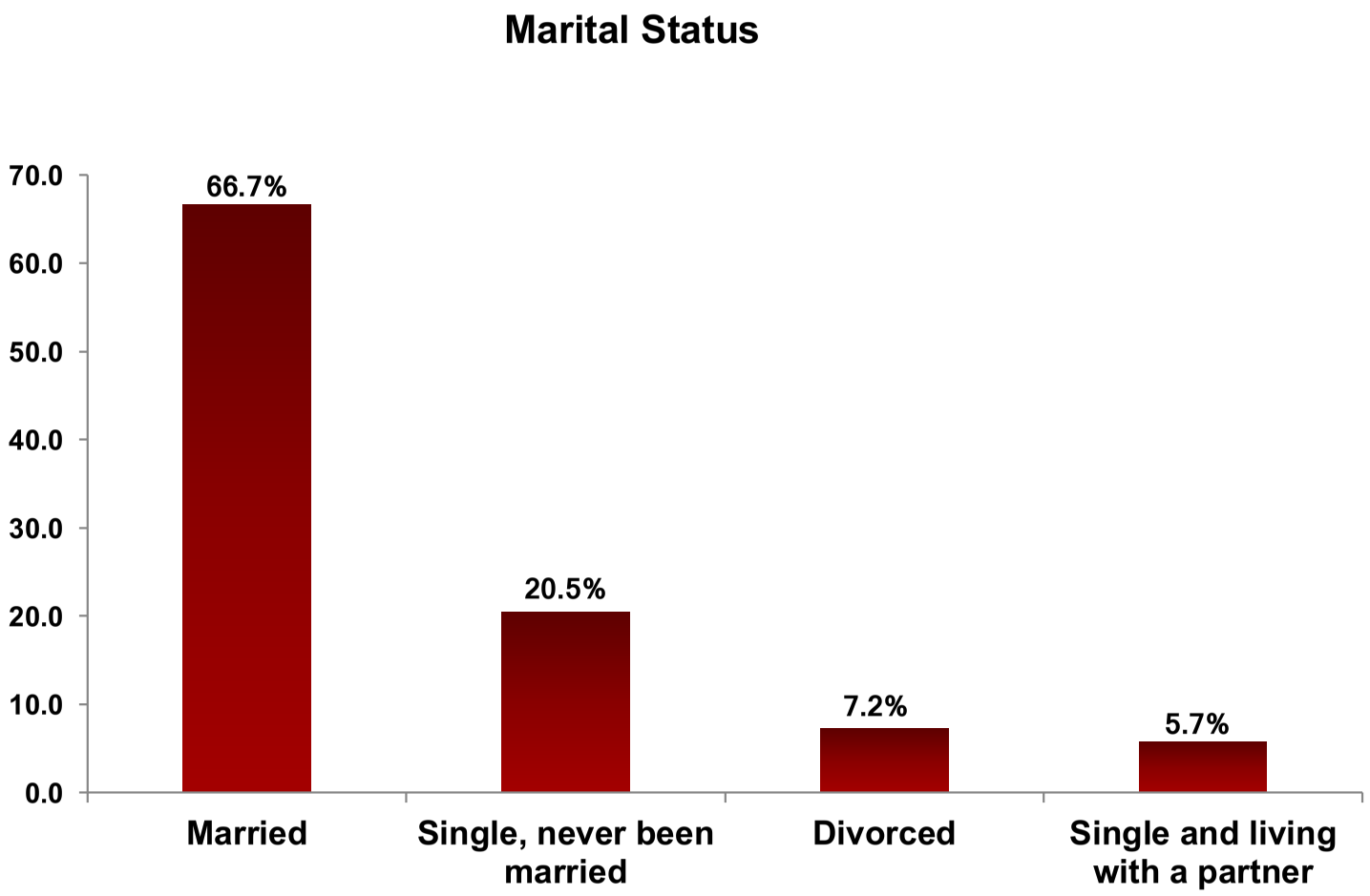
Respondent Marital Status



n=264

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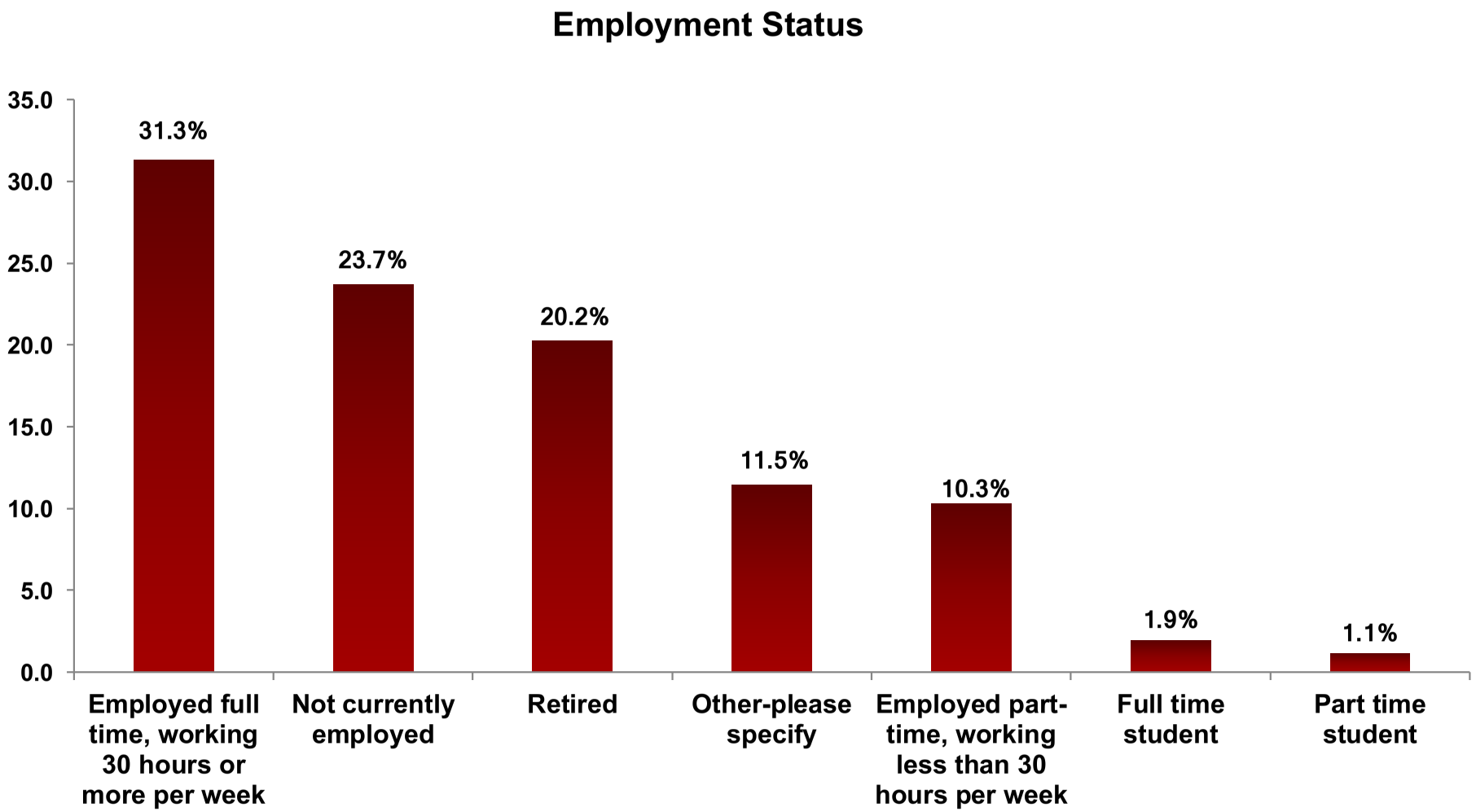
Respondent Employment Status



n=262

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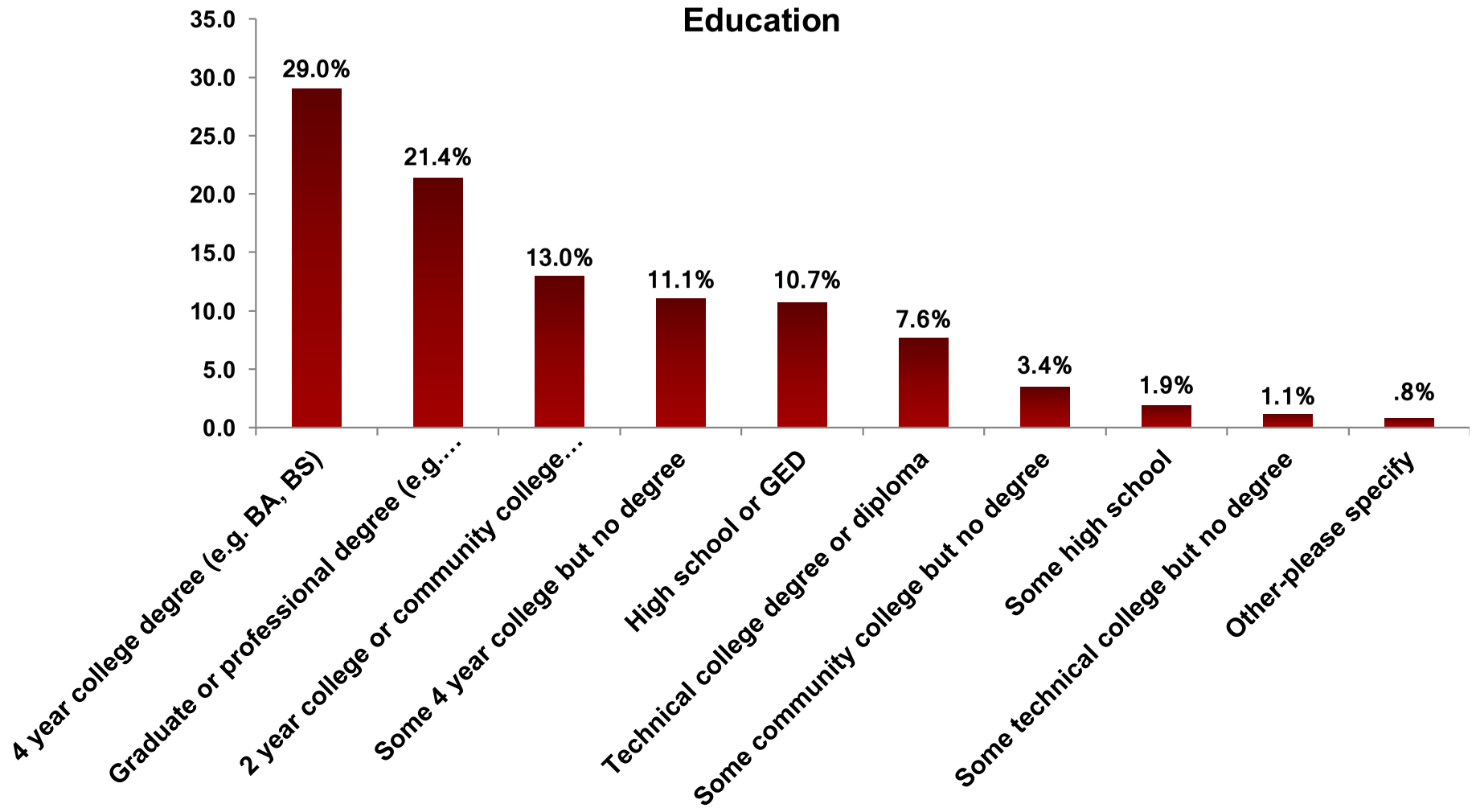
Highest Level of Education Attained by Respondent



n=262

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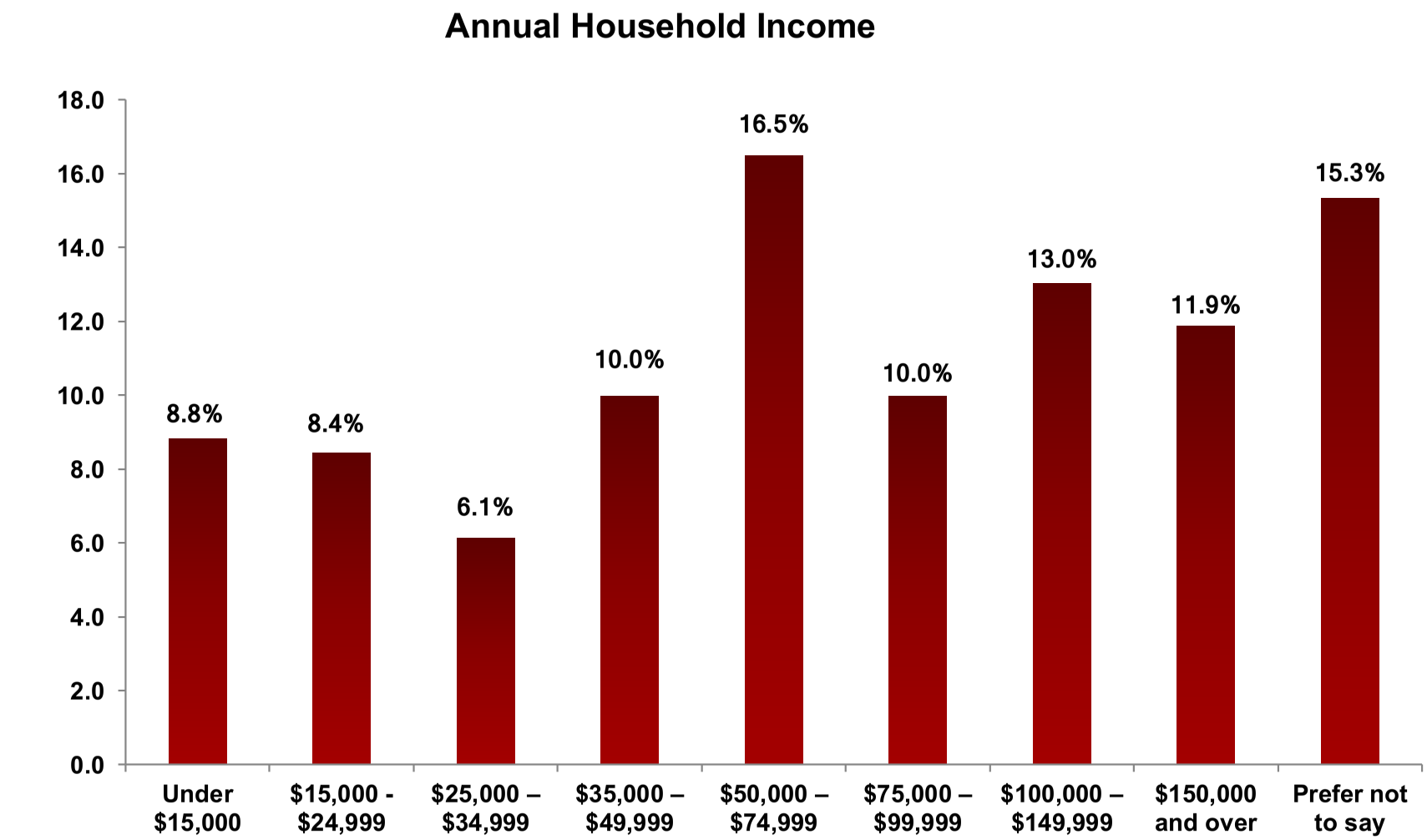
Annual Household Income of Respondents



n=261

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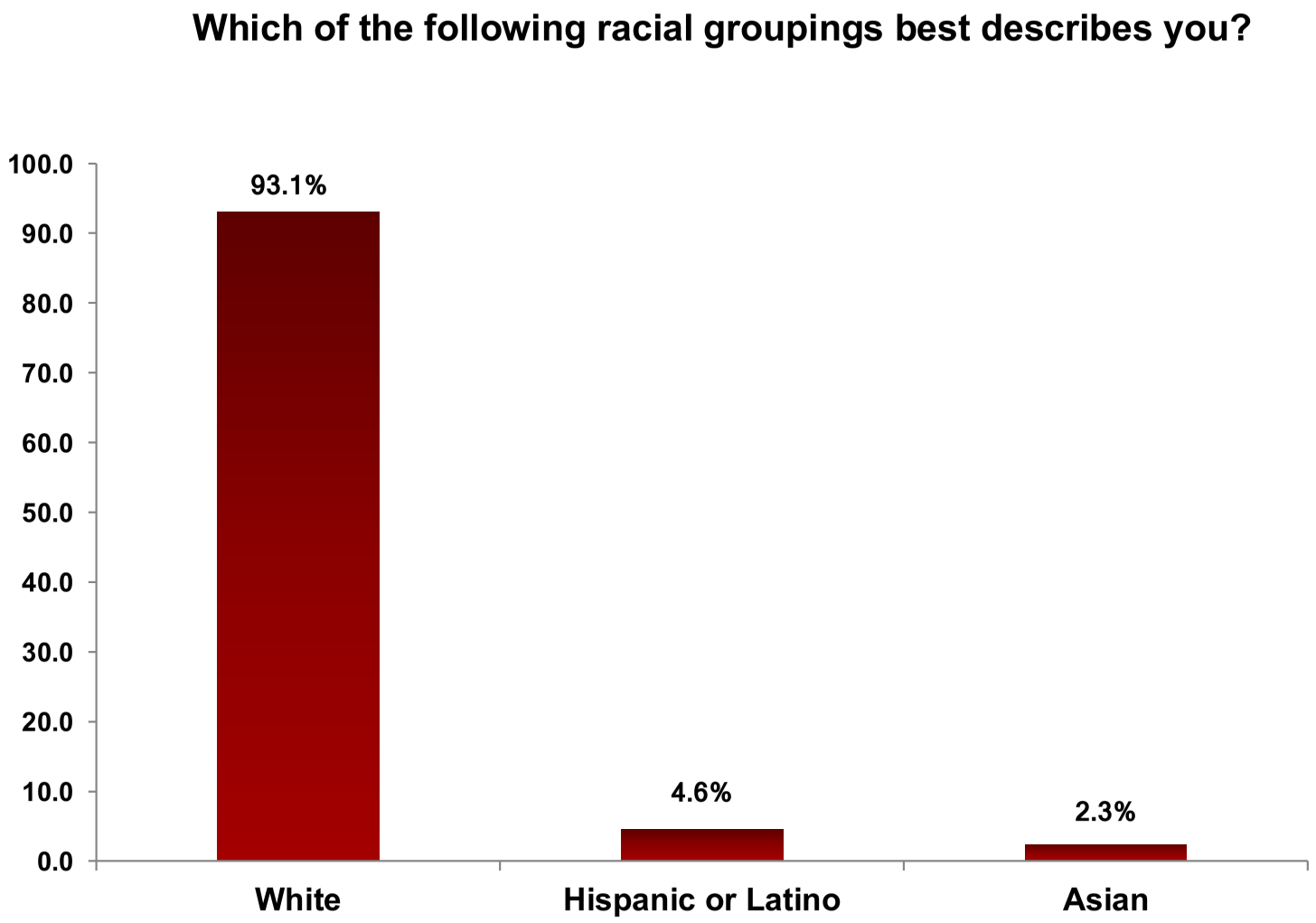
Respondent Racial Background



n=262

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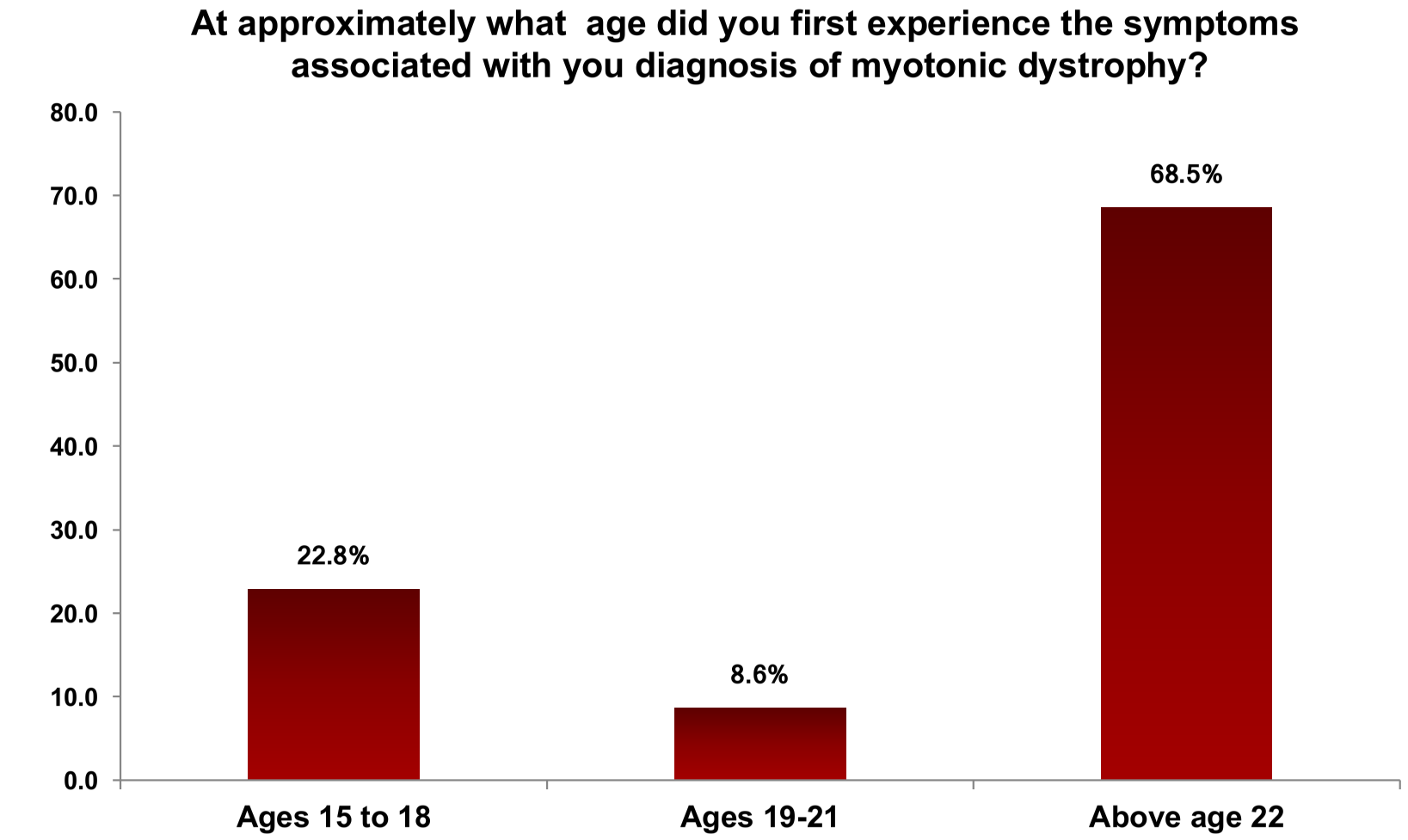
Age at Experience of First Symptoms



n=267

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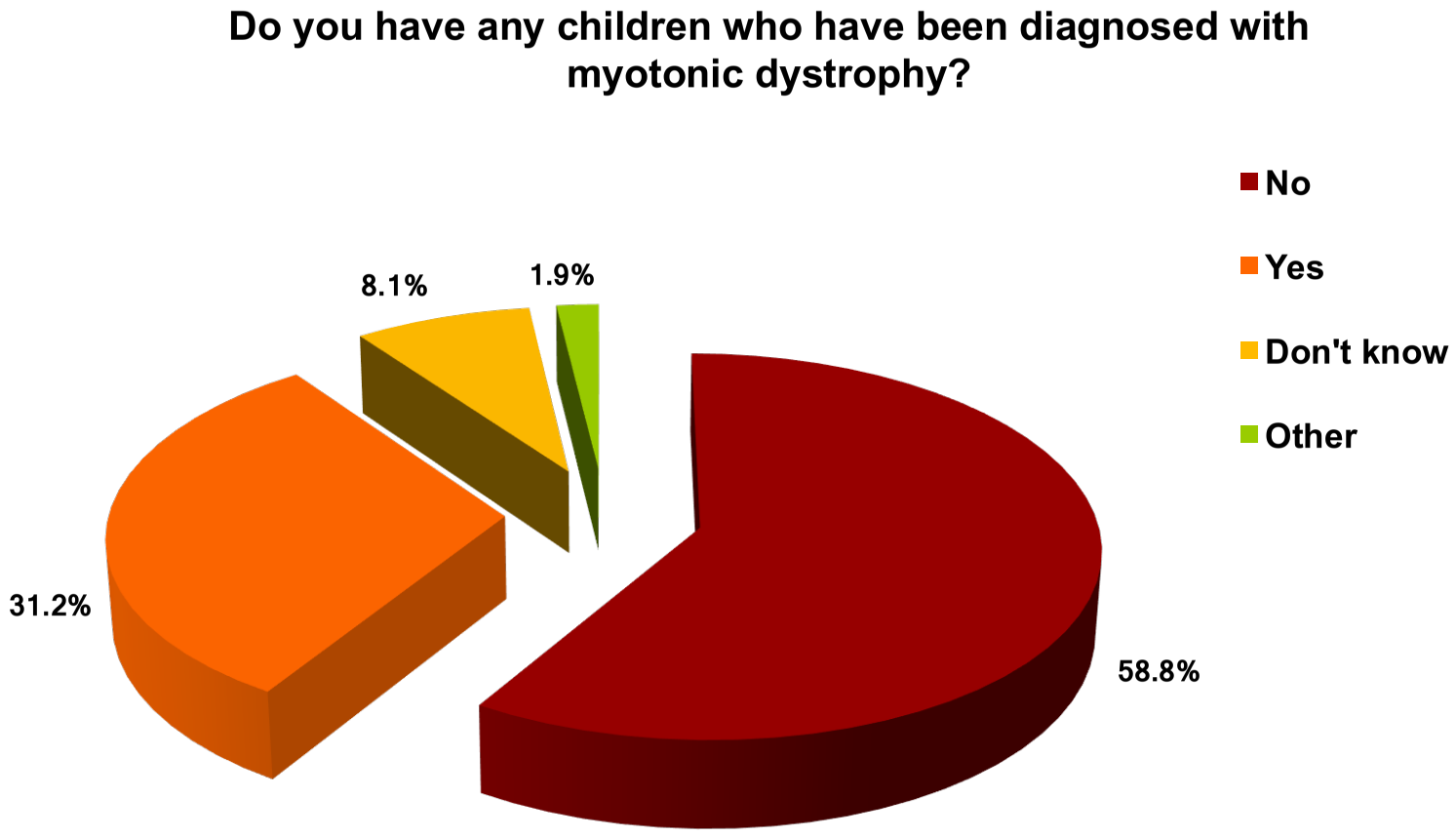
Presence of Children with Myotonic Dystrophy



n=260

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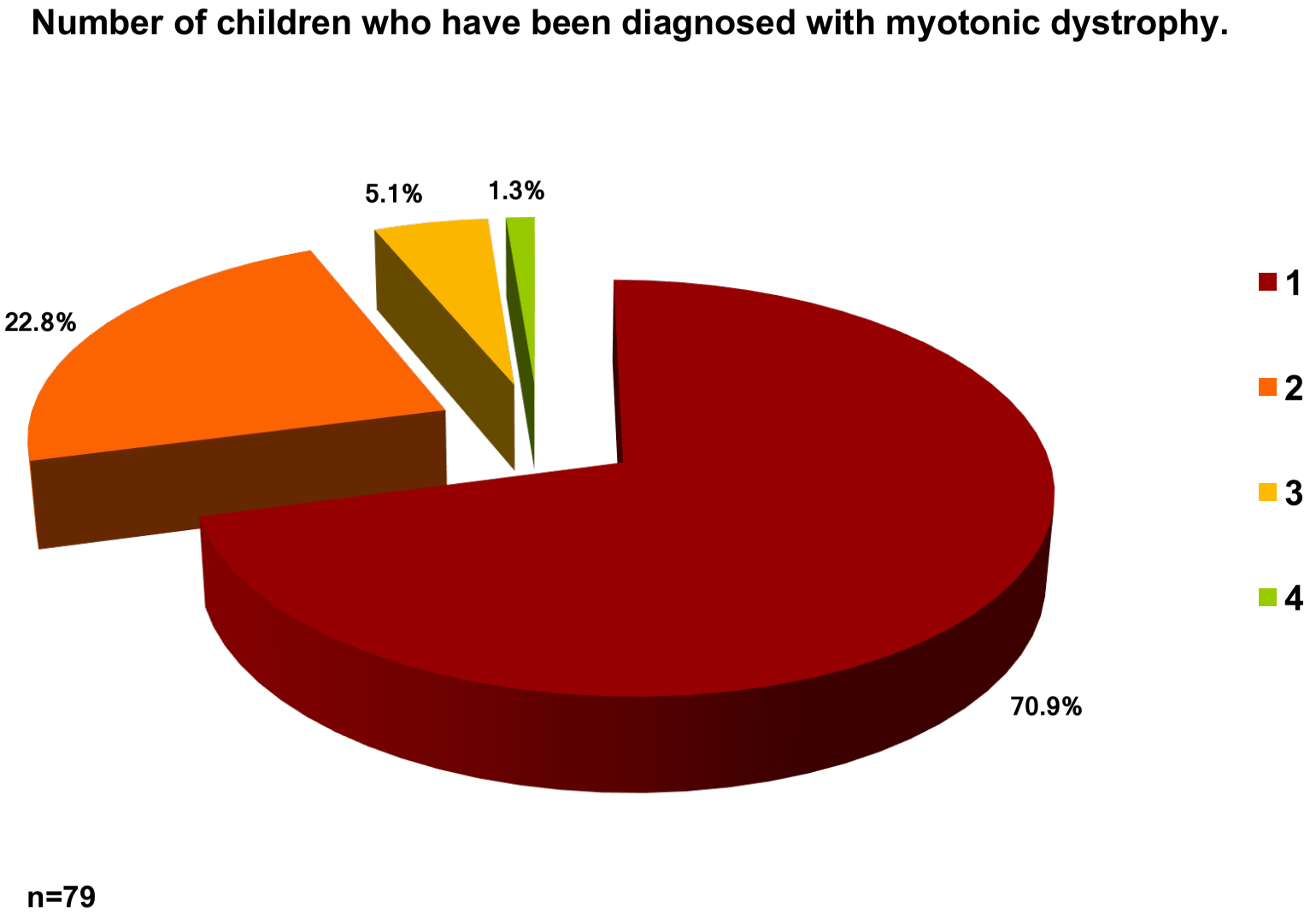
Number of Children with Myotonic Dystrophy



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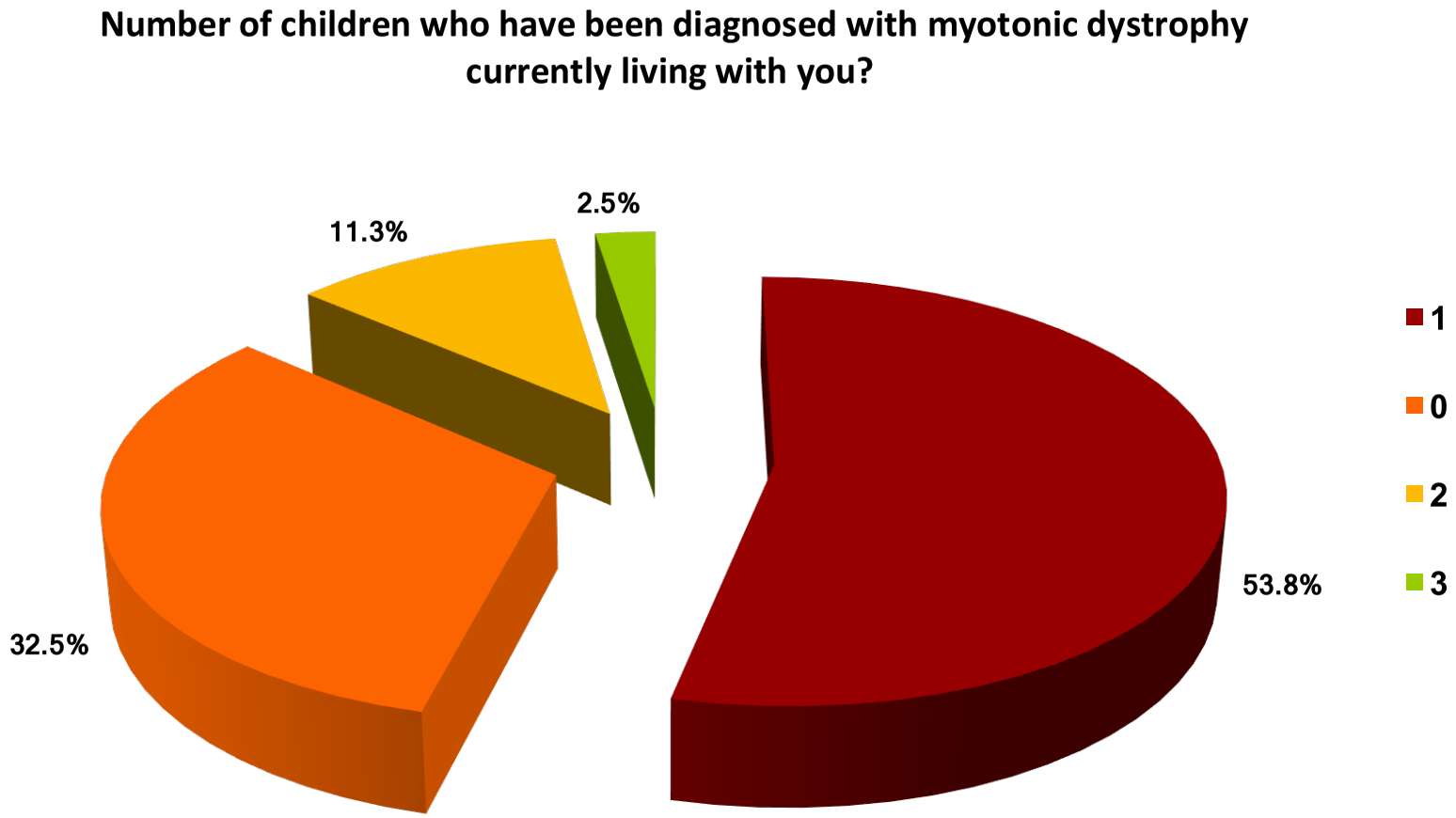
No. of Children with Myotonic Dystrophy Living with Respondent



n=80

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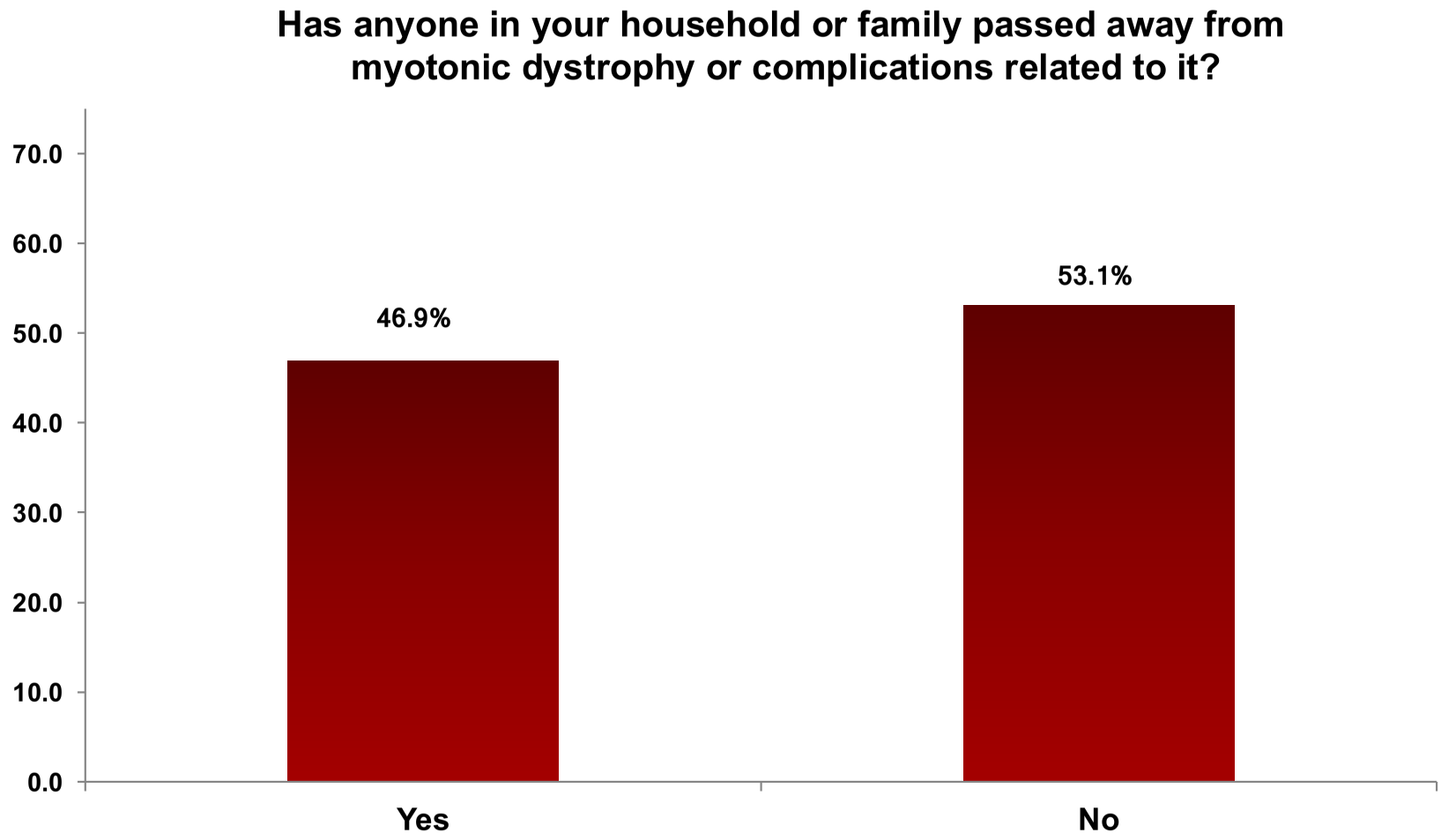
Incidence of family members of respondent who passed away from DM



n=258

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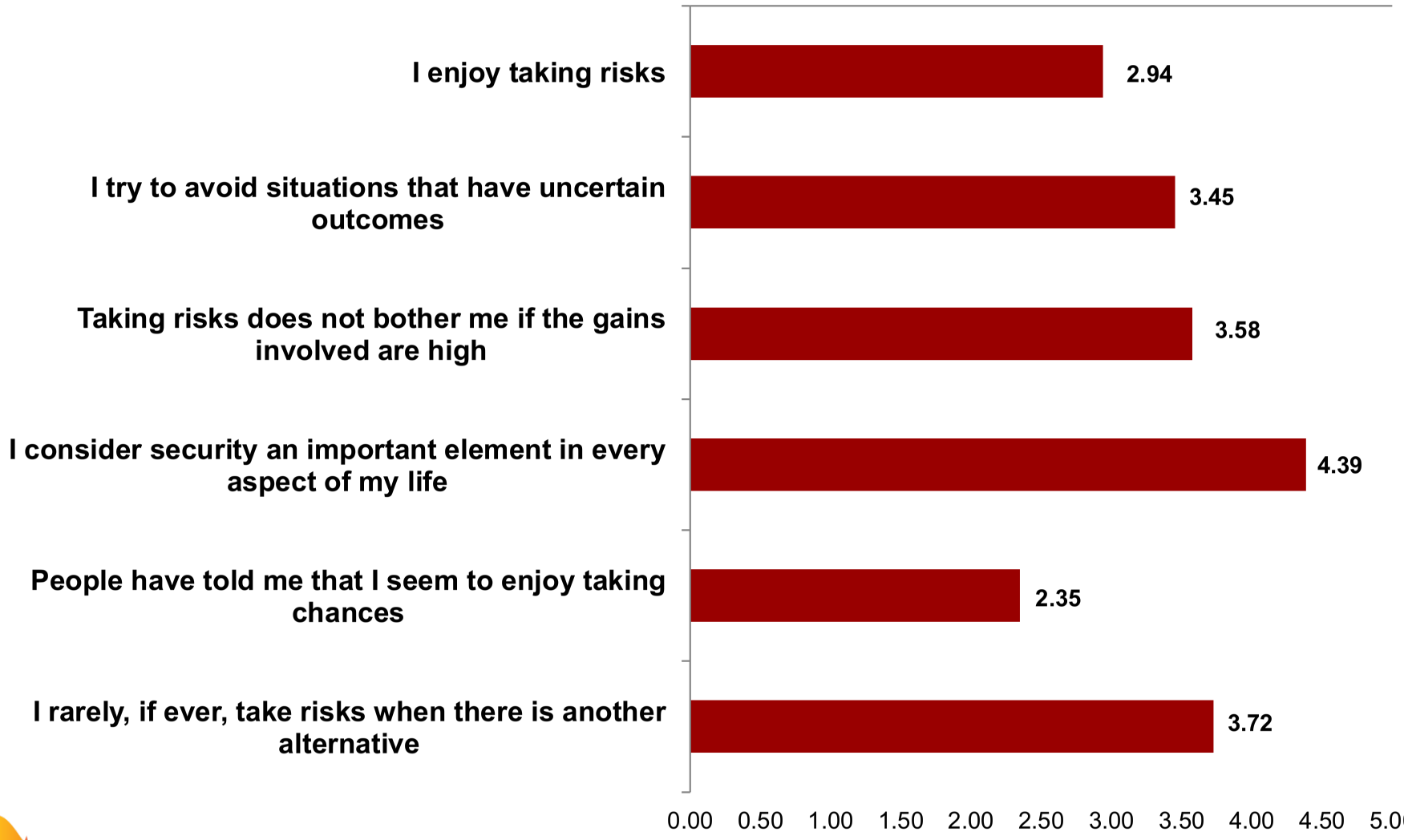
Respondent Risk Taking Profile



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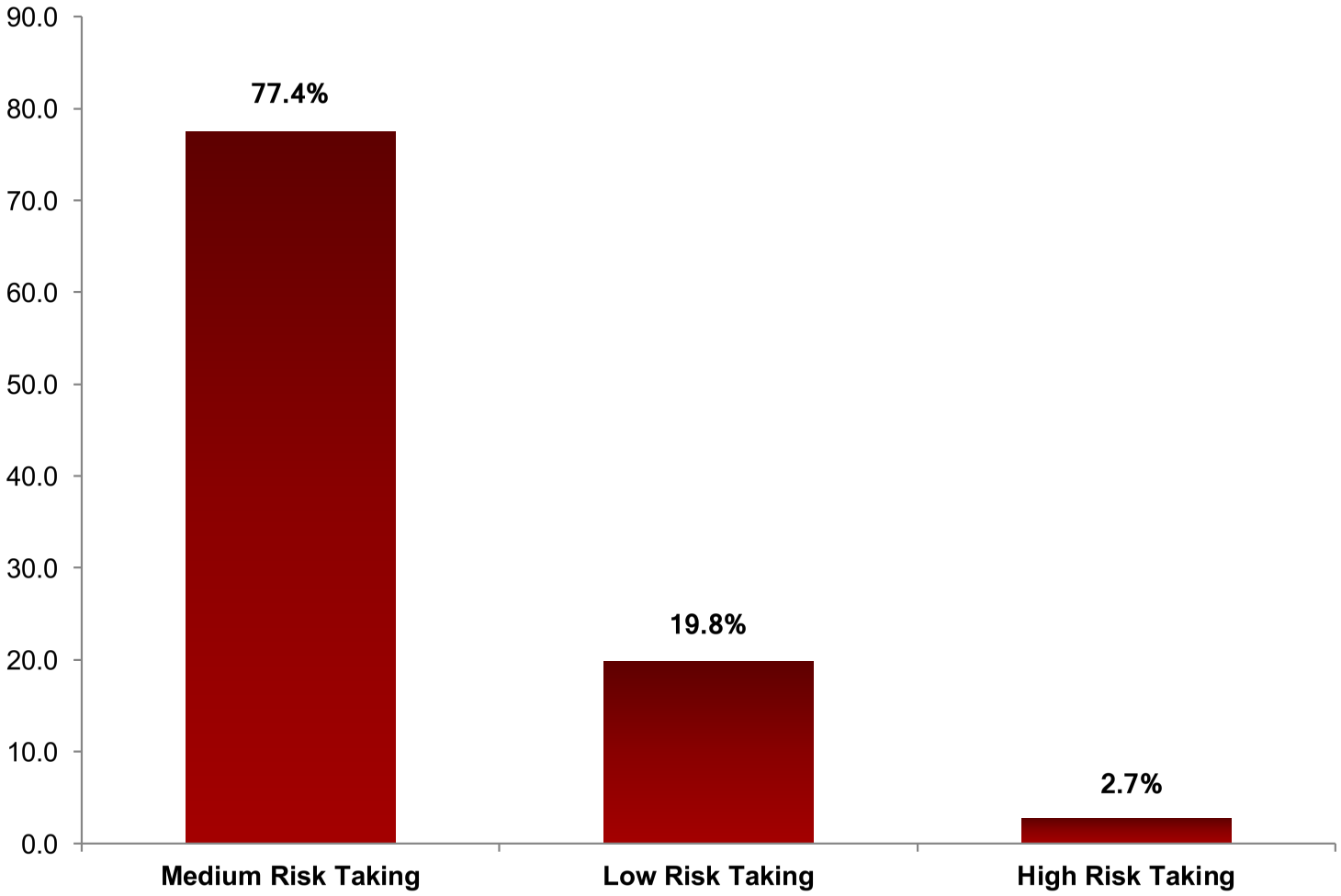
Respondent Risk Taking Profile



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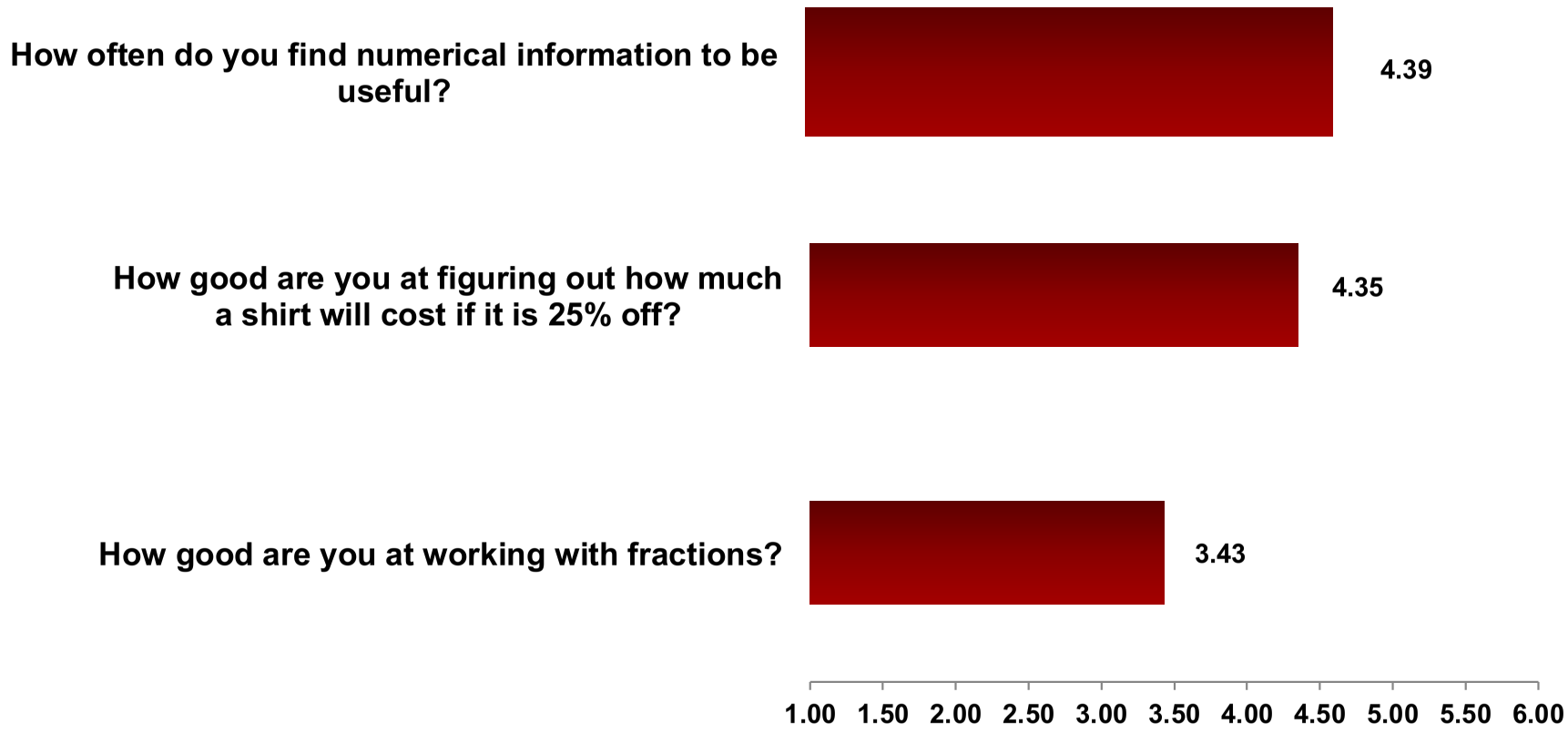
Respondent Numeracy Skill:



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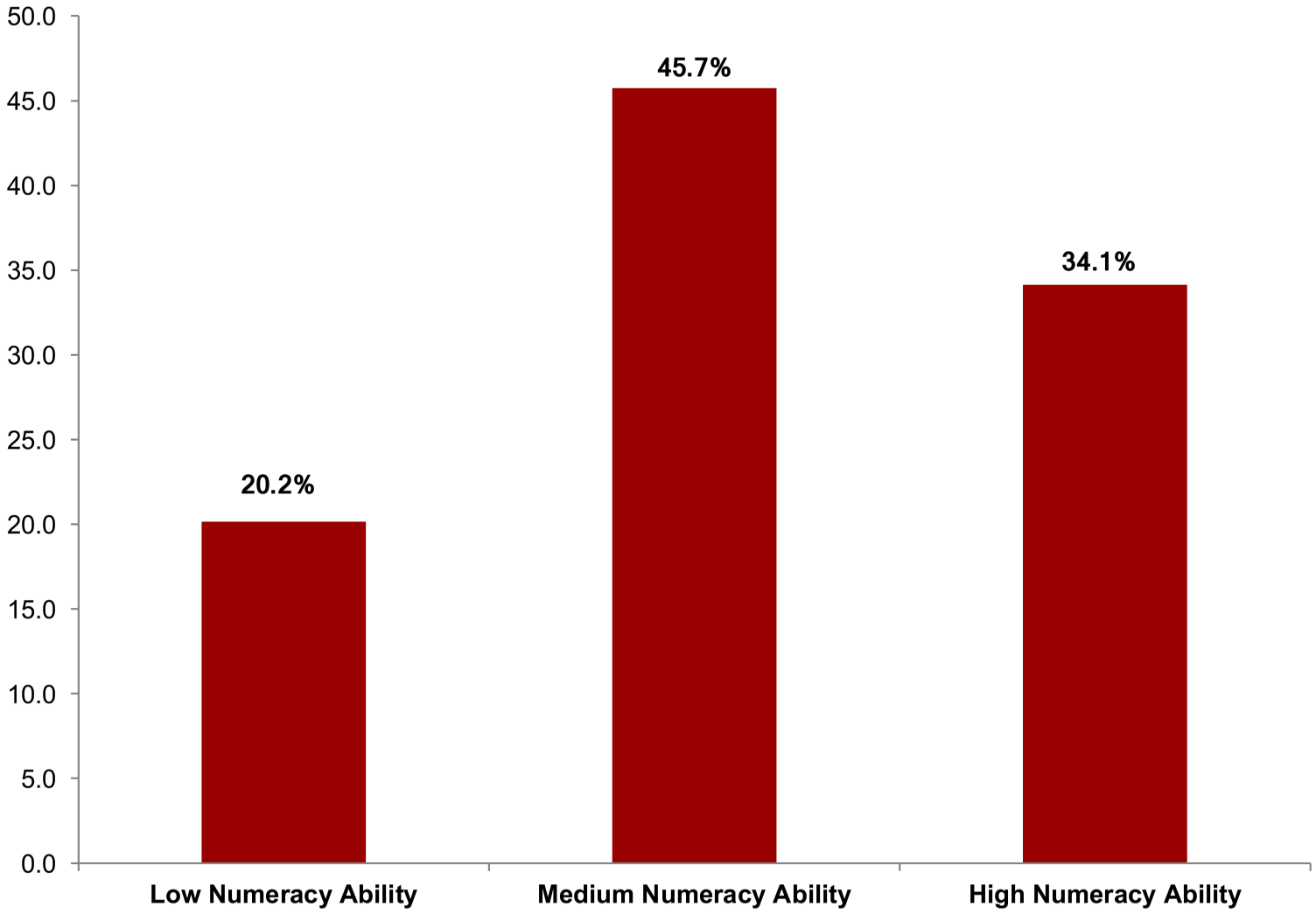
Respondent Numeracy Skill:



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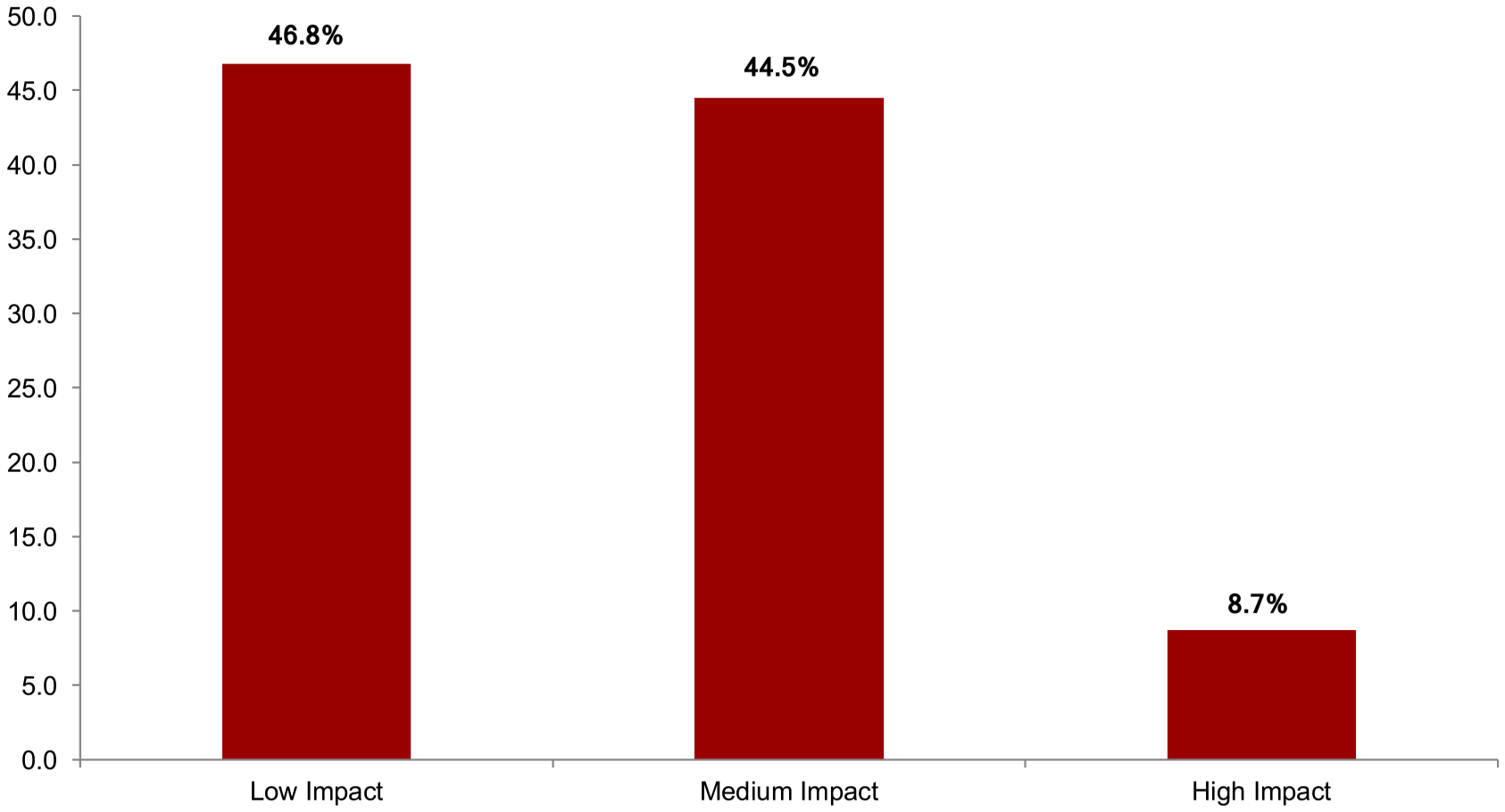
Impact



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Best/Worst Scaling Methodology Background

What is Best/Worst Scaling (also know as MaxDiff?)

- **Best/Worst Scaling** (MaxDiff) is a way of evaluating the importance (or preference) of a number of alternatives

- It is a *discrete choice* technique: respondents are asked to make simple best/worst choices

- **Best/Worst Scaling** has the advantage that it is very simple for the respondent, but gives extremely rich information to the researcher

Which of the following additional features would be most likely to make you choose a particular airline, and which would be least likely to make you choose it?

Most		Least
○	No charges for checked baggage	○
○	Ability to earn air miles	○
○	Free meal on board	○
○	4" more legroom than competitors	○
○	In-flight TV programs	○
○	Guaranteed Aisle or Window seat	○

Best/Worst Scaling vs Standard Rating Scales

- Best/Worst Scaling is an antidote to Standard Rating Scales or Importance Scales.
  - With Importance Scales respondents find that these ratings scales are very easy but they do tend to deliver results which indicate that everything is "quite important", making the data not especially actionable.

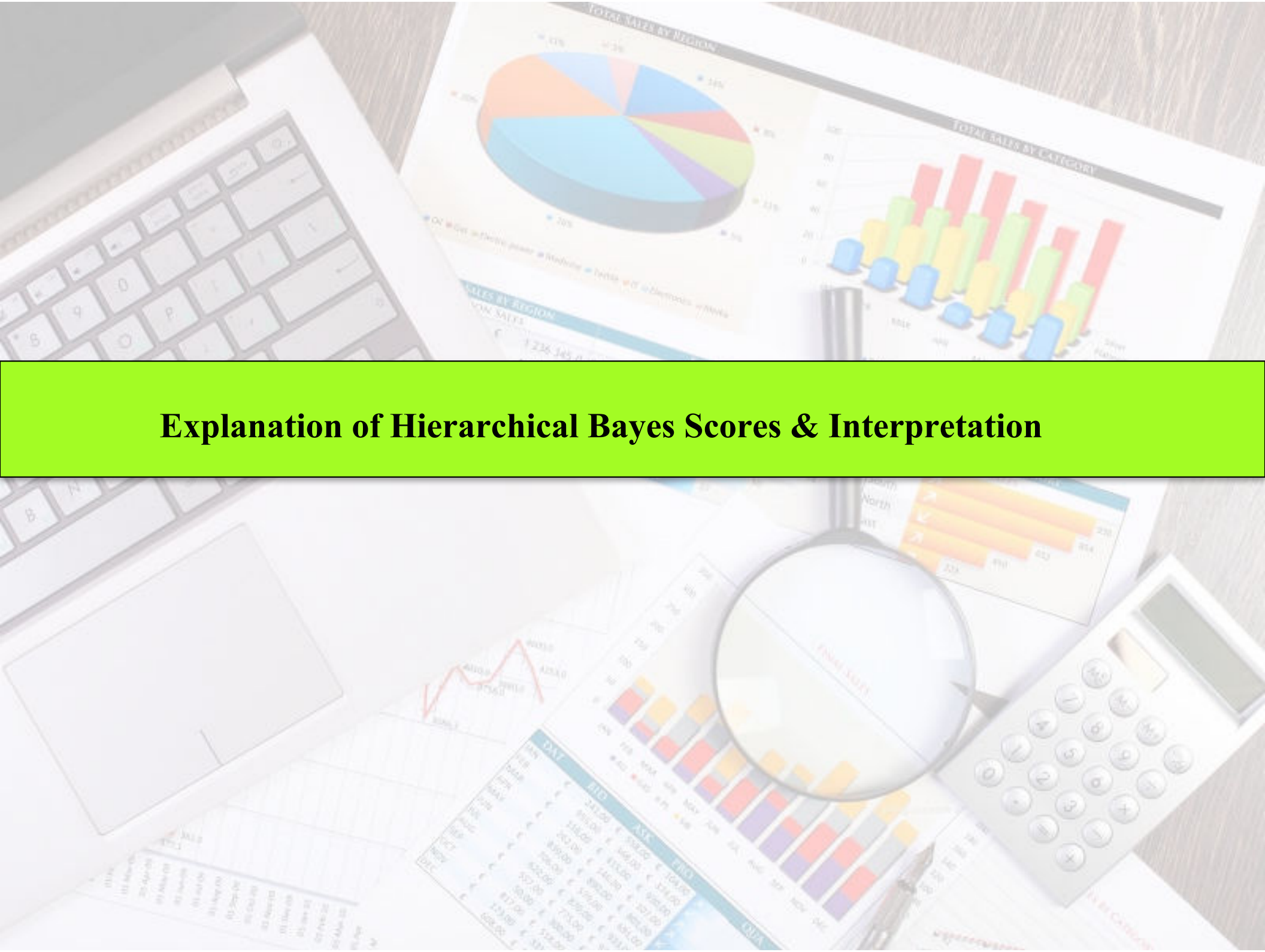
- Best/Worst Scaling on the other hand forces respondents to make choices between options, while still delivering rankings showing the relative importance of the items being rated.

Best/Worst Scaling Simple Example (MaxDiff)

Best/Worst Scaling may be thought of as a variation of the method of Paired Comparisons. Consider a set in which a respondent evaluates four items: A, B, C and D. If the respondent says that A is best and D is worst, these two responses inform us on five of six possible implied paired comparisons:

- A > B, A > C, A > D, B > D, C > D

The only paired comparison that cannot be inferred is B vs. C. In a choice among five items, MaxDiff questioning informs on seven of ten implied paired comparisons. MaxDiff questionnaires are relatively easy for most respondents to understand.



Explanation of Hierarchical Bayes Scores & Interpretation

Hierarchical Bayes Scores and Interpretation

What is Hierarchical Bayes estimation?

How does a different kind of analysis technique improve the results of a conjoint analysis study?

- Hierarchical Bayesian estimation is a complex but powerful approach of modeling data sets to yield more precise and granular analysis. The HB model internalizes prior probabilities and data-produced likelihoods to compute posterior probabilities in an iterative process. Its methods are optimized by utilizing Markov Chain Monte Carlo (MCMC) simulations as a means of estimation.

- HB estimation is being used in conjoint analysis to determine the part-worth utilities because it does so more accurately than other linear or logit models. This along with the fact that HB estimation has the recovery ability to calculate these more precise results while showing fewer packages has created the excitement about HB estimation in discrete choice modeling including Conjoint and Max-Diff surveys.

Hierarchical Bayes Scores and Interpretation

In the context of conjoint analysis, HB estimation takes into account the prior knowledge of the features, the individual's preference selections as well as the preferences of all who participated in the survey to derive preference scores.

The mathematics driving the MCMC simulation allows the process to borrow information from the full data set to estimate the part-worth utilities, providing estimates in situations where classical methods fall short.

Additional Useful Links

1. What is a Bayesian rating?
http://fulmicoton.com/posts/bayesian_rating/

2. Bayesian average supersedes the t-test

http://www.indiana.edu/~kruschke/BEST/BEST.pdf

3. additional insight on significance test limitations

http://blog.philbirnbaum.com/2010/03/statistical-significance-is-only-one.html

4. Bayesian versus frequentist viewpoints

https://stat.duke.edu/~berger/papers/interplay.pdf

5. Bayes theorem explanation:

http://www.kevinboone.net/bayes.html

6. Additional link:

http://www.evanmiller.org/bayesian-average-ratings.html

Sample Survey Questions

Example of Best-Worst Question

TREATMENT 1 - IMPROVES MUSCLE STRENGTH

"Muscle Strength" describes the ability of your muscles to move against resistance in performing day to day activities. For example, muscle strength affects your ability to walk, rise from a seated position, go up or down stairs and lift or hold objects.

Every treatment or therapy will have potential side effects or risks. Click the **best** and **worst** side effect or risk.
By "**Best**" side effect or risk we mean the side effect or risk *you* are **most willing** to live with.
By "**Worst**" side effect or risk we mean the side effect or risk *you* are **least willing** to live with.
(Please choose one "**Best Risk**" ***and*** one "**Worst Risk**" in order to proceed) *

Best Risk	Side Effect of Treatment	Worst Risk
○	1 in 1,000 risk of liver failure	○
○	Loss of appetite is experienced by most people	○
○	Causes a small increase in tiredness during the day in most people	○
○	Loss of appetite with occasional vomiting is experienced by most people	○
○	Causes a large increase in tiredness during the day in most people	○

1 of 4 sets

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Example of Best/Worst Question

Please read the following carefully as the instructions to the question have changed.
Every treatment or therapy has potential risks or side effects. We would like to get your thoughts on which risks or side effects you are most and least willing to live with.
Choose the side effect or risk you are **most willing to live with** by clicking the circle under "most willing to live with."
Choose the side effect or risk you are **least willing to live with** by clicking the circle under "least willing to live with".

[Please choose one most willing and one least willing to live with option in order to proceed] *

Most willing to live with	Side Effect or risk of treatment	Least willing to live with
○	A small increase in tiredness during the day	○
○	1 in 100,000 risk of liver failure	○
○	1 in 1000 risk of liver failure	○
○	Loss of appetite	○
○	A large increase in tiredness during the day	○

1 of 4 sets

Age of First Symptoms Question

At approximately what age did you first experience the symptoms associated with your diagnosis of myotonic dystrophy? We are referring to symptoms such as muscle weakness and fatigue etc.

(Please select the one best response) *

- Under age 10
- Ages 11 to 14
- Ages 15 to 18
- Ages 19-21
- Above age 22

MDHI Short Form Survey Instrument (severity of symptoms)

How much does the following impact your life now? [Please check the ***one*** box that applies to you for each item]

	I don't experience this	I experience this but it does not affect my life	It affects my life a little	It affects my life moderately	It affects my life very much	It affects my life severely
Limitations with your mobility or walking	☐	☐	☐	☐	☐	☐
Problems with your hands or arms	☐	☐	☐	☐	☐	☐
Inability to do activities	☐	☐	☐	☐	☐	☐
Fatigue	☐	☐	☐	☐	☐	☐
Pain	☐	☐	☐	☐	☐	☐
Gastrointestinal issues	☐	☐	☐	☐	☐	☐
Problems with your vision	☐	☐	☐	☐	☐	☐
Communication difficulties	☐	☐	☐	☐	☐	☐
Impaired sleep or daytime sleepiness	☐	☐	☐	☐	☐	☐
Emotional issues	☐	☐	☐	☐	☐	☐
Difficulty thinking	☐	☐	☐	☐	☐	☐
Decreased satisfaction in social situations	☐	☐	☐	☐	☐	☐
Decreased performance in social situations	☐	☐	☐	☐	☐	☐
Myotonia	☐	☐	☐	☐	☐	☐
Breathing difficulties	☐	☐	☐	☐	☐	☐
Choking or swallowing issues	☐	☐	☐	☐	☐	☐
Hearing difficulties	☐	☐	☐	☐	☐	☐

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Risk Taking Attitude Question

For each of the following, please choose the number that best reflects how strongly you agree with that statement. "1" = Strongly Disagree and "6" = Strongly Agree.

	1-Strongly Disagree	2	3	4	5	6-Strongly Agree
I enjoy taking risks	○	○	○	○	○	○
I try to avoid situations that have uncertain outcomes	○	○	○	○	○	○
Taking risks does not bother me if the gains involved are high	○	○	○	○	○	○
I consider security an important element in every aspect of my life	○	○	○	○	○	○
People have told me that I seem to enjoy taking chances	○	○	○	○	○	○
I rarely, if ever, take risks when there is another alternative	○	○	○	○	○	○

Numeracy Skill Question

For each of the following questions, please choose the number that best reflects how good you are at doing the following things:

	1-Not good at all	2	3	4	5	6-Excellent
How good are you at working with fractions?	○	○	○	○	○	○
How good are you at figuring out how much a shirt will cost if it is 25% off?	○	○	○	○	○	○

For the following question, please choose the number that best reflects how often you find the following useful:

	1-Never	2	3	4	5	6-Very often
How often do you find numerical information to be useful?	○	○	○	○	○	○

Myotonic Dystrophy Foundation Benefits/Risks Study

Data Analysis Presentation

September 2015

Presented by: Alan Nazarelli

Contact: Alan Nazarelli aln@siliconvalleyrg.com

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