ASSOCIATION BETWEEN PHYSICAL ACTIVITY & SEDENTARY TIME ON FRAILTY STATUS IN ADULTS LIVING WITH DIABETES MELLITUS

by

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Abstract

BACKGROUND: Increased physical activity (PA) is as a cornerstone for the prevention and the treatment of diabetes mellitus (DM) and frailty. However, no consensus exists on which types of PA, resistance training (RT), and sedentary time are associated with frailty status among individuals living with DM.

OBJECTIVE: To investigate the association between time engaged in PA, RT, and sedentary time on frailty status in males and females living with DM.

METHODS: A cross-sectional analysis of 711 participants living with self-reported DM from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) was performed. Frailty status was measured using the 46-item deficit model. PA levels were measured by accelerometer, while RT was measured via questionnaire.

RESULTS: RT was not associated with frailty status, while total time spent performing light PA was associated with improved frailty status ($p<0.05$). In women only, total moderate-to-vigorous PA (MVPA) was associated with improved frailty status ($p<0.05$), while sedentary time was associated with worsened frailty status ($p<0.05$). Every minute performing MVPA was associated with a 5% and 6% lower likelihood of frailty in men and women, respectively (all $p<0.05$).

CONCLUSIONS: Although RT is not associated with improved frailty status, each minute performing PA is associated with improved frailty status in men and women with DM. For women with DM, replacing sedentary time with PA is especially important for reducing frailty. These results provide further understanding on types of PA and sex differences in relation to prevention and management of frailty for individuals with DM.

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List of Abbreviations

Diabetes Mellitus ……... DM

Gestational Diabetes Mellitus ……. GDM

Moderate to Vigorous Physical Activity …….…….. MVPA

National Health and Nutrition Examination Survey …… NHANES

Physical Activity ……. PA

Resistance Training ……. RT

Standard Deviation …….……. SD

Type 1 Diabetes …….…… T1DM

Type 2 Diabetes …….…… T2DM

World Health Organization …….…… WHO

Chapter 1: Introduction

Worldwide, the average age is constantly increasing with more individuals being over the age of 65 years. In fact, many countries including developed countries are facing physical, psychological, and social challenges. These challenges are impacting different spheres of older adults, however all of them can impact frailty (WHO, 2015).

Frailty is not trivial as both policy makers and older individuals agree that independent living and autonomy are desired for as long as possible. A rapid decline in all spheres of health, including physical function, overall physical independence, and an increase in frailty status have detrimental impacts on health status and mortality (WHO, 2015, 2017). Although many reasons for these specific declines have been proposed, physical activity (PA) has also been proposed as a solution to prevent decline in physical function, and even more importantly to prevent frailty in older adults (WHO, 2015, 2017). However, a universally recommended type of PA remains uncertain in older adults, especially for individuals living with frailty (Zech et al., 2012).

The most important aspect to maintaining independence and preventing frailty during ageing is to continue being physically active (WHO, 2017). In addition to frailty, DM is also known to impair physical function in older adults. Therefore, it is tremendously important for those older adults living with both DM and frailty to implement an appropriate and effective exercise routine in order to increase their quality of life. However, individuals living with frailty and individuals living with DM have historically displayed lifestyles containing inadequate PA levels and excessive sedentary time. There are few

studies investigating the association between PA and sedentary time on individuals living with both of these conditions simultaneously.

Chapter 2: Literature Review

2.1 Ageing

2.1.1 The Definition of Ageing

According to the World Health Organization (WHO), ageing in its simplest form is typically recognized as the point in which an individual has been living for 65 years or more, often termed as an "older adult" (Kowal & Dowd, 2001). However, ageing is a complex phenomenon characterized by an interaction of mental, physiological, and physical changes to stress. Humans are exposed to various forms of stress throughout a lifetime, but the body's ability to adapt, exert resilience, and continue to function under stress has been identified as an indicator for ageing (Abrass, 1990). Therefore, ageing has been defined as "a persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration" (Rose et al., 2012). As an older adult becomes less resilient to various forms of stress throughout a lifetime, their risk for impaired function, the onset of chronic diseases, as well as premature mortality increase significantly (Abrass, 1990; T. Fulop et al., 2010; Gault & Willems, 2013; A. B. Mitnitski, Rutenberg, Farrell, & Rockwood, 2017). In summary, ageing can be defined as a progressive decline in the ability and capacity to function under mental or physiological stress invoked by either intrinsic or extrinsic factors over a chronological period of time.

2.1.2 The Heterogeneity of Ageing

Despite the variety of definitions, there are different types of ageing: chronological age, and biological age (Couoh, 2017; Mitnitski, Howlett, & Rockwood, 2017). Ageing is

extremely heterogeneous, meaning individuals of the same age may not be at the same stage of life, nor may the decline of their bodily and functional systems occur in the same order (Fulop et al., 2010; Fulop, 2013). Chronological age is defined as "the amount of elapsed time from birth to a specific moment in life or death" (Couoh, 2017). On the other hand, biological age is defined as "a gradual, lifelong accumulation of molecular and cellular damages that result in a progressive, generalized impairment in many body functions, an increased vulnerability to environmental challenges, and a growing risk of chronic diseases and death" (Kirkwood, 2008; WHO, 2015). The difference between chronological and biological age is "a repercussion of individual variations in longevity as well as individual differences in the onset and variations in the aging processes due to genetic, epigenetic, and environmental conditions (Bae et al., 2013; Belsky et al., 2015; Cho, Park, & Lim, 2010; de Rooij & Roseboom, 2013; Levine, 2013)" (Couoh, 2017). Therefore, two individuals of the same chronological age may have completely opposed biological ages, expressing such broad variability in their health status (Mitnitski et al., 2017). In fact, literature suggests that biological age can vary by up to a decade between individuals of the same chronological age, and that this variability can occur at any stage of life, not only in older adulthood (Couoh, 2017).

2.1.3 The Prevalence of Ageing

The proportion of older adults in Canada has increased steadily for more than 40 years and will continue to increase, according to recent statistics on the Canadian population. In fact, Statistics Canada released data in 2019 stating that adults aged 65 years and older represent over 17% of the total Canadian population (Statistics Canada, 2019). It

is expected that by the year 2030, this number will rise to 23% of the Canadian population, which equates to over 9.5 million Canadian older adults (Canada, 2014). In 2019, Statistics Canada projected that by the year 2068 older adults 65 years and above could represent up to 30% of the total Canadian population (Statistics Canada, 2019). In 2014, the Government of Canada also stated that by the year 2036 life expectancy is projected to increase by 1.8 years for females (from 87 to 88.8 years) and 1.9 years for males (from 84.6 to 86.5 years) (Canada, 2011). However, the WHO suggests that this increase in life expectancy is rarely due to older adults maintaining better health into older age. Contrarily, this increase in life expectancy is primarily due to increased survival rates early in life; leading to an overall population increase (WHO, 2015).

Furthermore, the proportion of older adults in New Brunswick exceeds all other age groups. Also, the proportion of older adults in New Brunswick is higher, relative to the New Brunswick population, than that of Canada as a whole (Statistics Canada, 2019). This increases the importance for healthy ageing not only within Canada but specifically within New Brunswick.

2.1.4 Ageing, Chronic Disease, and Cost

Canadian health care costs were expected to reach over $264.4 billion for the year 2019, which equates to $7068 per Canadian, nation-wide. (Canadian Institute For Health Information, 2019). Funds spent toward Canadian health care are increasing even more rapidly in recent years. In 2019, the Canadian Institute for Health Information released a report on National Health Expenditure Trends which stated that from 2014 to 2019, in real terms, health spending increased by about 1.4% per person per year, and total

health care expenditure was expected to increase, after inflation, by 3.9% in 2019 (Canadian Institute For Health Information, 2019). In New Brunswick specifically, 2019 health expenditures were predicted to reach an equivalent of $7187 per person, which is a 2.8% growth per capita from previous years. Health expenditures also vary per age group in Canada. Figure 1.0 represents data form 2017 on Canadian health expenditure per person, per age group (Canadian Institute For Health Information, 2019). This data shows that once older adulthood is reached, health expenditures per person rise dramatically, with adults aged 90 years or older accumulating around $30000 per person in health care expenditure (Canadian Institute For Health Information, 2019).

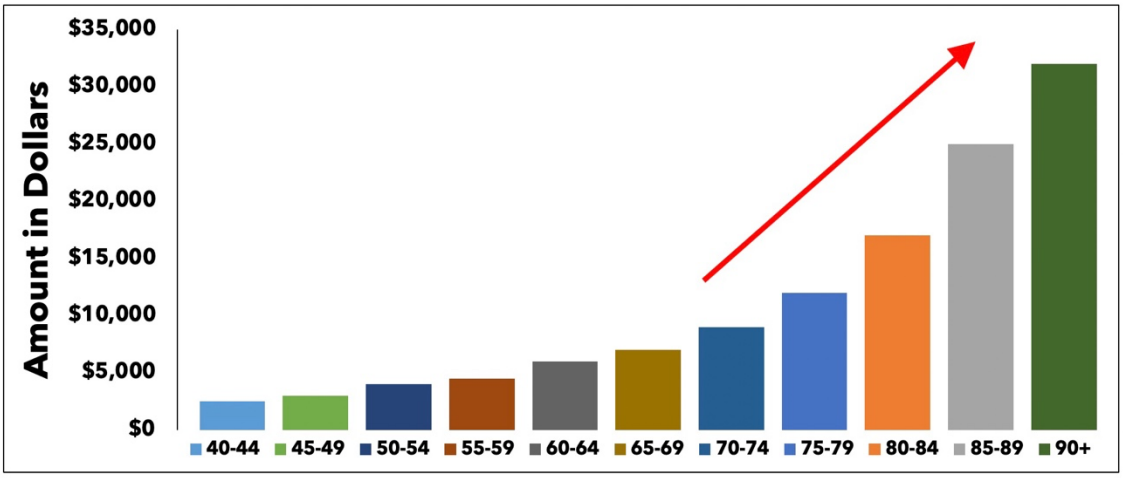

Figure 1.0: The 2017 Canadian health expenditure per person, per age group (adapted from Canadian Institute For Health Information, 2019).

The WHO suggests that many of the mechanisms leading to impaired physical function and onset of chronic disease with ageing are random; however, environmental factors and individual behaviours have also been recognized as having a strong impact on the ageing process (WHO, 2015). Statistics Canada reported that several factors over which

individuals do have control, including exercising regularly, have been associated with good health (Canada, 2011). In fact, many of the disorders or diseases associated with ageing are preventable; and the determinants for onset of disorders or disease often begin earlier in life (WHO, 2017). The WHO also listed PA as an important component to healthy ageing (WHO, 2017). However, the 2009 review by Manini and Pahor (2009) explained that in the United States, older adults are the least physically active population. In fact, older adults who are functionally dependent represent 20% of the older adult population, yet are accountable for 46% of healthcare expenses (Manini & Pahor, 2009).

Chronic disease is defined as a long-term condition involving abnormal structural and functional changes in the body, typically with a delayed or slow onset of symptoms, caused by interactions between both genetic and environmental factors (Hui, 2015). Chronic diseases usually occur later in life and are quickly becoming the leading cause of mortality worldwide (Hui, 2015). According to the Government of Canada's 2014 Action for Seniors Report, approximately 90% of Canadians aged 65 and over live with at least one chronic disease or condition, such as cardiovascular disease, cancer, respiratory conditions, DM, dementia, arthritis or obesity (Canada, 2014). Chronic health conditions require more focus than ever to ensure effective health care support and good health management (Canada, 2014).

2.2 Frailty

2.2.1 The Definition and Assessment of Frailty

Literature has begun to conceptualize frailty as a potential link between healthy ageing versus chronic conditions and increased mortality (Cacciatore et al., 2013). In fact, Cacciatore (2013) explained that frailty is considered the primary or pre-clinical state when no other conditions are present, and as a secondary state when symptoms of frailty are present in addition to other chronic conditions. Clinical frailty may be considered the line separating healthy aging from premature mortality and increased use of health care resources due to its characteristics, which include: the use of multiple drugs and/or adverse reactions to drugs, hospitalization and increased use of health services, and an increase in age-associated deficits (Cacciatore et al., 2013).

Several definitions of frailty have been proposed to conceptualize and operationalize frailty (Theou, Walston, & Rockwood, 2015). However, international consensus has yet to be reached and a universal definition of frailty is still lacking in the literature, despite the long-lasting and extensive debates about the most relevant way to define frailty. Nevertheless, most frailty definitions have some factors in common including decreased reserves/capacity to tolerate minor stressors, increased vulnerability to adverse health outcomes, and impairment in multiple physiological systems (Fried et al., 2001; Fulop, 2013; Mitnitski, Mogilner, & Rockwood, 2001; Rockwood, Song, MacKnight, Bergman, Hogan, McDowell, & Mitnitski, 2005; WHO, 2015). In addition, frailty is conceptually defined as a clinically recognizable state in which there is a compromised ability for older adults to cope with everyday or acute stressors, which

increases vulnerability to the age-associated declines in physiological reserve and function across multiple organ systems (WHO, 2015). The consequence of such increases in vulnerability and health deficits result in increased risk of falls, disability, institutionalization/hospitalization, or even death (Davis, Rockwood, Mitnitski, & Rockwood, 2011; Fried et al., 2001; Fulop, 2013). With numerous definitions of frailty available in literature, Table 1.0 outlines the current most widely accepted definitions.

Table 1.0: Current most widely accepted definitions of frailty, sorted by author/organization.

Author/Organization	Definition
Fried et al., 2001	A clinical syndrome in which at least three of the following criteria are present (detailed in Appendix A): ● Unintentional weight loss of >10 lbs in the past year. ● Self-reported exhaustion measured by two questions from the modified 10-item Center for Epidemiological Studies-Depression scale (CES-D). ● Weakness measured by a grip strength test result in the lowest 20% based on gender and body mass index. ● Slow walking speed measured by a walking time per 15 feet test result in the slowest 20% based on gender and height. ● Low physical activity measured by a short version of the Minnesota Leisure Time Physical Activity questionnaire, and subsequently calculated weekly kcal expenditures of <383kcal for males and <270kcal for females.
Mitnitski et. al., 2001	● An age-associated non-specific state of increased risk, which reflects multisystem physiological change. ● In this model, symptoms, signs, diseases, disabilities, and abnormal test results are considered as deficits. The deficits are combined to create the Frailty Index (detailed in Appendix B). ● A Frailty Index score is calculated by the sum of reported deficits divided by the total number of deficits included in the Index. ● The Frailty Index scale ranges between 0 and 1. ● An individual is classified as frail if their Frailty Index score ranks equal to or greater than 0.25. ● At least 30 variables (deficits) are required for stable results.
World Health Organization, 2015, p. 63	"Progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes."

Although clinicians are usually able to identify an individual living with frail status rather intuitively, it is important to systematically quantify the symptoms or markers of frailty (Davis et al., 2011). However, there are several different methods for quantifying frailty through the measurement of its associated deficits in older adults. The two most widely accepted and validated frailty measurement tools are Fried's phenotype method and Rockwood's accumulation of deficits method known as the Frailty Index (Hoogendijk et al., 2019; Lee, Lee, & Jang, 2020).

Fried et al. (2001) identified five criteria of frailty and indicated that individuals with at least three of the five criteria are considered individuals living with frailty (Fried et al., 2001). The benefit to this assessment method is its efficient nature because it only involves five tests (Fried et al., 2001; Lee et al., 2020). However, the small test battery also incorporates a more limited evaluation of the whole-body function (Lee et al., 2020).

Alternatively, the Frailty Index, outlined by Rockwood et al. (2007) measures an accumulation of deficits (Rockwood & Mitnitski, 2007). Rockwood et al. (2005) defined frailty as an increase in vulnerability due to functional deficits across multiple systems. The concept of the Frailty Index involves numerically quantifying the accumulation of age-related functional deficits expressed in an individual and categorizing the level of frailty in the individual based on the number of deficits present (Theou & Rockwood, 2015; Theou et al., 2015). Briefly, a frailty index must meet the following criteria: 1) the variable must be associated with poor health outcomes, 2) the variable's prevalence must increase with age, 3) all variables included must cover a wide range of physiological systems, 4) the same frailty index variables must be used from one assessment to the next among the same sample population, and 5) a different set of variables can be used when assessing a different

sample population (Searle et al., 2008). Using this model, individuals with a higher total score are considered at higher risk for premature mortality (Mitnitski et al., 2001; Rockwood et al., 2017). The Frailty Index is a good tool for predicting the onset of mortality without reference to chronological age, and the Frailty Index can be considered a measure of ageing. Previous literature suggests the Frailty Index may be a more detailed and sensitive tool than the phenotype, especially when investigating within the low-to middle-end of the frailty continuum (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015a).

Although both Fried's phenotype and the Frailty Index are widely accepted operational definitions of frailty, there are obvious differences between them. There are known discrepancies in the prevalence of frailty among individuals in a given population, depending on the operational definition used to assess the population. Literature suggests the Frailty Index identifies more individuals in a population as frail than does the phenotype (Blodgett et al., 2015a). This discrepancy in prevalence is likely in association with the operational differences between them. Fried's phenotype includes far less criteria (only five items) and is more focused on identifying the performance-based and self-reported issues presented by an individual to define them as frail (Theou & Rockwood, 2015). In contrast, the Frailty Index is more heavily based on the pure quantity of issues observed in an individual relating to frailty because this method recognized that several different biological factors can result in the same physical or functional outcome (Theou & Rockwood, 2015). The Frailty Index also uses more in-depth information to assess frailty status such as objective lab values, signs/symptoms, comorbidities, physical function, and

other miscellaneous data such as the use of medications and self-reported health (Blodgett et al., 2015a).

There have been many different versions of the Frailty Index, all of which include slightly different variables and different quantities of variables, although 30 or more variables is ideal for obtaining the strongest results (Theou & Rockwood, 2015; Theou et al., 2015). However, the Frailty Index is still considered a valuable tool in clinical frailty research because of the consistency in output observed across all models (Theou & Rockwood, 2015).

Along with Fried's phenotype and the Frailty Index, other operational definitions of frailty have also been developed and recognized. These include the Edmonton Frailty Scale, the Tilburg Frailty Indicator, the Groningen Frailty Indicator, the 'FRAIL' scale, and the Barthel Index (Aimo, Barison, Mammini, & Emdin, 2018; Theou et al., 2015).

The Edmonton Frailty Scale was designed to facilitate the evaluation of frailty among institutionalized older adults over the age of 65, at hospital admission (Perna et al., 2017). This index measures the following nine characteristics: cognition, general health status, functional independence, social support, medication usage, nutrition, mood, continence, and functional performance. This tool was validated in hospitalized older adults by comparing outcome measures to other widely accepted measures such as the Mini-Mental State Examination (MMSE), the Geriatric Depression Index, handgrip outcomes and the Barthel Index (Petty, House, Knapp, Raynor, & Zermansky, 2006). The Edmonton Frailty Index is most commonly used among older adults over the age of 70 and has been proven to be a useful measure to quantify frailty and predict all-cause mortality in these populations (Jankowska-Polańska et al., 2019).

The Tilburg Frailty Index is a valid and reliable self-reported questionnaire encompassing physical, social, and psychological factors (Gobbens, van Assen, Luijkx, Wijnen-Sponselee, & Schols, 2010). The predictability of disability and hospitalization, nursing needs, informal care and quality of life were validated as well, compared to the 'FRAIL' scale, the Clinical Frailty Scale, and the Frailty Index (Chong et al., 2017; Gobbens et al., 2010; Gobbens, van Assen, Luijkx, & Schols, 2012). This test was validated in community dwelling older adults, who were able to self-report on questionnaires, and has been identified as an effective tool in predicting all-cause mortality (Theou, Brothers, Mitnitski, & Rockwood, 2013). The psychology component of this index did not correlate to the MMSE tool and may not be the best option for evaluating severely frail, cognitively impaired older adults.

The Groningen Frailty Indicator is a 15-item tool designed to measure frailty through screening 4 domains of function: physical, social, cognitive, and psychological (Schuurmans, Steverink, Lindenberg, Frieswijk, & Slaets, 2004; Theou et al., 2015). This test was validated in a population of Dutch older adults participating in the LifeLines study (Peters, Boter, Burgerhof, Slaets, & Buskens, 2015). However, frailty scores observed in this study were consistently lower than other frailty studies which used a broad sample size of Dutch older adults. Peters et al. (2015) suggested that the difference could be due to the sample population included in the LifeLines study, since the mean age was slightly younger than other similar studies, and since older adults with cognitive impairments were also excluded (Peters et al., 2015).

The 'FRAIL' scale was based on components of Fried's frailty phenotype and includes measurement of five health deficits which form its acronym: Fatigue, Resistance,

Ambulation, Illness, Loss of weight (Abellan van Kan, Rolland, Bergman, Morley, Kritchevsky, 2008; Theou et al., 2015). The validity of the 'FRAIL' scale has been assessed and accepted in a longitudinal cohort of older Australian women (Gardiner, Mishra, & Dobson, 2015), and other studies have assessed validity among modified versions of the 'FRAIL' scale (Dong et al., 2018; Rosas-Carrasco et al., 2016). However, the predictive validity of the 'FRAIL' scale is yet to be determined among a more diverse population of older adults (Theou et al., 2015).

The Barthel index is a measure of 10 factors of daily living: fecal incontinence, urinary incontinence, grooming aid, dressing, stair climbing, bathing, toileting, feeding, walking and sit to stand transfers (Aimo et al., 2018). This index considers whether the participant needs assistance during these tasks and is used as a predictor of mortality. This scale also demonstrates association with advanced age, dementia and institutionalization. This scale demonstrates moderate validity and is frequently used when assessing progress in cardiovascular recovery among community dwelling adults (Aimo et al., 2018). However, this scale is not validated for prediction of mortality, and the usefulness of this index has not been demonstrated among frail adults over 80 years old.

2.2.2 The Development and Effect of Frailty

The National Institute on Ageing and the Canadian Frailty Network explained in a 2018 report that frailty can be considered more of a spectrum rather than a uniform condition because of the ability for individuals to improve or worsen their health and independent abilities (Sinha et al., 2018). Therefore, the development of frailty is not necessarily the presence of each individual symptom, but the overall result in decreased

physical function and increased vulnerability. The 2018 report explains that frailty can be thought of as a continuum, and that individuals may reduce their frailty status as their physical function improves, as well as increase frailty status with worsened physical function (Sinha et al., 2018).

2.2.3 The Prevalence of Frailty

It is known that the prevalence of frailty increases with age; however, it is difficult to obtain the exact prevalence among a population because of the lack of consensus in defining and measuring frailty (Kehler et al., 2017b; Shamliyan, Talley, Ramakrishnan, & Kane, 2013). The prevalence of frailty using the two most widely accepted frailty measurement models (Fried's frailty phenotype, and the Frailty Index) were used to measure the prevalence of frailty among Canadian adults using data from the Canadian Health Measures Survey (Kehler et al., 2017a). There were differences in prevalence observed between the two models for each age group, although prevalence was generally not significantly different between males and females. Specifically, Fried's frailty phenotype reported a 6.9% prevalence among Canadians aged 50-64 years, and a prevalence of 7.8% among Canadians aged 65-79 years. Alternatively, the Frailty Index model reported an 11.6% prevalence among Canadians aged 50-64 years, and a prevalence of 20.2% among Canadians aged 65-79 years (Kehler et al., 2017a). A systematic review by Shamliyan et al. (2013) assessed the prevalence of frailty among community-dwelling older adults using both Fried's frailty phenotype and the Frailty Index and reported similar results between each model. Using Fried's frailty phenotype, the review reported a 14% prevalence of frailty in older adults aged 65 years or more, while the Frailty Index reported

a 24% prevalence in this age group (Shamliyan et al., 2013). The difference in frailty prevalence between both models is likely in accordance with the criteria involved with each model. The Frailty Index accounts for many more deficits than Fried's 5-item frailty phenotype. This likely explains the increase in prevalence detected using the Frailty Index model.

2.2.4 The Financial Burden of Frailty

Canada currently spends about $264 billion on health care annually (Canadian Institute For Health Information, 2019). Older adults above the age of 65, many of whom are living with frailty, currently use 46% of the total health care expenditures. The Canadian Frailty Network reported that over 1.5 million Canadians are currently living with frailty, and over the next decade, it is expected that well over 2 million Canadians will be living with this destructive condition ("Frailty Matters - Canadian Frailty Network", 2020).

The National Institute on Ageing released a report in 2018 outlining the prevalence of frailty among a variety of ages and populations. According to the report, there is a clear trend of increased prevalence of frailty with age. In fact, approximately 7% of Canadians aged 18-79 years are living with frailty, although this prevalence was reported to change depending on the frailty measurement tool used (Kehler et al., 2017). Moreover, 16% of Canadians aged 65-74 are living with frailty; 28.6% of Canadians aged 75-84 are living with frailty; and 52.1% of Canadians aged 85 and older are living with frailty (Clegg et al., 2013; Kehler et al., 2017; Sinha et al., 2018). Approximately 50% of older adults above the age of 85 are considered to be frail, approximately 50% of Canadians living in nursing

homes have frailty; and finally, 42% of older cancer patients and 60% of cardiovascular disease patients are living with frailty (Sinha et al., 2018). With increasing prevalence of frailty in the population, there is increased demand on the health care system to support the needs of frail individuals (Sinha et al., 2018). The importance of addressing a preventative action plan to reduce and delay the onset of frailty in the population is evident (Sinha et al., 2018).

2.3 Diabetes Mellitus

2.3.1 The Definition and Assessment of Diabetes Mellitus

DM is defined as a state of "chronic hyperglycemia" resulting in numerous health complications including microvascular complications (retinopathy, neuropathy, nephropathy), and macrovascular complications- all of which may lead to impaired physical function (Yanase, Yanagita, Muta, & Nawata, 2018). Currently, there are three major types of DM: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (Colberg et al., 2010).

T1DM is an auto-immune disease characterized by a complete lack of insulin production from the beta cells of the islets in the Langerhans in the pancreas (Colberg et al., 2010; Van Belle, Coppieters, & Von Herrath, 2011). Therefore, individuals with T1DM are insulin-dependent and need exogenous insulin to live. Usually, individuals are first tested for DM of any kind, then a secondary test must be done to determine the type of DM with which the individual has. T1DM diagnosis is confirmed by testing for markers (islet cell antibodies, insulin autoantibodies, glutamic acid decarboxylase antibodies, and antibodies against tyrosine phosphatase and against zinc transporters) of autoimmune

destruction of insulin-producing cells in the pancreas (Public Health Agency of Canada, 2011; Zhang & Eisenbarth, 2011).

On the other hand, T2DM still involves the production of insulin from the pancreas, but the body's cells are unable to adequately respond to and use the insulin properly (known as "insulin resistance") and the secretion of the insulin is inadequate (Colberg et al., 2010). Consequently, glucose builds up into the blood stream generating a chronic hyperglycemic state. One of the compensatory mechanisms of hyperglycemia is an increase in the secretion of insulin which then increases the demand on the beta cells (Weir & Bonner-Weir, 2004). When this is maintained over many years, the beta cells become exhausted and eventually fail; meaning they start producing less insulin and this process continues to the point in which insulin production is ceased altogether (Weir & Bonner-Weir, 2004). Typically, the onset of T2DM occurs gradually; therefore, the disease can go easily unnoticed for several years prior to clinical diagnosis (Public Health Agency of Canada, 2011; Weir & Bonner-Weir, 2004). This process usually occurs over a total of 10 years according to the available literature, and can be considered as a continuum involving five stages because it has been reported that individuals can experience both progression and remission in the stages of insulin resistance and beta cell dysfunction (Weir & Bonner-Weir, 2004) With the proper treatment and management of T2DM, it is possible to experience remission from a worsened stage of insulin resistance and beta cell dysfunction to one of lesser severity (Weir & Bonner-Weir, 2004). However, this is only possible until a certain threshold (between stages 1-4), after which remission is impossible (stage 5) because of such a severe reduction in beta cell function resulting in ketosis and complete dependence on exogenous insulin for survival (Weir & Bonner-Weir, 2004). Figure 2.0

displays the onset of T2DM in a timeline continuum with the five stages of insulin resistance and beta cell dysfunction, based on literature by Weir & Bonner-Weir (2004).

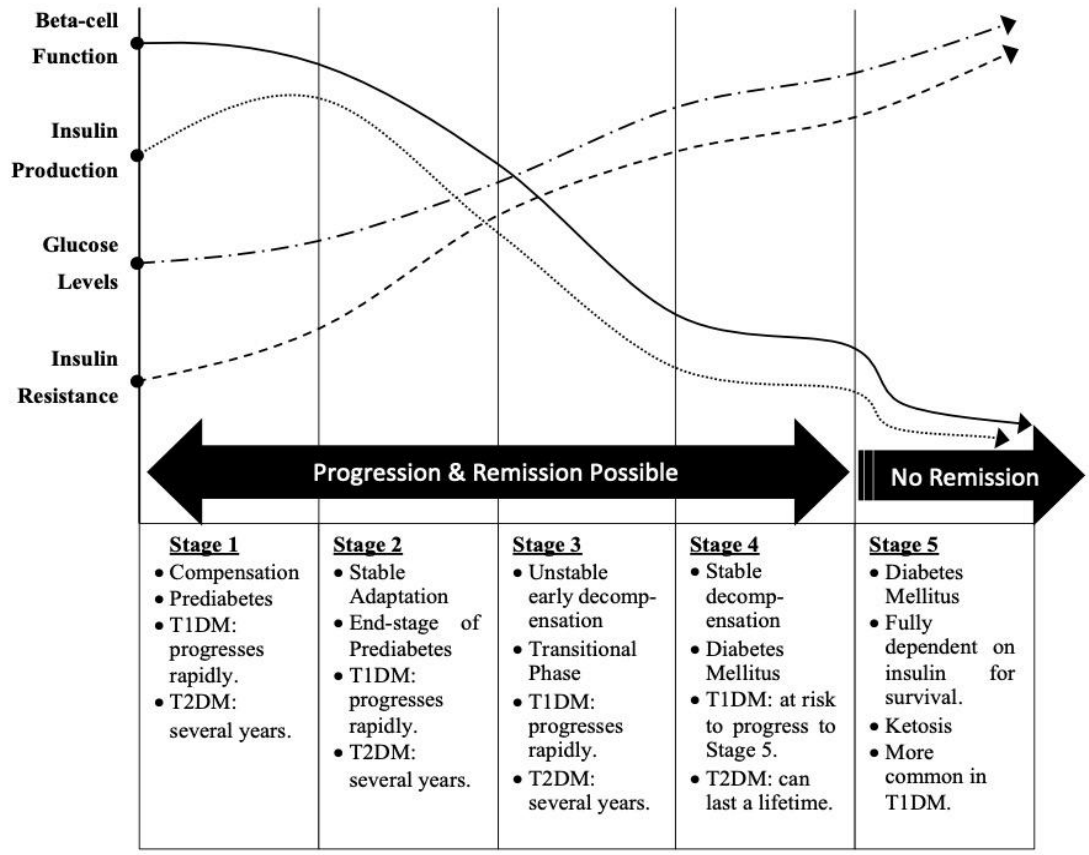

Figure 2.0: A timeline continuum of the stages of diabetes mellitus (adapted from Weir & Bonner-Weir, 2004).

GDM is a form of DM that is characterized by a state of hyperglycemia which occurs for the first time in pregnant women. This type of DM is developed during the second and third trimester of pregnancy and could impact the health of the mother as well as the child (Chiefari, Arcidiacono, Foti, & Brunetti, 2017). The onset of GDM increases the mother's chances of developing T2DM over the next 5 to 10 years by 40% to 60%

(Colberg et al., 2010). Also, there is increased risk for the child to develop T2DM early in life if the mother experienced GDM (Chiefari et al., 2017). GDM is beyond the scope of this thesis and therefore will not be further discussed.

In addition to these three types, prediabetes has also been recognized (Punthakee, Goldenberg, & Katz, 2018; Sénéchal, Slaght, Bharti, & Bouchard, 2014). Prediabetes is the term used to diagnose individuals living with impaired glucose metabolism without being altered enough to be fully diagnosed with diabetes. Nevertheless, these individuals have higher than normal blood glucose levels (Public Health Agency of Canada, 2011; Punthakee et al., 2018; Sénéchal et al., 2014). It has been reported that among individuals living with prediabetes, between 29% to 93% will develop T2DM in the years following their diagnosis (Sénéchal et al., 2014), therefore reinforcing the importance of blood glucose management for the progression towards DM.

Several tests exist to determine if an individual has DM or prediabetes, all of which involve laboratory methods using samples of venous blood (Punthakee et al., 2018). These include a fasting plasma glucose test, a casual/random (non-fasted) plasma glucose test, a two-hour plasma glucose measurement using an oral glucose tolerance test (OGTT), and a glycated hemoglobin (HbA1c) test (Public Health Agency of Canada, 2011; Punthakee et al., 2018). These methods have different requirements and provide different information to the health care provider.

A fasting plasma glucose test requires the individual to avoid consumption of any foods and liquids (except water) at least 8 hours prior to assessment. This test is simple and efficient; however, it can also have high variability from day-to-day, between samples, and only represents the individuals' blood glucose levels at this specific time point (Punthakee

et al., 2018). A casual/random (non-fasted) plasma glucose test is similar to the fasting plasma glucose test but does not require fasting of any kind. This is obviously more convenient for the participant; however, it also involves high variability from day-to-day, between samples, and again, represents only individuals' blood glucose at a single point in time (Punthakee et al., 2018). An OGTT is a dynamic test that involves the ingestion of 75g of glucose followed by a 2-hour waiting period prior to testing plasma glucose levels (Punthakee et al., 2018; Wallander, M., Malmberg, Klas, Norhammar, Anna, Rydén, Lars, Tenerz, 2008). This test is well-established as a standard procedure for testing for DM. Nevertheless, it is less convenient for the participant due to its time-consuming nature and the unpalatable taste of the glucose mixture (Punthakee et al., 2018). Another test for DM that has become more popular is the measurement of the HbA1c. There are many advantages of using HbA1c. First, this measurement is an accurate representation of long-term blood glucose. In fact, this measurement is performed on the hemoglobin, which is a protein found in the red blood cells. Since the red blood cells have a turnover rate of about three months, it has been accepted that the measure of HbA1c is a good representation of an individual's blood sugar over the last three months. Secondly, HbA1c measurement does not require a fasting state and therefore, can be performed at any time of the day (Punthakee et al., 2018). Third, although this test can be variable among individuals of different ethnicities, ages, or those with certain medical conditions (Punthakee et al., 2018), this test is usually less sensitive to the error of the device compared to typical blood samples. If an individual tests positive for DM based on any of the previously described testing methods, clinicians are recommended to perform a secondary test to confirm the diagnosis unless the individual is already experiencing symptoms of hyperglycemia

(Punthakee et al., 2018). Table 2.0 clearly displays the quantity of blood sugar levels required to be diagnosed with impaired fasting glucose, impaired glucose tolerance, prediabetes, or DM (Public Health Agency of Canada, 2011; Punthakee et al., 2018).

Table 2.0: Clinical criteria for the diagnosis of diabetes mellitus and prediabetes/impaired glycemic levels.

	Fasting Plasma Glucose (mmol/L)	2-Hour Plasma Glucose (OGTT)(mmol/L)	Glycated Hemoglobin (HbA1c) (%)	Casual/Random Plasma Glucose (mmol/L)
Impaired Fasting Glucose	5.6 – 6.9			
Impaired Glucose Tolerance		7.8 – 11.0		
Pre-diabetes	5.6 – 6.9	7.8 – 11.0	5.7 – 6.4	
Diabetes Mellitus	≥ 7.0	≥ 11.1	≥ 6.5 (in adults)	≥ 11.1; with symptoms of diabetes (polyuria, polydipsia, unexplained weight

Sources: Public Health Agency of Canada, 2011; Punthakee et al., 2018.

2.3.2 The Prevalence of Diabetes Mellitus

T1DM accounts for 5% to 10% of all cases, whereas T2DM accounts for 90% to 95% of all cases of DM (Colberg et al., 2010; Diabetes Canada, 2019; Lekan & McCoy, 2018). It was reported that in Canada between the years 2008 and 2009, one in every ten deaths were associated with complications relating to DM (Diabetes Canada, 2019; Public Health Agency of Canada, 2011). In fact, DM has been reported to reduce an individual's lifespan by up to 15 years (Diabetes Canada, 2019). In the United States, between 10% to 30% of older adults are living with DM, and greater than 50% of all cases of DM in the United States are among adults over the age of 60 years (Sinclair & Rodriguez-Mañas, 2016). Figure 3.0 represents the prevalence of diagnosed DM cases in Canada between the years 2008 and 2009. Notably, the prevalence of DM increased with age with the most dramatic increase occurring after 40 years of age (Public Health Agency of Canada, 2011).

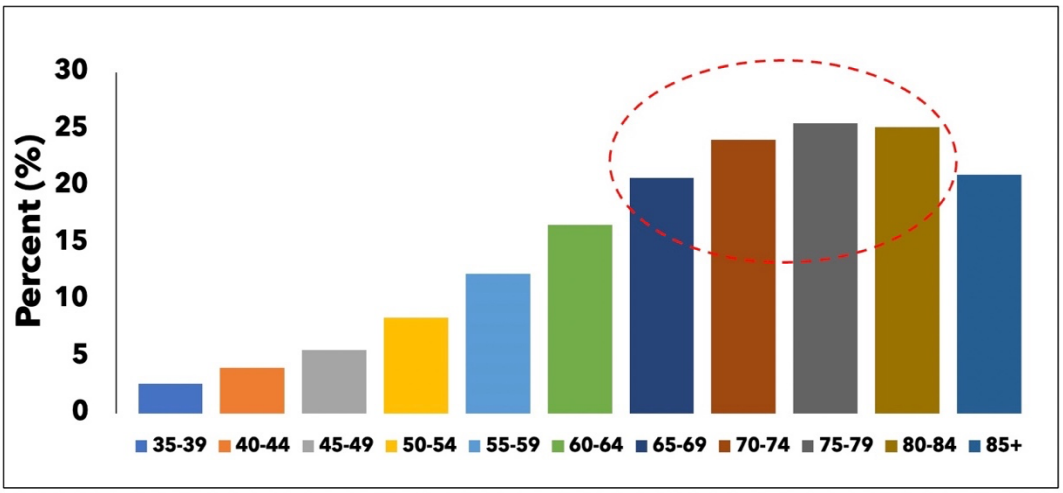

Figure 3.0: The prevalence of diagnosed diabetes mellitus in Canada (adapted from Public Health Agency of Canada, 2011).

Living with DM involves an abundance of serious health concerns. In fact, Diabetes Canada (2019) reported that the likelihood of hospitalization for cardiovascular disease is more than triple for individuals living with DM compared with the general population, and risk of hospitalization for end-stage renal disease is 12 times higher (Diabetes Canada, 2019). It was also reported that each year, DM leads to 30% of strokes, 40% of heart attacks, and 50% of kidney failure requiring dialysis (Diabetes Canada, 2019).

Amputation is common among individuals living with DM. In fact, DM is culprit to 70% of non-traumatic lower limb amputations, equating to 33.33% of all amputations performed in 2011 to 2012 (Diabetes Canada, 2019). Risk of hospitalization for non-traumatic lower-limb amputations is 20 times higher for individuals living with DM compared to the general population (Diabetes Canada, 2019).

Diabetes Canada (2019) reported that individuals living with DM are also 25 times more at risk of developing blindness than those living without DM. It was also reported that 500,000 Canadians are affected by diabetic retinopathy; and that among Canadians younger than 50 years of age, DM is currently the leading mechanism of acquired blindness (Diabetes Canada, 2019).

Along with the physical health concerns relating to DM, there also exists serious mental health concerns. Diabetes Canada reported that individuals living with depression are around 60% more likely to develop T2DM than individuals who are not living with depression (Diabetes Canada, 2019). In fact, among individuals already living with DM, 30% of those individuals express symptoms of depression (Diabetes Canada, 2019).

2.3.3 The Financial Burden of Diabetes Mellitus

In New Brunswick, DM costs $100 million on the health care system, and it is projected that this cost will increase up to $127 million within this decade (Diabetes Canada, 2019). Diabetes Canada reported in 2019 that adherence to treatment for DM is frequently affected by cost. In fact, individuals living with T1DM who use multiple-day insulin injections as treatment pay between $30 to $3100 out-of-pocket annually; and those who use insulin pump therapy pay between $100 to $6200 out-of-pocket annually (Diabetes Canada, 2019). Furthermore, New Brunswickers living with T2DM using oral medication to manage their condition pay between $1100 to $2000 out-of-pocket annually (Diabetes Canada, 2019). However, for the majority of Canadians living with DM, the out-of-pocket costs associated with the treatment and management of this disease are greater than $1500 per year, consuming more than 3% of their annual income (Diabetes Canada, 2019). This is primarily concerning because the poor diet and nutritional status that is associated with DM is also linked to low socio-economic status; thereby reducing accessibility of treatment for individuals living with low socio-economic status and DM (Public Health Agency of Canada, 2011).

2.3.4 The Relationship between Diabetes Mellitus and Frailty Status

Older adults are at increased risk of developing both DM and frailty compared to younger adults (Cacciatore et al., 2013; Sinclair & Rodriguez-Mañas, 2016). The presence of DM in older adults is associated with decreased muscle strength, muscle quality, and muscle mass; and also increases risk for older adults to experience an accelerated ageing process and the development of frailty (Cadore & Izquierdo, 2015). In fact, it was reported

that older adults living with DM are twice as likely to report physical function challenges (such as performing activities of daily living) compared with older adults without DM (Pariser, Hager, Gillette, Golemboski, & Jackson, 2014). Emerging evidence suggests that frailty may be an important predictor of premature mortality among individuals living with DM, and that individuals living with DM are at greater risk for becoming frail (Cacciatore et al., 2013; Lekan & McCoy, 2018). Cacciatore et al. (2013) compared mortality in relation to clinical frailty status using the "Frailty Staging System" between individuals with and without DM after a 12-year follow-up. The authors found that individuals who were living with both DM and frailty were at increased risk for mortality, and that men living with frailty (both with and without DM) were at higher risk than women for mortality (Cacciatore et al., 2013).

The association between frailty and poor blood glucose control has been reported by many (Ali, McKeever Bullard, Imperatore, Barker, & Gregg, 2012; Bruce, Davis, & Davis, 2005; De Rekeneire et al., 2003; Figaro et al., 2006; Gregg et al., 2000; Pariser et al., 2014). A review by Yanase et al. (2018) explained that insulin resistance and insulin depletion may be important factors in the progression of frailty among individuals living with DM (Yanase et al., 2018).

Both frailty and DM have detrimental health implications resulting in decreased physical function and increased risk for disability, hospitalization, and mortality; however, increased PA has been suggested as a method for the treatment and management of both conditions (Marzetti et al., 2017; Sinclair, Abdelhafiz, & Rodríguez-Mañas, 2017; Sinclair & Rodriguez-Mañas, 2016; Yanase et al., 2018). A combination of both aerobic and RT has been widely accepted for the older adult population living with T2DM (Cadore &

Izquierdo, 2015; Davidson et al., 2009; O'Hagan, De Vito, & Boreham, 2013). However, the added functional detriments included with frailty suggest that for older individuals living with both frailty and T2DM, an emphasis should be placed on RT in order to aid in the maintenance of frailty and DM simultaneously, while still including some additional aerobic exercise components (Cadore & Izquierdo, 2015; Praet & Van Loon, 2007).

2.4 Physical Activity and Sedentary Time

2.4.1 The Definition of Physical Activity and Sedentary Time

PA is defined as any movement of the body that elevates the metabolic rate above a resting state by use of skeletal muscles (Colberg et al., 2010). Whereas exercise is defined as a form of PA that is intentionally performed for the purpose of improving one's level of physical fitness (Colberg et al., 2010). For example, aerobic and strength training are forms of exercise (Colberg et al., 2010). Often, the terms exercise and PA are used interchangeably in order to encompass all forms of movement that may have a positive impact on health (Colberg et al., 2010).

Sedentary time is defined as any time spent using minimal energy levels while seated, reclined, or lying down, except for sleeping (Patterson et al., 2018; Tremblay et al., 2017). The consensus established to define sedentary time according to the Sedentary Behavior Research Network is similar, but with the specific addition of any waking time expending ≤1.5 metabolic equivalents (METs) (Tremblay et al., 2017).

2.4.2 Physical Activity and Sedentary Time and Older Adults

The PA guidelines for Canadians were developed based on research outlining a dose-response relationship between PA for different age groups and different health outcomes (Tremblay et al., 2011; Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2012). For adults between the age 18 to 64 years, the guidelines are focused on PA for the prevention of all-cause mortality and seven chronic diseases: cardiovascular disease,

stroke, hypertension, colon cancer, breast cancer, T2DM, and osteoporosis (Tremblay et al., 2011; Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2012). Whereas, the guidelines for adults aged 65 years or older are based on research evidence supporting the relationship between PA and physical function (Tremblay et al., 2011; Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2012). However, the current guidelines were designed as a guide to promote healthy behaviours for the general Canadian population and are not specifically tailored to individuals living with chronic conditions or frailty (Gault & Willems, 2013; Tremblay et al., 2011; Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2012).

However, according to Statistics Canada survey results from the year 2017, Canadians aged 60-79 years engaged in an average of 590 minutes per day of sedentary time, while only engaging in an average of 18 minutes per day of moderate to vigorous PA (MVPA) (Statistics Canada, 2020). Of all Canadians aged 60-79 years, 83.1% were not meeting the Canadian Physical Activity Guidelines (Statistics Canada, 2020). Moreover, of all Canadians aged 40-59 years, 83.2% were not meeting the Canadian Physical Activity Guidelines (Statistics Canada, 2020). According to these statistics, it is evident that physical inactivity is problematic for the majority of Canadians- especially for older adults.

2.4.3 Physical Activity and Sedentary Time and Frailty

PA has been reported as an effective method for the prevention and management of frailty for individuals and preserves or improves physical function (Fried, 2016; Lee et al., 2020; Marzetti et al., 2017; Sinha et al., 2018; Theou et al., 2011). Data supports the importance of meeting the national PA guidelines for the prevention of frailty (Department

of Health & Human Services, 2018; Kehler et al., 2020; Liu & Fielding, 2011; Tremblay et al., 2011; Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2012).

Recent literature suggests that sedentary time should be considered independently from PA for the prevention and management of frailty because the association of sedentary time with frailty is independent from the association of PA with frailty (Blodgett, Theou, Kirkland, Andreou, & Rockwood, 2015b; Kehler & Theou, 2019; Thorp, Owen, Neuhaus, & Dunstan, 2011; Tremblay, Colley, Saunders, Healy, & Owen, 2010). However, more research is needed to obtain a consensus on specific guidelines for sedentary time (Thorp et al., 2011; Tremblay et al., 2017; Tremblay et al., 2010).

As bouts of sedentary time last longer, it has been associated with an increase in odds of frailty status (Kehler et al., 2018; Kehler, 2018; Kehler & Theou, 2019; Nagai et al., 2018). Consequently, individuals with higher frailty status have been shown to exhibit higher sedentary time and reduced PA patterns (Blodgett et al., 2015b). A systematic review by Ekelund et al. (2016) reported that increased sedentary time is also associated with increased mortality risk. Although increased levels of PA may reduce the risks associated with high sedentary time, it does not eliminate the risks altogether (Ekelund et al., 2016). A cross-sectional study by Nagai et al. (2018) examined the effect of replacing 30 minutes of sedentary time with light PA and MVPA, separately. This study reported that risk for frailty was significantly decreased by 16% in the light PA group, and by 42% in the MVPA group; however, when adjusted for covariates, only the light PA group maintained a significant reduction in risk of frailty (Nagai et al., 2018). This study suggests that replacing sedentary time with light PA seems more attainable for individuals living with or at risk of developing frailty than engaging in MVPA to replace sedentary time

(Nagai et al., 2018). Therefore, not only is it important to remain physically active to reduce risk of frailty with ageing, but also important to reduce sedentary time (Kehler, 2018; Kehler et al., 2019; Kehler & Theou, 2019; Marzetti et al., 2017; Nagai et al., 2018).

However, to the best of our knowledge there are currently no structured PA guidelines for individuals who have already been diagnosed with frailty. The Canadian Physical Activity Guidelines advise that older adults living with frailty, a disability, or a medical condition may find the guidelines appropriate to follow although the guidelines are only tailored to apparently healthy older adults (Tremblay et al., 2011). Most studies support that more research is needed to determine the most effective type, frequency, and duration of exercise specifically for frail individuals (Chin A Paw, Van Uffelen, Riphagen, & Van Mechelen, 2008; Daniels, Metzelthin, van Rossum, de Witte, & van den Heuvel, 2010; Daniels, Van Rossum, De Witte, Kempen, & Van Den Heuvel, 2008; Giné-Garriga, Roqué-Fíguls, Coll-Planas, Sitjà-Rabert, & Salvà, 2014; Marzetti et al., 2017).

2.4.4 Physical Activity and Sedentary Time and Diabetes Mellitus

PA has been known to significantly improve blood glucose in individuals living with T2DM (Colberg et al., 2010; Lumb, 2014; Schwingshackl, Missbach, Dias, König, & Hoffmann, 2014; Sigal et al., 2007; Umpierre et al., 2016). The American Diabetes Association has reported that regular PA can also improve blood pressure and blood lipids, reduce risk of cardiovascular events and mortality, improve quality of life, and even prevent or delay T2DM (Colberg et al., 2010).

The American Diabetes Association recommends 150 minutes of MVPA per week for individuals living with T2DM and specifies that the bouts of MVPA should be spread

out over at least 3 days of the week, with no more than 2 consecutive days between bouts of aerobic activity (Colberg et al., 2010; Little et al., 2011). It is also recommended that individuals living with T2DM participate 2-3 times per week in moderate-to-vigorous RT (Colberg et al., 2010). A systematic review by Umpierre et al. (2016) supports the positive health impacts of the PA guidelines for individuals living with T2DM; however, the review also concluded that individuals who performed more than the recommended 150 minutes of MVPA weekly experienced even greater HbA1c declines than those who met the guidelines or less (Umpierre et al., 2016).

Sigal et al. (2007) reported that performing a combination of aerobic exercise and RT was more effective in managing glycemic control than only aerobic or only RT. Sigal et al. (2007) noted significant reduction in HbA1c of about 1% for the combination group; however, in this study the combination group performed a much higher overall volume of exercise compared to the other groups. Nevertheless, all exercise groups experienced significant improvements in glycemic control compared to individuals in the control condition (Sigal et al., 2007). A similar study was conducted by Church et al. (2010) which addressed the issue of training volume among training groups. After matching the total volume of exercise training across all three groups, this study reported that the combined training group still experienced a significantly greater reduction in HbA1c compared with the aerobic training and RT groups (Church et al., 2010). Although, the improvements reported by Church et al. (2010) were slightly less than the improvements reported by Sigal et al. (2007) it can be concluded that for similar total work, combining aerobic exercise and RT is more efficient for glycemic control in individuals with T2DM.

While the health benefits and importance of PA is widely known, most individuals living with T2DM do not engage in enough PA to acquire any of the associated benefits (Falconer, Page, Andrews, & Cooper, 2015). Sedentary time may exhibit a powerful role in the mechanism of DM, especially prolonged bouts of sedentary time (Falconer et al., 2015). In fact, a meta-analysis by Patterson et al. (2018) investigated the dose-response relationship between sedentary time and T2DM. They calculated relative risk of the exposure variables through regression models and adjusted for PA. It was reported that relative risk for T2DM generally increased with increasing hours of TV viewing (sedentary time) per day (Patterson et al., 2018). Similar results were observed for total sedentary time and all-cause mortality; with small increases in relative risk present with lower levels of exposure to sedentary time, and larger increases in relative risk with larger levels of sedentary time (Patterson et al., 2018). A meta-analysis by Dempsey et al. (2014) reported that among developed countries, studies that were performed using accelerometers identified that adults spent between 55% to 70% of their non-sleeping hours engaged in sedentary time (Dempsey, Owen, Biddle, & Dunstan, 2014).

2.5 Gap in the Literature

Frailty as well as DM have been associated with increased health complications and premature mortality. New evidence suggests that the combination of both frailty and DM is associated with greater complications and greater premature mortality compared to frailty alone. To date, increased PA and reduced sedentary time have been proposed as corner stones for the prevention, treatment, and management of frailty in older adults. In fact, emerging evidence suggests that PA can reduce severity of frailty and sedentary time and confer a protective effect against frailty severity and premature mortality. Although this is the case for individuals living with frailty, to the best of our knowledge, no studies have been investigating the association between PA types and intensities and sedentary time on frailty status in frail individuals living with DM. This an important research question as it targets a subgroup of the population that could benefit the most from recommendations for PA and sedentary time, since these individuals are already at higher risk of health complications compared to an apparently healthy individual. Currently, some PA guidelines exist for individuals living with frailty and DM, but no current guidelines exist targeting sedentary time for this population. Evidently, the investigation of the association between PA and sedentary time on frailty status in individuals living with DM is pertinent to the development of specific PA and sedentary time guidelines for these individuals.

2.6 Purpose and Hypotheses

2.6.1 Purpose of the Study

The purpose of this study is to explore the relationship between various types of PA (RT, Light PA, MVPA) and frailty status in adults living with DM. This information will add to existing literature by assessing what might be the best types of PA for the prevention or management of frailty in adults who are already living with DM.

2.6.2 Hypotheses

1. Adults with DM with lower total PA levels and/or higher total sedentary time will be associated with worse frailty status (more frail).
2. Adults with DM with higher total PA levels and/or lower total sedentary time will be associated with improved frailty status (less frail).
3. Adults with DM who perform RT on a weekly basis will be associated with an improved frailty status (less frail).

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Chapter 3: Article

Association Between Physical Activity & Sedentary Time on Frailty Status in Men and Women Living with Diabetes Mellitus: A Cross-Sectional Analysis

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3.1 Abstract

Background: Increased physical activity (PA) is as a cornerstone for the prevention and the treatment of diabetes mellitus (DM) and frailty. However, no consensus exists on which types of PA, resistance training (RT), and sedentary time are associated with frailty status among individuals living with DM.

Objective: To investigate the association between time engaged in PA, RT, and sedentary time on frailty status in males and females living with DM.

Methods: A cross-sectional analysis of 711 participants living with self-reported DM from the 2003-2006 National Health and Nutrition Examination Survey (NHANES) was performed. Frailty status was measured using the 46-item deficit model. PA levels were measured by accelerometer, while RT was measured via questionnaire.

Results: RT was not associated with improved frailty status, while total time spent performing light PA was associated with improved frailty status ($p<0.05$). In women only, total moderate-to-vigorous PA (MVPA) was associated with improved frailty status ($p<0.05$), while sedentary time was associated with worsened frailty status ($p<0.05$). Every minute performing MVPA was associated with a 5% and 6% lower likelihood of frailty in men and women, respectively (all $p<0.05$).

Conclusions: Although RT is not associated with improved frailty status, each minute performing PA is associated with improved frailty status in men and women with DM. For women with DM, replacing sedentary time with PA is especially important for reducing frailty. These results provide further understanding on types of PA and sex differences in relation to prevention and management of frailty for individuals with DM.

3.2 Introduction

Diabetes mellitus (DM) is a constantly growing health condition that leads to complications resulting in impaired physical function or disability.[1-4] Current data suggests that individuals living with DM are at greater risk of developing frailty, and that the two conditions often go hand-in-hand, presenting very similar consequences.[1-10] This is not trivial as frailty is characterized by a decrease in physiological reserve and function of multiple organs and systems, which increases vulnerability and compromises the ability for older adults to cope with daily minor stressors.[11] This is of great concern since new evidence has shown that the combination of both frailty and DM is associated with a greater health burden and greater risk for premature mortality.[6-8] Together, these data reinforce the need for a better understanding of the utility of different interventions for the prevention and the management of frailty in individuals with DM.

Increasing physical activity (PA) and reducing sedentary time have been suggested as a strategy of choice for the treatment and management of DM and frailty.[2,3,10,12-15] In fact, the American Diabetes Association recommends that individuals living with DM participate in weekly moderate-to-vigorous PA as well as resistance training (RT).[16-19] The current body of evidence also highlighted RT as an important component to the prevention and management of frailty due to its positive effects on muscle strength, muscle mass, and physical function.[12,18,20-25] However, a multi-modal intervention approach including a combination of aerobic exercise and RT has been shown effective for frailty management. Nevertheless, RT prescription parameters are inconsistent among the literature, which presents a challenge for health care providers.[20,21,24,26,27] Although some data supports the importance of meeting the national PA guidelines for the prevention of frailty,[13,28-31]

emerging evidence has shown a dose-response relationship between higher amounts of PA and lower frailty levels,[14,32] and suggests that moderate-to-vigorous-intensity PA (MVPA) has a greater protective effect against frailty severity and premature mortality compared to light-intensity physical activity.[33] Furthermore, reducing sedentary time has been shown as a crucial aspect for the management of frailty.[33,34] Nevertheless, to the best of our knowledge no structured PA guidelines exist for people living with both DM and frailty and the limited information on this topic remain unclear;[12,18,22,35] therefore, no studies have investigated the association between PA, sedentary time, and RT in a sample of men and women living with both frailty and DM.

Consequently, the objective of this study was to investigate the association between sedentary time, light PA, MVPA, and RT on frailty status in a sample of men and women living with DM. We hypothesized that individuals living with DM who performed higher level of light PA, MVPA, and RT would have lower frailty status compared to less active individuals.

3.3 Methods

3.3.1 Study Design and Population

This study is a cross-sectional analysis from the National Health and Nutrition Examination Surveys (NHANES), which was conducted in the United States. Individuals from the 2003-2004 and 2005-2006 NHANES cycles were included. During the 2003-2004 and 2005-2006 cycles, NHANES began using accelerometry to objectively measure PA data of the United States population.[36,37] This objective measure of PA levels has allowed a more in-depth analysis of various intensities and durations of PA in the population, as opposed to self-reported data alone.[36,37]

To be eligible for this study, participants were required to have at least one valid week of accelerometer data, which was defined as four or more days of wear-time with a minimum of 10-hours of wear-time per day. Participants were also required to have self-reported DM. In order to maintain consistency with previous studies and guidelines for using the frailty index,[34,41,42] participants were only eligible if they presented data for at least 80% of the items required to create the 43-item frailty index. In addition, in order to maximize our sample size, we included participants that were aged 21 years or older. Selection of this lower age threshold was based on the rationale that frailty is not exclusive to an older adult population and has been shown to begin at an early stage of life.[6,38,39] Therefore, the inclusion of younger adults in addition to an older adult population allowed further insight on the relationship between various PA and sedentary time on frailty status in a population of individuals living with DM.

Briefly, from the original 18702 participants, 17642 were excluded because they had missing data or reported “no” for self-reported DM. Of the 1060 remaining

participants, none were missing for the 43-item frailty index and RT, while 349 were excluded because they had missing data for valid days of accelerometry wear-time. Thus, our final sample size was 711 participants living with DM, as displayed in Figure 1.0. The study protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) prior to data collection and all participants provided a written informed consent.[40]

In NHANES, participants were randomly selected with stratified multistage probability sampling. Participants completed surveys and attended the NHANES Mobile Examination Centre (MEC) for a physical examination. The MEC was set up in a location that was familiar and easily accessible to the residential areas of participants. Data was collected in a standardized environment to avoid site-specific error.

3.3.2 Frailty Status

A frailty index was constructed according to standardized procedures, which has been published elsewhere.[41] Briefly, a frailty index must meet the following criteria: 1) the variable must be associated with poor health outcomes, 2) the variable's prevalence must increase with age, 3) all variables included must cover a wide range of physiological systems, 4) the same frailty index variables must be used from one assessment to the next among the same sample population, and 5) a different set of variables can be used when assessing a different sample population.

Based on the rationale that our sample consisted of a broad age group, a sensitive frailty index was necessary. Therefore, we used a modified version of the 46-item deficit model developed in NHANES by Searle et al. (2008).[41] The 46-item deficit model is sensitive and included a combination of self-reported and objectively measured data spread

through 5 main categories: comorbidities, functions, signs and symptoms, laboratory values, and others self-reported information.[42] Since our sample was strictly composed of individuals with DM, we used a modified 46-item deficit model from which DM, blood glucose serum, and glycohemoglobin were removed. Therefore, our final frailty index was composed of 43-items.

Measurement of each participants' frailty status was executed by counting the sum of the deficits present for each individual, divided by the total number of deficits (43 in our case).[41,42] Following that calculation, each participant's frailty index score ranged on a scale between 0 and 1, as has been used in previous studies.[33,34,41] This scale was multiplied by a factor of 100 to provide a final frailty score on a 100-point scale in order to quantify percent frailty per individual.[33]

3.3.3 Physical Activity Measures

PA and Sedentary Time: Participants were asked to wear an accelerometer for seven consecutive days. The accelerometer was worn on their right hip attached to an elastic belt and customized to each participant's waist circumference. The accelerometer used was an ActiGraph (Model: AM-7164 ActiGraph Corp., Pensacola Fl). Participants were instructed to wear the accelerometer during all waking hours for seven consecutive days and to remove it at night and during water-based activities (e.g., bathing, swimming).[36,40] The accelerometer was set to record activity in 1-minute epochs and only participants who had worn the accelerometer for a minimum of four days with a minimum of 10 hours per day were included in this study.[34,36]

Non-wear time was assessed as any time interval of 60 minutes or greater of continuous zero counts,[36] while sedentary activity was considered 0-100 counts/minute,

light activity 101-2020 counts/minute, moderate activity 2021-5999 counts/minute, and vigorous activity ≥ 6000+ counts/minute. Moderate and vigorous PA were merged as Moderate-to-Vigorous Physical Activity (MVPA). Total sedentary time and total time engaged in light PA and MVPA were measured by any bout length lasting ≥1 minute.[13,33,43,44]

3.3.4 Resistance Training Activities

Resistance Training Activities: Participants were asked two questions regarding their RT activities. The questions specifically targeting RT included the following:

1) Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles such as lifting weights, push-ups or sit-ups?
2) Over the past 30 days, how often did you do these physical activities? (This number was multiplied by 12 months to provide a yearly frequency, then divided by 52 to provide a number per week of strength training activities performed.)

3.3.5 Confounding Variables

Confounding variables included age, sex, ethnicity, marital status, education status, smoking status, alcohol consumption, and BMI. Apart from BMI, which was collected in the mobile examination center, the other confounders were collected through in-person household interviews.

All anthropometric data [height, weight, waist circumference, and body mass index BMI)] were measured according to the Anthropometric Standardization Reference Manual. The subjects' BMI were calculated by dividing their weight in kilograms (kg) by the square of their height in meters (m^2).

Age, sex, ethnicity, marital status, education status, smoking status, and alcohol consumption were self-reported. Categories were created for ethnicity including Hispanic, non-Hispanic white, non-Hispanic black, and other; marital status was organized in the following categories: married, without partner, and living with a partner; education levels of participants were divided as high school or lower, some college/university, and college/university graduate or above; smoking status was divided as non-smoker, former smoker, current smoker; and alcohol intake was calculated as follows: non-drinker (0 drinks/day), light-moderate drinker (0.001-2.99 drinks/day), and heavy drinker (≥3 drinks/day).

3.3.6 Statistical Analysis

Data are presented as Mean ± Standard Deviation (SD) unless otherwise stated, while categorical variable are presented as n (%). Data was statistically and visually assessed for normality. An interaction analysis was conducted between sex and sedentary time, light PA, MVPA, and RT and was found to be significant ($p<0.05$). Additionally, previous literature has identified sex differences in frailty status;[13] therefore, results are presented stratified by sex. Multiple linear regression analyses were performed to assess the association between RT, PA, sedentary time, and frailty status in individuals living with DM. Linear regression models were run for total time in light PA, MVPA, and sedentary time. The RT multiple linear regression included a model for both RT questions (yes/no, frequency).

In the literature, studies using the 46-item frailty status categorized the stages of frailty in this continuum using the following categorization: Non-frail= 0-0.10; Vulnerable= 0.10-0.20; Mildly frail= 0.21-0.30; Moderately frail= 0.31-0.40; Severely

frail= >0.41.[42] Therefore, we created dichotomous variables of frailty status to be used in the logistic regression analyses. This was done by combining individuals with a frailty status ≤0.2 (non-frail and vulnerable individuals), and individuals with a frailty status >0.2 (mild, moderate, and severely frail individuals).[42] Logistic regression analyses were performed to evaluate the odds of a worse frailty status between total time in light PA, MVPA and sedentary time among individuals living with DM. Separate models were conducted for each type of PA and sedentary time for logistic regression as well. The RT models for logistic regression included a model for both RT questions (yes/no, frequency). Each analysis was adjusted for the following potential confounding variables: age, sex, race/ethnicity, education, marital status, alcohol consumption, smoking status, and BMI. All the analyses accounted for the complex survey design and sample weight. Data management and statistical analysis were performed using RStudio software version 1.2.1335.

3.4 Results

Table 1 describes general characteristics of our sample as a whole or stratified by sex. Overall, our sample has a mean age of 62.6 ± 13.8 years and was mainly composed of men (51.3%), and Caucasian (43.2%) individuals. Men and women were significantly different for marital status, education level, smoking status, and alcohol consumption (all $p<0.05$). Men spent less hours per day in light PA compared to women (Men: 3.93 ± 1.18 vs. Women: 4.17 ± 1.30; $p<0.05$) and more hours per day in MVPA compared to women (Men: 0.24 ± 0.30 vs. Women: 0.13 ± 0.19; $p<0.05$). No such differences were observed between men and women for RT ($p>0.05$)

Table 2 shows multiple linear regression models for types of PA and sedentary time stratified by sex. Analyses stratified by sex revealed that total time in light PA was negatively associated with frailty status in men ($p<0.05$) and women ($p<0.05$). Total MVPA time was negatively associated with frailty status in women ($p<0.05$), while total sedentary time was positively associated with frailty status in women only ($p<0.05$). Similar results were observed for light PA and MVPA (all $p<0.05$; Table 3) once further adjustments were performed for the opposite PA component (sedentary time, light PA, or MVPA). However, although sedentary time was positively associated with frailty status once adjusted for total MVPA ($p<0.05$), this association did not remain once adjusted for light PA ($p>0.05$). Performing RT was not associated with frailty status in men and women in Table 2.0 models ($p>0.05$); however, an association ($p<0.05$) was observed in females between performing RT and worse frailty status when linear models were adjusted for MVPA alone (Table 3).

As displayed in Table 4, total time in light PA showed a statistically significant reduced odds of frailty in women OR 95% CI: 98.5 (0.980 - 0.991) and men OR 95% CI: 99.3 (0.989 - 0.998). Total time in MVPA showed a statistically significant reduced odds of frailty in both women OR 95% CI: 94.6 (0.908 - 0.986) and men OR 95% CI: 95.0 (0.909 - 0.993). Every minute spent in sedentary time was associated with increased odds of frailty OR 95% CI: 100.7 (1.004 – 1.010) in women only. Table 5 clearly displays congruent results for odds of frailty status in women and men with DM for total time in light PA, MVPA, and sedentary time all independent of opposing activity levels. RT did not display any statistically significant associations with odds of frailty status in female or male participants ($p>0.05$).

3.5 Discussion

The main objective of our study was to investigate the association between time engaged in PA, RT, and sedentary time on frailty status in a sample of men and women living with DM. Our study showed that increasing total time engaged in light PA was helpful toward reducing risk of frailty in both men and women living with DM. However, the intensity of PA appeared to be an important factor for women only, with MVPA associated with an even greater reduction in risk of frailty for women only. Additionally, every minute spent engaged in sedentary time was associated with an increased risk of frailty for women only. These data suggest that replacing sedentary time with any intensity of PA is beneficial especially for women living with DM in order to reduce risk of frailty. Finally, RT was not associated with improved frailty status in our sample of men and women living with DM. These results are important as they provide further insights into the prevention and the management of frailty in individuals living with DM and further understanding in the associations between types of PA and sex.

In our study we found that total sedentary time, and total light and MVPA were associated with frailty status, and logistic regression showed increased odds of frailty with increased sedentary time and reduced odds of frailty with increased PA time, suggesting that independent of intensity, sedentary time and PA time are associated with frailty status. These results align with a whole body of evidence suggesting the importance of increasing PA and reducing sedentary time.[13,14,26,32,33,45-47] A recent study reported that low PA levels combined with excessive sedentary time were associated with increased frailty (2.83 95% CI: 1.26-6.52). Similarly, Kehler & Theou (2019) reviewed the association between sedentary time and PA on frailty status in individuals aged 50 years and above and they

found that sedentary time was associated with frailty independently of PA levels.[33] Our data also support this result, since total sedentary time adjusted for total MVPA was associated with reduced frailty status (Table 3). Altogether, our data confirm existing data on the importance of reducing sedentary time and increasing PA, but also add to the body of evidence by providing further information on the association between sedentary time and PA and frailty in individuals living with DM.

Previous literature has shown sex differences in frailty status. In fact, it is well established that females have higher prevalence of frailty[4,48-52] and are at a higher risk for frailty than males.[13,49,53] In our data, we observed sex differences in the association between frailty status and PA and sedentary time. A recent study by Kehler et al. (2019) investigated sex differences in relation to the association of PA and sedentary time with frailty status among a population of adults 50 years or older.[13] Their study found that increased levels of sedentary time were significantly associated with a worse frailty status in females, but not males.[13] Our study supports these findings and adds to that data by confirming a significant difference between men and women for the relationship between sedentary time and frailty status in individuals living with DM. In fact, in females living with DM, we observed that total sedentary time was associated with an increased frailty status in women only and total MVPA time was associated with a decreased frailty status in women only. The data from our study are valuable as they highlight the importance of reducing sedentary time and increasing MVPA in females with DM, who are at a higher risk of frailty.[13,53] To the best of our knowledge this is the first study that has investigated the association between PA and sedentary time and frailty status in a sample of men and women living with DM.

In our study, no association was found between RT and improved frailty status in individuals living with DM. On the contrary, for women only, RT displayed an association with worse frailty status once adjusted for opposing activity levels. These findings were surprising since many studies suggest that RT is associated with improved frailty status (being less frail).[12,22,54-58] In fact, a systematic review conducted by Nagaia et al (2018) investigated the impact of RT combined with PA on frailty status in older adults.[22] Despite no significant changes to a non-frail status, they observed a 43% improvement in frailty status in the group that performed RT and PA, while only 25% improvement was observed in the RT group alone. Furthermore, a small randomized controlled trial has been studying the impact of 8-weeks of elastic band RT on frailty status in pre-frail individuals.[59] Compared to the control conditions, they observed that following 4 and 8 weeks of elastic band RT, 51.5% and 81.8% of participants went from a mid-frail status to a non-frail status. Altogether, these results strongly suggest the importance of RT to better manage frailty in older adults. Nevertheless, our results do not support these data and the discrepancies could be explained by different reasons. First, the sample selection in the study conducted by Chen et al. (2019) included only people who were pre-frail based on the Fried definition.[59] In our study we first included only people living with DM and used a 43-item deficit accumulation frailty index. Therefore, since they excluded people with major health issues, it is likely that our population was potentially frailer based on potential complications of DM. Nevertheless, our data align with new data highlighting the challenges of changing frailty status (reverting to a non-frail status) when DM is combined with frailty.[6]

3.5.1 Limitations

This study had some limitations that need to be highlighted. Firstly, the cross-sectional association does not allow to make causal inference. Second, the RT questionnaire used in the study, in addition to the low number of participants who confirmed participating in RT, potentially did not allow us to capture RT properly, which might have impacted our results. Third, although we tried to maximize our sample size, we had a small final sample size because of the research question that required valid accelerometry, RT data, and people with DM. And finally, although the use of accelerometry in this study to objectively measure PA was beneficial compared with subjective measures, the accelerometry technology used also had limitations. Due to the placement of the accelerometers on participants' hip, the accelerometer did not accurately account for postural differences in certain types of PA where individuals might be seated, such as cycling. The cut-points for the accelerometry intensities (sedentary, light PA, MVPA) were also absolute values based on validated counts per minute; however, since these values are not relative to everyone's personal fitness level, the actual PA intensities with which an individual engaged could be skewed. Therefore, it is possible MVPA was under-estimated.

3.5.2 Strengths

Nevertheless, our study has some strengths that must be identified. First, our exposure variable of PA was objectively measured using accelerometry and only valid data were included in these analyses. Second, all the analyses were adjusted for multiple confounders and were weighted, which help increase external validity of our findings. Finally, the use of the Frailty Index for quantifying frailty status in our study provided the

ability to manipulate the index in order to study frailty status in a population living with DM.

3.5.3 Conclusion

It is known that the prevalence of frailty and DM is on the rise and that oftentimes, both conditions occur together and worsen together. However, PA has been well-established as a possible solution to the treatment and management of both conditions. This study provides further insight into the relationship of PA and frailty in this population of men and women living with DM by the discovery that every active minute counts toward a reduced association and odds of frailty in men and women with DM. However, an important sex difference with females was observed, showing that for females living with DM, minimizing sedentary time and replacing that time with light or MVPA appears to be especially important for reduced frailty status. Our data shows that MVPA has a more meaningful association with reduced frailty status than light PA; however, it is known that this population sample does not realistically engage in high levels of MVPA. In conclusion, if females living with DM, can achieve more minutes of MVPA, that has the greatest association with reduced frailty status, but an increase in any PA intensity in replacement of sedentary time is associated with reduced frailty status. Finally, further research is warranted to better understand the relationship between RT and frailty in a population of men and women living with DM, since in this study RT did not appear to have any association with improved frailty status.

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Table 1: Descriptive Characteristics of our Sample.

	Full sample (n=711)	Male (n=365)	Female (n=346)	p-value
Sex (% male)	365 (51.34)			
Age (years)	62.60 ± 13.84	62.62 ± 13.56	62.58 ± 14.16	.97
Weight (kg)	86.11 ± 21.31	90.15 ± 20.46	81.87 ± 21.38	<.01
BMI (kg/m^2)	31.05 ± 6.83	29.89 ± 5.76	32.28 ± 7.63	<.01
Waist Circumference (cm)	106.15 ± 15.00	107.28 ± 14.82	104.93 ± 15.11	.04
Race/Ethnicity n (%)				.95
Mexican American	183 (25.74)	94 (25.75)	89 (25.72)	
Non-Hispanic white	307 (43.18)	157 (43.01)	150 (43.35)	
Non-Hispanic black	175 (24.61)	90 (24.66)	85 (24.57)	
Other	46 (6.47)	24 (6.58)	22 (6.36)	
Marital Status n (%)				<.01
Not Married	281 (39.52)	111 (30.41)	170 (49.13)	
Married	430 (60.48)	254 (69.59)	176 (50.87)	
Education n (%)				.11
≤11th Grade	270 (37.97)	145 (39.73)	125 (36.13)	
High School/GED or Equivalent	180 (25.32)	72 (19.73)	108 (31.21)	
Some College or AA degree	173 (24.33)	88 (24.11)	85 (24.57)	
College Graduate or above	88 (12.38)	60 (16.44)	28 (8.09)	
Smoking Status n (%)				<.01
Non-Smoker	340 (47.82)	125 (34.25)	215 (62.14)	
Previous Smoker	250 (35.16)	166 (45.48)	84 (24.28)	
Current Smoker	121 (17.02)	74 (20.27)	47 (13.58)	
Alcohol Consumption n (%)				<.01
Non-Drinker	353 (49.65)	157 (43.01)	196 (56.65)	
Light-Moderate Drinker	326 (45.85)	189 (51.78)	137 (39.60)	
Heavy Drinker	6 (0.84)	6 (1.64)	0 (0.00)	
Sedentary Time (hours/day)	8.77 ± 2.12	8.81 ± 2.22	8.74 ± 2.01	.64
Light PA (hours/day)	4.05 ± 1.24	3.93 ± 1.18	4.17 ± 1.30	.01
Moderate PA (hours/day)	0.18 ± 0.25	0.23 ± 0.30	0.13 ± 0.18	<.01
Vigorous PA (hours/day)	0.00 ± 0.02	0.00 ± 0.01	0.00 ± 0.03	.88
MVPA (hours/day)	0.19 ± 0.26	0.24 ± 0.30	0.13 ± 0.19	<.01
RT Participation n (%)				.47
Yes	112 (15.75)	61 (16.71)	51 (14.74)	
No	599 (84.25)	304 (83.29)	295 (85.26)	
If Yes, Weekly RT Frequency n (%)	4.51 ± 5.25	4.84 ± 6.72	4.12 ± 2.59	.48

Data are presented as mean ± SD for continuous variables and as n (percentages) for categorical variables; p-value = significant difference between men and women.

Table 2: Association Between Types of Physical Activity and Sedentary Time on Frailty Status in Men and Women Living with Diabetes Mellitus

	Male (n=365)		Female (n=346)	
	Beta (SE)	**p-value**	**Beta (SE)**	**p-value**
Total Time Sedentary	0.005 (0.009)	0.57	0.034 (0.005)	**<0.01**
Total Time Light PA	-0.041 (0.012)	**<0.01**	-0.070 (0.010)	**<0.01**
Total Time MVPA	-0.138 (0.094)	0.14	-0.235 (0.061)	**<0.01**
RT: Yes/No (Yes)	-3.079 (1.919)	0.11	1.625 (1.974)	0.41
RT: Weekly Frequency	-0.222 (0.180)	0.22	0.658 (0.483)	0.17

Data are presented as Beta, Standard Error (SE). Each linear regression model was adjusted for age, ethnicity, education, marital status, BMI, smoking status, and alcohol consumption.

Table 3: Association Between Types of Physical Activity and Sedentary Time on Frailty Status in Men and Women Living with Diabetes Mellitus Independent of Opposing Activity Levels

	Male (n=365)		Female (n=346)	
	Beta (SE)	**p-value**	**Beta (SE)**	**p-value**
Total Time Sedentary**	-0.004 (0.009)	0.63	0.022 (0.005)	**<0.01**
Total Time Sedentary ***	-0.0002 (0.008)	0.98	0.029 (0.005)	**<0.01**
Total Time Light PA *	-0.044 (0.011)	**<0.01**	-0.059 (0.011)	**<0.01**
Total Time Light PA***	-0.036 (0.011)	**<0.01**	-0.068 (0.010)	**<0.01**
Total Time MVPA*	-0.138 (0.083)	0.10	-0.168 (0.062)	**<0.01**
Total Time MVPA**	-0.108 (0.091)	0.24	-0.216 (0.053)	**<0.01**
RT Yes/No (Yes) *	-3.092 (1.925)	0.11	2.209 (1.875)	0.24
RT Yes/No (Yes) **	-3.082 (1.879)	0.10	1.228 (1.718)	0.48
RT Yes/No (Yes) ***	-2.837 (1.854)	0.13	3.939 (1.886)	**0.04**
RT Weekly Frequency *	-0.214 (0.181)	0.24	0.707 (0.441)	0.11
RT Weekly Frequency **	-0.173 (0.179)	0.34	0.465 (0.405)	0.25
RT Weekly Frequency ***	-0.237 (0.168)	0.16	0.935 (0.412)	**0.02**

Data are presented as Beta, Standard Error (SE). Each linear regression model was adjusted for age, ethnicity, education, marital status, BMI, smoking status, alcohol consumption, and the PA component identified by the following (* total sedentary time, ** total light PA, *** total MVPA).

Table 4: Odds of Frailty in Men and Women Living with Diabetes Mellitus

	Male (n=365)		Female (n=346)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Total Time Sedentary	1.001 (0.998 - 1.003)	0.70	1.007 (1.004 -1.010)	**<0.01**
Total Time Light PA	0.993 (0.989 - 0.998)	**<0.01**	0.985 (0.980 - 0.991)	**<0.01**
Total Time MVPA	0.950 (0.909 - 0.993)	**0.02**	0.946 (0.908 - 0.986)	**0.01**
RT: Yes/No (Yes)	0.625 (0.248 - 1.573)	0.32	0.813 (0.318 - 2.080)	0.67
RT: Weekly Frequency	0.955 (0.849 - 1.073)	0.44	1.027 (0.829 - 1.272)	0.81

Data are presented as Odds Ratio (OR), 95% Confidence Interval (CI); Each logistic regression model was adjusted for age, ethnicity, education, marital status, BMI, smoking status, and alcohol consumption.

Table 5: Odds of Frailty in Men and Women Living with Diabetes Mellitus Independent of Activity Levels

	Male (n=365)		Female (n=346)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Total Time Sedentary**	0.999 (0.996 - 1.002)	0.45	1.005 (1.001 - 1.008)	**<0.01**
Total Time Sedentary***	0.999 (0.996 - 1.002)	0.39	1.006 (1.003 - 1.009)	**<0.01**
Total Time Light PA*	0.992 (0.987 - 0.997)	**<0.01**	0.987 (0.982 - 0.993)	**<0.01**
Total Time Light PA***	0.995 (0.990 - 1.000)	**0.04**	0.986 (0.980 - 0.991)	**<0.01**
Total Time MVPA*	0.946 (0.906 - 0.988)	**0.01**	0.961 (0.926 - 0.998)	**0.04**
Total Time MVPA**	0.956 (0.914 - 0.999)	**0.04**	0.951 (0.919 - 0.983)	**<0.01**
RT: Yes/No (Yes)*	0.622 (0.245 - 1.579)	0.32	0.913 (0.362 - 2.306)	0.85
RT: Yes/No (Yes)**	0.654 (0.262 - 1.632)	0.36	0.664 (0.266 - 1.658)	0.38
RT: Yes/No (Yes)***	0.668 (0.264 - 1.688)	0.39	1.204 (0.451 - 3.217)	0.71
RT: Weekly Frequency*	0.954 (0.847 - 1.076)	0.45	1.036 (0.858 - 1.250)	0.71
RT: Weekly Frequency**	0.962 (0.846 - 1.094)	0.56	0.977 (0.811 - 1.178)	0.81
RT: Weekly Frequency***	0.956 (0.858 - 1.066)	0.42	1.087 (0.877 - 1.346)	0.45

Data are presented as Odds Ratio (OR), 95% Confidence Interval (CI); Each logistic regression model was adjusted for age, ethnicity, education, marital status, BMI, smoking status, and alcohol consumption, and the PA component identified by the following (* total sedentary time, ** total light PA, *** Total MVPA).

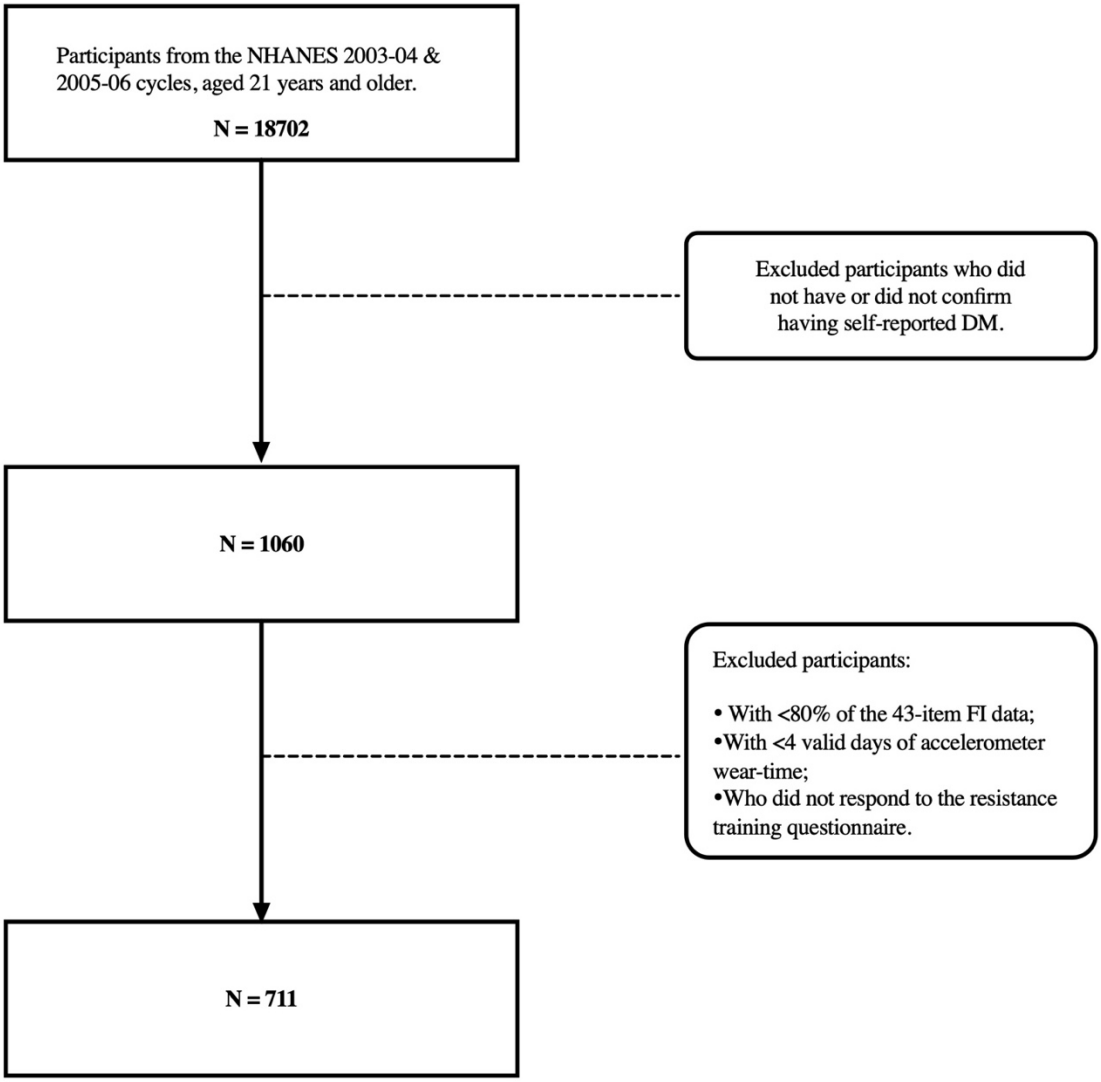

Figure 1.0: Participant Flow Chart

Appendices

Appendix A

Criteria Used to Define Frailty

- **Weight loss:** "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss criterion. At follow-up, weight loss was calculated as: (Weight in previous year – current measured weight)/(weight in previous year) = K. If K ≥ 0.05 and the subject does not report that he/she was trying to lose weight (i.e., unintentional weight loss of at least 5% of previous year's body weight), then frail for weight loss = Yes.
- **Exhaustion:** Using the CES–D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. The question is asked "How often in the last week did you feel this way?" 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1–2 days), 2 = a moderate amount of the time (3–4 days), or 3 = most of the time. Subjects answering "2" or "3" to either of these questions are categorized as frail by the exhaustion criterion.
- **Physical Activity:** Based on the short version of the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Kcals per week expended are calculated using standardized algorithm. This variable is stratified by gender.
  Men: Those with Kcals of physical activity per week <383 are frail.
  Women: Those with Kcals per week <270 are frail.
- **Walk Time**, stratified by gender and height (gender-specific cutoff a medium height).

Men	*Cutoff for Time to Walk 15 feet criterion for frailty*
Height ≤ 173 cm	≥7 seconds
Height > 173 cm	≥6 seconds
Women	
Height ≤ 159 cm	≥7 seconds
Height > 159 cm	≥6 seconds

- **Grip Strength**, stratified by gender and body mass index (BMI) quartiles:

Men	*Cutoff for grip strength (Kg) criterion for frailty*
BMI ≤ 24	≤29
BMI 24.1–26	≤30
BMI 26.1–28	≤30
BMI > 28	≤32
Women	
BMI ≤ 23	≤17
BMI 23.1–26	≤17.3
BMI 26.1–29	≤18
BMI > 29	≤21

Fried's Frailty Phenotype (L. P. Fried et al., 2001).

Appendix B

46 deficits included in frailty index.

Comorbidities	*Signs/symptoms*
• Stroke	• Heart rate at rest
• Thyroid condition	• Systolic blood pressure
• Cancer	• Cough regularly
• Heart attack	• Leaked/lost control or urine
• Heart disease	• General vision
• Ever had high blood pressure	• Difficulty seeing steps/curbs in dim light
• Angina/angina pectoris	• General hearing
• Osteoporosis	• Confusion or inability to remember things
• Diabetes	
• Arthritis	*Lab values*
• Ever had broken hip	• Homocysteine (μmol/L)
	• Folatc, scrum (nmol/L)
• Cataract operation	• Glycohemoglobin (%)
• Weak/failing kidneys	• Red blood cell count (million cells/μL)
	• Hemoglobin (g/dL)
Function	• Red cell distribution width (%)
• Difficulty using fork and knife	• Lymphocyte percent (%)
• Difficulty dressing yourself	• Segmented neutrophils percent (%)
• Difficulty getting in/but of bed	
• Difficulty standing up from armless chair	*Other*
• Difficulty managing money	• Medications
• Difficulty preparing meals	• Self-reported health
• Difficulty standing for long periods of time	• Health compared to 1 year ago
• Difficult stooping, crouching, kneeling	• Frequency of healthcare use
• Difficulty grasping/holding small objects	• Overnight hospital stays
• Difficulty lifting or carrying	
• Difficulty pushing or pulling large objects	
• Difficult attending social event	

Accumulation of Deficits 46-Item Frailty Index Model (Blodgett et al., 2015a)**.**

Curriculum Vitae

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Conference Presentations:

- Hilary M. Pond, Ken Seaman, Martin Sénéchal (2019). **The Cross-Validation of the Dynamic Strength Index with the Force Velocity Profile in High Performance Varsity Athletes.** *NBKA Poster Presentation.* (2019 New Brunswick Kinesiology Association Annual Conference, Fredericton, NB, Canada)

- Hilary M. Pond, Scott Kehler, Ken Seaman, Danielle R. Bouchard, Martin Sénéchal (2021). **A Cross-Sectional Analysis Investigating the Association of Physical Activity & Sedentary Behaviour Patterns on Frailty Status in Adults Living with Diabetes Mellitus.** *APES+ Oral Presentation.* (Atlantic Provinces Exercise Scientists + Kin Research Day Conference, Virtual)