OPTIMIZING FUNCTIONAL PERFORMANCE OF FRAIL OLDER ADULTS AND THEIR CAREGIVERS

OPTIMIZING FUNCTIONAL PERFORMANCE OF FRAIL OLDER ADULTS AND THEIR CAREGIVERS

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LAY ABSTRACT

There is a need to develop rehabilitation interventions to reduce the prevalence and disabling effects of frailty. This thesis reports the rationale and design of two studies and findings of three studies aimed to improve health outcomes of frail older adults and their caregivers. The second and third chapters of this thesis describe the protocol and results of a review aims to identify the effect of interventions targeting frailty, the review found that physical activity and medication management are the most effective frailty interventions. The fourth chapter describes a study examining the possibility of comparing a complex intervention to usual care in frail older adults undergoing joint replacements. The fifth chapter showed that a primary care intervention did not improve the caregivers' health outcome. The sixth chapter presents the fracture rating scale, a valid tool for identifying Long-term care residents at risk of hip fracture in three Canadian provinces. These findings aim to improve the care for older adults and their caregivers.

ABSTRACT

Aging and age-related frailty are important public health problems. There is a need to develop rehabilitation interventions to reduce the prevalence and disabling effects of frailty. This thesis reports the rationale and design of two studies and findings of three studies aimed to optimize health outcomes of frail older adults and their caregivers. The second chapter describes the protocol of the first network meta-analysis to determine the comparative effect of interventions targeting the prevention or treatment of frailty. In the third chapter, the results of frailty network meta-analysis were presented and 89 RCTs were included. The review shows that physical activity and medication management are the most effective frailty interventions. The fourth chapter describes a protocol of pilot randomized controlled trial (RCT) to examine a preoperative multi-modal frailty intervention in pre-frail/frail older adults undergoing elective joint replacements.
The fifth chapter describes the results of a subgroup analysis of a RCT examining the effect of complex primary care intervention to support caregivers of frail older adults. There were no differences between caregivers of frail older adults and non-caregivers in quality of life, social support, hospitalization, and emergency department visits. The sixth chapter examines the construct validity and discriminative properties of the fracture rating scale (FRS) (a tool designed for fracture risk assessment in long term care (LTC)). The FRS is a valid tool for identifying LTC residents at different risk levels for hip fracture in three Canadian provinces.

The work presented in this thesis is proposing and examining the comparative effect of frailty interventions, a preoperative frailty intervention/ model, a primary care intervention to identify and support caregivers, and a predictive tool to optimize care

planning of LTC residents. These findings will support the rehabilitation and care program for older adults and their caregivers and improve their health outcomes.

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This dissertation is dedicated to frail older adults and their caregivers across the world. I hope this work contributes to the care for older adults in different setting. I will continue to work with colleagues and mentors around the world to improve frailty model of care and create better health services.

PREFACE

This thesis is structured as a "sandwich thesis", which includes five individual manuscripts as prepared for peer-reviewed publication.

Ahmed Negm lead the conception, design, data acquisition, analysis and drafting of all manuscripts and was in charge of submitting them to peer-reviewed journals for their publication.

For the first manuscript (chapter 2) titled "Management of frailty: a protocol of a network meta-analysis of randomized controlled trials" Ahmed M. Negm, Lehana Thabane, Jonathan D. Adachi, Julie Richardson, and Alexandra Papaioannou contributed ideas for the conceptualization and design of the protocol.

For the second manuscript (chapter 3) titled "Management of frailty: A systematic Review and Network Meta-analysis of Randomized Controlled Trials" Ahmed M. Negm, Lehana Thabane, Jonathan D. Adachi, Julie Richardson, Alexandra Papaioannou contributed to the study conception and design, analysis and interpretation of data, drafting of the manuscript and revisions based on the comments of the coauthor. All authors read and approved the final version of the manuscript.

For the third manuscript (chapter 4) titled "Getting fit for hip and knee replacement: a protocol for the Fit-Joints pilot randomized controlled trial of a multi-modal intervention in frail patients with osteoarthritis" Ahmed Negm contributed to the study design, and writing of the protocol. Lehana Thabane, Jonathan D. Adachi, Alexandra Papaioannou, and Julie Richardson contributed to the study design. All the authors read and approved the final protocol.

For the fourth manuscript (chapter 5) titled “Impact of the Health TAPESTRY Approach in Primary Care on Caregivers and Non-Caregivers- Subgroup Analysis of Randomized Controlled Trial” Ahmed M. Negm, Lehana Thabane, Jonathan D. Adachi, Julie Richardson, Alexandra Papaioannou were responsible for study design, data analysis and interpretation and drafting of manuscript. All authors read and approved the final manuscript.

For the fifth manuscript (chapter 6) titled “Validation of a One Year Fracture Prediction Tool For Absolute Hip Fracture Risk in Long Term Care residents” Ahmed M. Negm, Lehana Thabane, Jonathan D. Adachi, Julie Richardson, Alexandra Papaioannou contributed to the study conception and design, analysis and interpretation of data, drafting of the manuscript and revisions based on the comments of the coauthor. All authors read and approved the final version of the manuscript.

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CHAPTER 1

INTRODUCTION TO THE THESIS

1.1 Aging Canada and worldwide

Aging is a phenomenon associated with gradual accumulation of a variety of molecular and cellular damage (1, 2), which leads to a gradual decline in physiological reserves and general capacity, and an increased risk of many diseases. In 2015, the number of people ≥ 65 years was higher than people 0-14 years old for the first time of the Canadian history (3). The number of older adults could reach between 9.9 and 10.9 million Canadians by 2036 (3). The number of older adults around the world is increasing dramatically (4). However, the proportion of older adults exceeded 30% only in Japan, many other European and North American countries will have a similar proportion of older adults by 2050 (4).

1.2 Consequences of population aging

Aging related physiological changes and gradual accumulation of molecular and cellular damage leads to a progressive, generalized impairment in many body functions, an increased vulnerability to environmental challenges and a growing risk of chronic disease and death (5). The impairment associated with age includes sensory loss, physical performance and cognitive decline and multi-morbidity (such as heart disease, stroke, chronic respiratory disorders, cancer and dementia) (6-18).

Physical performance: Aging is associated with decline in physical performance measured by handgrip strength and gait speed (19-21). Handgrip strength and gait speed are strong predictors of mortality, independent of any disease-related influences (19-21). Several age-related musculoskeletal changes contribute to the decline in physical performance. These changes include: 1) decrease muscle mass which is associated with declines in strength and musculoskeletal function (22), 2) decrease bone mineral density (particularly among postmenopausal women), which lead to high fracture risk, disability and mortality (23, 24), and 3) structural, molecular, cellular and mechanical change in articular cartilage with increasing the vulnerability of the tissue to degeneration, which lead to osteoarthritis (25, 26).

Sensory function: Ageing is frequently associated with declines in both vision and hearing. Age-related hearing loss results from cochlear ageing; environmental exposures, such as noise; genetic predisposition; and increased vulnerability from physiological stressors and modifiable lifestyle behaviours (27). Age-related decline in visual focusing ability leads to the blurring of near vision (28). These complex changes in vision are associated with increasing opacity of the crystalline lens (result in cataract), and macular degeneration (lead to retinal damage and severe visual impairment).

The age related vision and hearing changes have important implications for the everyday lives of older adults. Hearing loss affects communication and can contribute to social isolation and loss of autonomy, with associated anxiety, depression and cognitive decline (29, 30). Visual impairments can limit mobility, affect interpersonal interactions, trigger depression, become a barrier to accessing information and social media, increase the risk of falls and accidents, and make driving hazardous (31).

Cognitive Function: Many cognitive functions begin to decrease at a relatively young age, with different functions decreasing at different rates. As a consequence, functioning becomes increasingly heterogeneous with increasing age (32). The variation from person to person in the decline in cognitive functions with age is influenced by many factors, including socioeconomic status, lifestyle, the presence of chronic disease and the use of medication, suggesting there are opportunities for public health interventions across the life course.

Not all cognitive functions deteriorate with age. Language features, such as reading and comprehension remain stable throughout life. However age-related cognitive deteriorations involve memory, the speed of information processing, reductions in the capacity to learn and master tasks that involve active manipulation, reorganization, integration or anticipation of various memory items, (33), and capacity to tackle complex tasks that require dividing or switching attention.

Multi-morbidity: A systematic review of studies in seven high-income countries concluded that more than half of all older adults are affected by multi-morbidity, with the prevalence increasing sharply in very old age (6). Among Canadians $\geq$ 40 years, the prevalence of having two or more chronic conditions is 26.5% (34). Multi-morbidity can lead to interactions among conditions; between one condition and the treatment recommendations for another condition; and among the medications prescribed for different conditions. As a result, the impact of multi-morbidity on functioning, quality of life and risk of mortality may be significantly greater than the sum of the individual effects that might be expected from these conditions (6, 35). Some disease combinations have particularly adverse impacts on functioning, with, for example, depression showing

a synergistic worsening impact in combination with heart failure, osteoarthritis and cognitive impairment (36).

Multi-morbidity risk factors include low socioeconomic status, a higher number of previous diseases, race or ethnicity, and age, although a large-scale historical cohort study in the United States found that a substantial proportion of multi-morbidity begins before age 65 years (6, 37).

We summarized some of the underlying changes that tend to occur to some degree in all humans as they age. Although there is marked diversity in how these changes are experienced at an individual level, general trends are seen when the population as a whole is considered (38). But these aging changes are neither linear nor consistent, and they are only loosely associated with age in years (39). For example, some 70-year-olds may enjoy good physical and mental functioning, while others may be frail or require significant support to meet their basic needs. This variability in the aging process could be due to genetic inheritance, environmental exposures or the impact of individuals' behaviours (4).

The burden of aging on older adults' capacity, health-care utilization and their cost of care arise mainly from geriatric syndromes. Geriatric syndromes are a loosely defined group of conditions that are common in the geriatric population and are often the result of cumulative multiple organ changes (40, 41). Unlike aging changes, the impact of geriatric syndromes is consistent. All older adults with geriatric syndromes tend to have higher health care use and lower quality of life.

1.3 Geriatric Syndromes

Geriatric syndromes are characterized by the emergence of several complex health states that tend to occur only later in life and that do not fall into discrete disease categories (41). They are often a consequence of multiple underlying factors and multiple organ systems, and the presenting complaint may not represent the pathological condition underlying it (42). For example, an older person may present with acute cognitive decline or delirium, but this may be a consequence of underlying causes as diverse as an infection or electrolyte disturbance. Similarly, a fall may be a consequence of many underlying characteristics, including drug interactions, environmental factors and muscle weakness.

There is still some debate as to which conditions may be considered geriatric syndromes, but they are likely to include frailty, urinary incontinence, falls, delirium, and pressure ulcers (41, 43). These appear to be better predictors of survival than age in years and the presence or number of specific diseases (44, 45). Yet because of their multisystem nature that crosses many disciplines, they present challenges for traditionally structured health services and are often overlooked in epidemiological research. Innovative approaches to managing these geriatric syndromes will need to be central to any societal response to population ageing. For the purpose of this thesis we will focus on one geriatric syndrome, frailty.

1.4 Frailty Definition, prevalence and consequences

The last decade has seen an exponential increase in the recognition of **frailty** as an important clinical state that contributes substantially to adverse events in ageing including mortality, disability, institutionalization, in-hospital complications and adverse

discharge disposition (46-53). A 2014 frailty consensus document defined frailty as: "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic reserve that increases an individual's vulnerability for developing increased dependency and/or death" (54). Vulnerable/pre-frail individuals are those who are at risk of becoming frail and are also at increased risk of adverse events compared with non-frail adults (8, 55).

Frailty is a common syndrome occurring in 5-17% of community-dwelling older adults (56). The prevalence of frailty increases to more than 32% in persons aged over 90 years (57) and it is expected to continue to increase as the population ages (49, 58). Approximately 23% of Canadians over age 65 are frail (3) and by age 85 this estimate increases to $\geq$ 40% (4).

Adverse outcomes associated with frailty include increased risk for functional disability, hospitalization, fractures (7), admission to long-term care, and increased mortality (8-12). Older adults who are frail are high users of healthcare services (5), have a 1.2 to 2.5-fold increase in the risk of falls, institutionalization, and mortality (13). Those with moderate or severe frailty have an 8-fold greater relative risk of institutionalization (6). Older adults are heavy users of the ER compared with younger cohorts (59) and those presenting to the ER are amongst the frailest (60). Frailty also affects quality of life, and morbidity and results in considerable medical and public spending expense (61) such that it is now seen as one of the major challenges for health services. Effective interventions are needed to manage and decrease the burden of frailty on older adults and their families/caregivers. Within our rapidly aging society, there is a clear need for feasible,

effective and sustainable community-based models to address the enormous problem of managing frailty.

1.5 Frailty interventions

Two important considerations about frailty from a management perspective are: 1) frailty is dynamic in nature (i.e., may improve or worsen over time) (4) and 2) frailty is reversible or treatable (7). Although frailty consensus recommendations (8) suggest treatment with specific modalities (exercise; reduction of poly-pharmacy; vitamin D3; protein supplementation), there is little evidence regarding the ultimate frailty intervention components and whether additional management approaches are required over and above exercise. Drawing on the principles of a standardized multi-modal approach in cardiac (9,10) and cancer rehabilitation (11,12), frailty interventions could be an accessible community-based intervention with the ultimate goal to improve physical function, reducing frailty, and enabling independence within the community. This will help to address the goals identified by the World Health Organization (WHO) Priorities in Healthy Aging Integrated Care for Older Adults (http://www.who.int/ageing/10-priorities/en/).

Several interventions were examined if they reduced frailty in older adults such as physical training programs (different exercise interventions) (62-65), nutritional (66, 67) physical training and nutrition (68-70), multicomponent (71, 72), and geriatric comprehensive assessment (73, 74). Similar interventions were also used to improve physical performance in frail older adults, such as physical training programs (75-77), nutritional (78-80), physical training and nutritional (81-83), multicomponent (84-86),

pharmacologic (87-89), and whole body vibration (90, 91). Despite the variety of interventions used to prevent or decrease frailty and improve physical performance, the most effective intervention has yet to be determined. Due to the rising burden of frailty and physical performance decline, determining the ideal intervention for these two health issues is critical for healthcare providers, public health and policy makers. In chapter two, we describe the protocol of a systematic review and network meta-analysis of all available interventions aimed at preventing/managing frailty and improving physical performance in older adults. In chapter three, we present the final results of this systematic review and network meta-analysis of frailty and frailty related outcomes including quality of life, short physical performance battery, cognition, depression, and adverse events.

1.6 Frailty and Joint Replacement Surgery

With our rapidly aging demographic, there is an increasing need to manage the needs of frail patients across the health services spectrum. Frailty has emerged as an important independent risk factor for sub-optimal post-operative health outcomes in older adults (92-96). Thus, targeting this high-risk group of patients during the pre-operative phase is particularly critical for improving post-operative outcomes. In patients undergoing general surgery, frailty was the strongest predictor of 30-day mortality, with greater predictive ability than American Society of Anaesthesiologists class, wound class, and age (97). In patients undergoing colorectal and cardiac surgery, frail patients had a greater risk of 30-day readmission post-operatively (98), and in patients undergoing abdominal surgery, frailty was independently predictive of the post-operative

complications and mortality, whereas age and comorbidity were not (99). Although few studies have examined frailty in arthroplasty, surgical cohort studies that have included frail patients have demonstrated elevated risk of post-operative delirium, increased length of hospitalization and institutionalization (100).

Osteoarthritis (OA) is one of the most common chronic conditions worldwide and leads to morbidity, physical limitation, and disability (101, 102). The cost of managing OA in Canada was $10.2 billion in 2010 (103). Joint replacement provides significant improvements in pain, physical function and quality of life in patients with OA (104). In Canada, during 2015-16, there were approximately 53,000 hip replacements and 64,000 knee replacements representing a 5 year increase of 18.1% and 15.7 5%, respectively (105). As our population ages, the number of older adults seeking total joint replacement will continue to rise (106).

Almost two thirds of elective hip or knee joint replacement surgeries are performed on Canadian adults aged 65 years of age and older (107). In a longitudinal cohort of American men 65 years and older (MrOs), radiographic hip osteoarthritis or a total hip replacement was associated with increased odds of being frail or pre-frail compared with being robust (adjusted odds ratio (CI) = 1.45 (1.18, 1.78)) (108, 109). Although few studies in joint replacement cohorts have assessed frailty using a reliable and valid assessment tool, preliminary estimates indicate that over 41% of patients are frail and an additional number are pre-frail (another 38%) (110). Pre-frail individuals are additionally an important group to target as they are at risk for further decline and may be responsive to interventions.

Given the strong link between frailty and poorer post-operative health outcomes in older adults (98, 100, 110, 111) targeting this high-risk group of patients during peri-operative care is particularly critical for improving post-operative outcomes. As each post-operative day in the hospital costs the healthcare system additional funds, it is of critical importance to ensure that total joint replacement patients are in optimal health before surgery, as pre-operative health status predicts post-operative outcomes (112). Previous studies have demonstrated that pain and function may deteriorate in patients waiting for total joint replacement surgery (112, 113). Preventing further decline or improving function during the pre-operative phase is important given the link between preoperative and postoperative physical function. There are many questions remaining how to best target, manage, and optimize pre-frail and frail arthroplasty patients and how outcomes and health system spending are impacted. Given the burden of frailty on both patients and healthy system spending, ensuring an approach to addressing peri-operative arthroplasty care is urgently needed.

In this thesis, chapter four, we describe the rationale and design of the Fit Joint randomized controlled trial, which examines the feasibility and effectiveness of a lifestyle intervention to improve functional and health status of osteoarthritis patients undergoing hip or knee replacement surgery. Although it is important to improve functional and health status of all patients, we are targeting older adults ≥ 60 years who are pre-frail or frail (114).

1.7 Caregivers and aging

As people age, they are increasingly likely to develop a physical or cognitive impairment that impacts their ability to function independently (115, 116). However, older people often identify a preference for growing old in their own homes or at least within the communities where they live (117, 118). This allows them to maintain the relationships and community networks that can foster well-being and act as resources in times of adversity. Ageing at home may require a wide array of services and family of caregivers (119).

Frail older adults require some form of care to stay at home safely. Most of the required care (about 80%) is provided by informal caregivers who often play an important role in the care plan (120). Informal caregivers are individuals who provide unpaid care to a family member or friend with a long-term health condition, a physical or mental disability (121). In addition to reducing the costs associated with health services and institutionalization, the informal caregiving also benefits the care-recipients, allowing them to remain at home and maintain a better quality of life (122). Informal caregivers are the "backbone" of the community care sector and can help alleviate demand on the public health care system (21). In 2012, 28% of Canadians (about 8 million people) provided help or care to a relative or friend with a chronic health problem (122). Family caregivers were more likely to be women (122). About half (48%) of caregivers reported caring for their own parents or parents in-law over the past year (121). Informal caregivers spend about 21 hours/week caring for home care patients (123, 124). On average, patients whose caregivers experienced distress received 31.5 hours per week of

care from those caregivers, compared to the 17.1 hours per week received by patients whose caregivers were not distressed (125).

Informal caregivers are often older adults themselves and may have their own health problems. One third of Canadian caregivers reported having at least one chronic condition and about one-quarter reported having two or more (124). Older caregivers who experience chronic stress are at a greater risk for injury or aggravating pre-existing health issues, and their activities are limited as a result of their caregiving responsibilities and lack of access to resources and services (126). Caregivers who are ≥ 65 years represent 12% of all caregivers in Canada, and are most likely to spend the most hours providing care (127). While there are rewards associated with caregiving, older caregivers have unique needs and are more vulnerable to the negative effects of caregiving (126).

Several strategies have been used to lessen the burden on and costs to informal caregivers. These strategies included: 1) payments are made directly to caregivers, both to support their caregiving functions and to compensate them for potential lost earning (Denmark, Finland, Norway and Sweden) (4), 2) Tax credits are available for caregivers (Canada) (128). To help caregivers maintain a role in the workforce, Canadian government have passed legislation that requires employers to provide paid leave from work for family members so that they can care for older relatives (129).

Most caregiver intervention studies have examined the effectiveness of psycho-educational, social counselling, coping, and problem-solving skills (130-133). Also, most of these studies have targeted specific populations such as caregivers for dementia or cancer patients (130-134). Other community-based interventions have been developed to

offer support and education to families of people with dementia by making use of locally available health and human resources. These resources provide basic information about dementia, the associated challenging behaviors and how to manage them, the availability of government services, how to help with activities of daily living (ADLs), how to obtain referrals to doctors or psychiatrists for severe symptoms, and informal support groups (4). These interventions have improved caregivers' mental health and reduced stress (135-137).

The Internet is a powerful tool for supporting family caregivers, especially those who face barriers to accessing in-person support. Internet interventions have been shown to reduce caregivers' depression, increase their confidence and improve their self-efficacy (138). A guided self-help Internet intervention (called Mastery over Dementia) was developed for caregivers of people with dementia and consists of eight core lessons and one booster lesson summarizing what has been taught. After each lesson, caregivers are asked to do homework and to send it to their coach, who has three working days to provide feedback. A randomized controlled trial of this intervention found that it decreased symptoms of depression and anxiety among caregivers (139). Being older than 75 years was not a barrier to participation; however, more than half (55.7%) of all participants did not complete all lessons, indicating that modifications need to be made to increase the feasibility and adherence to the intervention (140).

There are a number of successful initiatives in primary care to identify and support caregivers in the UK (141). These initiatives include: Royal College of General Practitioners Supporting Caregivers in General Practice Programme, Surrey NHS Carers Prescription, Caregiver Express and Surrey Healios (141). Since Canadian older adults

have regular access to primary care physicians (142), the primary care team is well positioned to identify and support caregivers. It is also critical to examine the differential effect of a primary care intervention on caregivers and non-caregivers. However, studies that aim to identify caregivers and optimize their integration into the health and social care systems in a primary care setting are lacking. Chapter five reports the study design and results of examining the effect of Health TAPESTRY approach (an intervention that aims to promote optimal aging through improved connections between inter-professional primary care teams, community service providers, and informal caregivers (143)) on identifying caregivers. We will also examine the differential effect of TAPESTRY approach in caregivers compared to non-caregivers.

1.8 LTC increasing needs

Despite the critical role of informal caregivers in supporting aging population, many factors will lead to decrease the pool of informal caregivers. These factors are: 1) globalization and global connectivity which make it easier for younger generations to migrate to areas of growth, leaving older family members without the traditional family caregiver support; 2) dramatic falls in fertility which lead to decrease of the relative number of younger people in families, 3) major changes in gender norms and job opportunities for women who had the role of caregiver, both for children and for older relatives in the past (4).

As people have fewer children and live longer, and as countries develop economically and women increasingly enter the paid workforce, relying on unpaid informal caregivers without providing additional support is unlikely to be sustainable (4).

The ageing of the population, the expected decline in the availability of unpaid informal caregivers, and the health complexity of older adults will lead to increasing the absolute number of older people who are care-dependent and hence, the demand for long-term care (LTC) will also increase. Currently, 7.1% of all older adults in Canada live in LTC and it has been estimated that by the year 2036, the number of individuals living in institutional care facilities will be more than double (144, 145). Residents in LTC often have multiple threats to their well-being, including pain, disability and mental health issues (146).

The role of long-term care systems is to enable an older person to maintain a level of functional ability. This requires enabling older people to perform with dignity the basic tasks that are necessary for their well-being. This includes early care to reduce declines in capacities and encouraging older people to become more active. One of the major concerns that lead to functional decline, disability and mortality in LTC is incident fractures (4).

Fracture prediction in LTC: Hip fractures are the most common type of fracture in LTC (49% of all fractures) (147). They are, more common in older adults living in LTC (49%) than in the community (29%) (147, 148), and lead to more hospitalizations (149) and worsening health-related quality of life (150). In Canada, 45% of LTC residents with hip fracture die within 12 months (151) and of the survivors, 48% are no longer ambulatory (151).

Hip fracture prediction and prevention in LTC residents receive little attention due to the multiple comorbidities and medical complexity of LTC residents (146, 152) and the challenges of predicting fracture in this population. It is difficult to identify LTC

residents with high fracture risk, as the commonly used fracture risk assessment tools in Canada, including the Canadian Fracture Risk Assessment Tool (FRAX) and the Canadian Association of Radiologists and Osteoporosis Canada tool (CAROC) (153-156), are not valid or generalizable for residents of LTC (157). FRAX and CAROC typically provide a 10-year fracture risk assessment timeframe, which is too long, given the mean 2.4-year life expectancy of LTC residents (158). A recent study showed that FRAX (with bone mineral density) may predict incident hip fracture over time periods shorter than 10 years (159). Bone mineral density is heavily weighted in current fracture risk assessment protocols, but bone mineral density is not feasible to obtain in LTC. In addition, FRAX is not tailored to frail, institutionalized LTC residents. Thus, fracture prediction outputs of FRAX-Canada and CAROC may not be suitable for decision making and care planning among frail LTC residents (160, 161).

In this thesis, chapter six reports the rationale, design and results of validation of a fracture risk assessment tool tailored for LTC residents which is critical for service delivery and care planning and may improve care for LTC residents across Canada (162).

In summary, aging is a global public health concern. Geriatric syndromes and specifically frailty and fractures are a major burden on the health care systems and individual older adults and their caregivers. However, most health systems are not equipped to provide the comprehensive care needed to manage these complex health states. Innovative approaches are therefore needed to identify the best management for frail older people and their caregivers. In this thesis, we aim to determine the ideal components of frailty intervention by conducting a systematic review and network meta-analysis, examine the feasibility of conducting a RCT examining the efficacy of

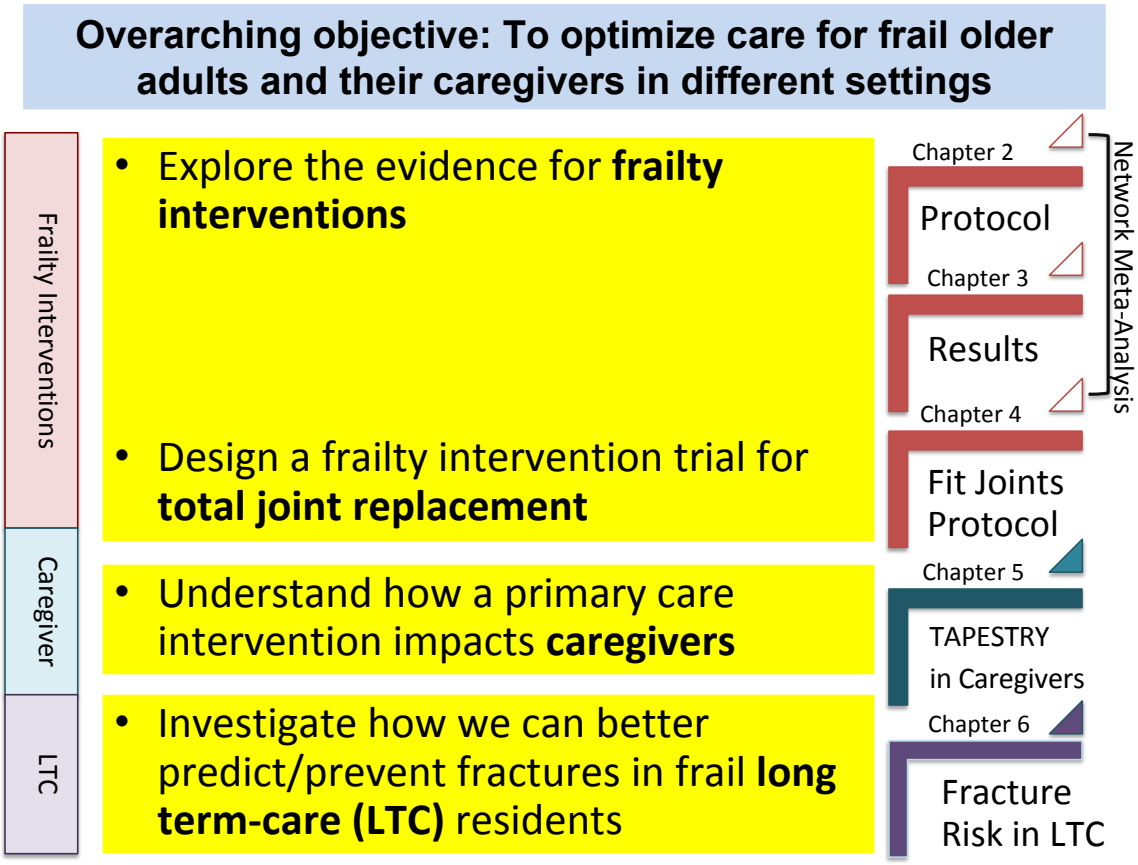
preoperative frailty intervention, identify caregivers of frail older adults and decrease their caregivers' strain and test the validity of fracture prediction tool in frail LTC residents.

1.9 Thesis structure

The overarching objective of the thesis is optimizing care for frail older adults and their caregivers in different settings by exploring the current evidence for frailty interventions and design a frailty intervention trial for joint replacement candidates, understanding how a primary care intervention impacts caregivers, and investigate how we can better predict and fractures in frail LTC residents (Figure 1). This thesis is structured in five chapters. Chapter two is a published manuscript that describes the rationale and methodology of a systematic review and network meta-analysis aims to determine the comparative effectiveness of frailty management interventions (163). Chapter three is the results of a systematic review and network meta-analysis aimed to determine the comparative effectiveness of frailty management interventions on frailty and frailty related outcomes including quality of life short physical performance battery, cognition, depression, and adverse (submitted for publication). Chapter four is a published manuscript that describes the rationale and methodology of a pilot RCT with a primary objective of examining the feasibility of a parallel group RCT comparing a preoperative multi-modal frailty intervention to usual care in pre-frail/frail older adults undergoing elective unilateral hip or knee replacement (164). Chapter five is a manuscript submitted for publication and it describes a subgroup analysis of a RCT with a primary objective determining if caregiver status (caregiver vs. non-caregiver) modified

the effect of the Health TAPESTRY approach compared to control on quality of life, social support, hospitalizations and emergency department (ED) visits. Chapter six describes a validation study aims to examine the construct validity of the Fracture rating scale (a tool designed for fracture risk assessment in LTC) by comparing incident hip fractures and all clinical fractures (includes hip, spine, humerus, forearm, pelvis fractures) for each fracture risk levels in LTC residents across three Canadian provinces (submitted for publication).

Figure 1-1: Overview of the thesis



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CHAPTER 2

MANAGEMENT OF FRAILTY: A PROTOCOL OF A NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

PREFACE TO CHAPTER 2

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2.1 Abstract

Background

Frailty is a common syndrome affecting 5-17% of community-dwelling older adults. Various interventions are used to prevent or treat frailty. Given the diversity of singular and multi-faceted frailty interventions, not all of them have been compared in head-to-head studies. Network meta-analyses provide an approach to simultaneous consideration of the relative effectiveness of multiple treatment alternatives. This systematic review and network meta-analysis of RCTs aims to determine the comparative effect of interventions targeting the prevention or treatment of frailty.

Method

We will identify relevant RCTs, in any language and publication date, by a systematic search of databases including; MEDLINE, EMBASE, CINAHL, AMED, the Cochrane Central Registry of Controlled Trials (CENTRAL), HealthSTAR, DARE, PsychINFO, PEDro, SCOPUS, Scielo. Duplicate title and abstract and full text screening will be performed. Authors will extract data and assess risk of bias (using the Cochrane Risk of Bias tool) of eligible studies. The review interventions will include: 1) Physical activity only; 2) Physical activity with protein supplementation or other nutritional supplementation; 3) Psychosocial intervention; 4) Medication management; 5) Pharmacotherapy; and 6) Multi-faceted intervention (defined as an intervention that combine physical activity and/or nutrition with any of the following; 1) Psychosocial intervention; 2) Medication management; 3) Pharmacotherapy). Our primary outcome is difference in change of physical frailty from baseline measured by a reliable and

valid frailty measure. Secondary outcomes and the assessments are: 1) Cognition; 2) Short Physical Performance Battery; 3) Any other physical performance measure; 4) Treatment cost; 5) Quality of Life; and 6) Any adverse outcome. We will conduct a network meta-analysis using a Bayesian hierarchical model. We will also estimate the ranking probabilities for all treatments at each possible rank for each intervention and will assess the certainty of the estimates of effect using the GRADE Approach.

Discussion

To the best of our knowledge, this will be the first systematic review and network meta-analysis considering the direct and indirect effect of interventions targeting frailty prevention or treatment. Given the established high prevalence and socio-economic burden of frailty, there is an urgent need for a high-quality systematic review to inform evidence-based management of frailty.

Systematic review registration: PROSPERO 2016:CRD42016037465

2.2 Background

Frailty is defined as a clinical condition with increased vulnerability, which results from aging-related degeneration across psychological, physical and social functioning [1, 2]. It is a common syndrome occurring in 5-17% of community-dwelling older adults [3]. The prevalence of frailty increases to more than 32% in persons aged over 90 years [4] and it is expected to continue to increase as the population ages [5, 6]. Individuals who are frail have a 1.2- to 2.5-fold increase in the risk of falls, institutionalization, and mortality [7]. Frailty affects quality of life, morbidity, and mortality and results in considerable medical and public spending expense [8] such that it is now seen as one of the major challenges for health services. Effective interventions are needed to manage and decrease burden of frailty on older adults and their families/caregivers.

Results of frailty management studies showed contradicting evidence; for example previous frailty intervention studies using comprehensive geriatric assessment [9, 10] and rehabilitation intervention models [11] showed effectiveness in improving physical function. In contrast, other studies used the same approach (comprehensive geriatric assessment) in the same population and did not show significant improvement in physical function [12, 13]. Two recent randomized-controlled trials (RCTs) applied multifactorial interdisciplinary intervention [14] and showed effectiveness in reducing frailty [15, 16]. Other systematic reviews examined individual interventions targeting frailty such as, exercise [17, 18] and home-based support [19] and showed beneficial effects as well. There are also a few ongoing frailty intervention trials that will be completed within the next few months [20, 21].

Since RCTs and previous traditional meta-analyses evaluated only the relative efficacy of two frailty interventions at a time, the relative effects of different frailty interventions are not well understood. Given the diversity of singular and multi-faceted interventions addressing frailty, not all of them have been compared in head-to-head studies. New methodological techniques are required to provide effect estimates for all comparisons. Network meta-analyses provide an approach to a simultaneous consideration of the relative effectiveness of multiple treatment alternatives [22, 23]. Due to the mixed evidence from the frailty intervention studies, a systematic review and network meta-analysis is needed to incorporate the recent studies to the current evidence of frailty intervention, and compare the effectiveness of individual versus multi-modal frailty interventions. Synthesizing the current evidence of frailty interventions will enable researchers, clinicians and policy makers to determine the effectiveness of the current frailty interventions. We will combine direct (i.e. head-to-head trials) and indirect comparisons (which provides the relative treatment effects between two treatments when head-to-head trials are not available [24]) using a network meta-analysis [25]. Therefore, we will conduct a network meta-analysis of RCTs to determine the comparative effectiveness of interventions targeting the prevention or treatment of frailty in older adults. We aim to examine all types of interventions targeting frailty including comprehensive geriatric assessment, physical activity, nutrition, psychosocial intervention, pharmacotherapy, medication management or multi-modal interventions.

2.3 Methods/Design

This review will conform to the Preferred Reporting Items for The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health

Care Interventions (see Additional file 1 shows the PRISMA-P checklist) [26]. This protocol is registered in PROSPERO; systematic review registration: PROSPERO 2016:CRD42016037465.

Search strategy: We will identify relevant RCTs, in any language and publication date, by a systematic search of MEDLINE, EMBASE, CINAHL, AMED, the Cochrane Central Registry of Controlled Trials (CENTRAL), HealthSTAR, DARE, PsychINFO, PEDro, SCOPUS, Scielo from the inception of each database. An experienced librarian will be involved in designing our search strategies in individual databases (see additional file 2 shows search strategies in the included databases).

The search strategy will combine text terms describing frailty with terms describing multi-faceted or singular interventions. We will scan the reference lists of all included trials, and relevant reviews. Also, the authors of this review who are leaders in the frailty field will identify publications about frailty interventions. We will search three clinical trial registries to identify ongoing trials: Clinical Trials Registry, Current Controlled Trials and the World Health Organization International Clinical Trials Registry Platform. We will search unpublished work using key meeting proceedings and the following websites: 1) ProQuest Dissertations and Theses; 2) E-Thos; and 3) OpenGrey.

Eligibility criteria: Studies will be included if: 1) One or more interventions (described below) was applied; 2) Comparator was a control, usual care or another intervention; 3) Primary or secondary outcome was frailty or physical function change (using frailty measure or any other physical performance measure); 4) The study design is RCT; 5) The study include only adults.

Definition of Interventions: Based on our preliminary search and clinical judgment of this review authors, the included interventions will be 1) Physical activity interventions program

only; 2) Physical activity program with protein supplementation or other nutritional supplementation; 3) Psychosocial intervention only; 4) Medication management (such as reducing poly-pharmacy); 5) Pharmacotherapy (such as sarcopenic medication or hormone therapy); and 6) Multi-faceted intervention (defined as an intervention that combine physical activity and/or nutrition with any of the following; 1) Psychosocial intervention; 2) Medication management; 3) Pharmacotherapy). Relevant analyses will most likely include a 7-node network meta-analysis (including a control node).

Types of outcome: The primary outcome will be difference in change of physical frailty from baseline measured by a reliable and valid frailty measure or physical performance measure when used as a surrogate for frailty measure [28]. If a study included both frailty and physical performance measure, the frailty measure will be included in the analysis. Secondary outcomes will include: 1) Cognition, which include any measure of cognitive functions (such as memory, attention, language, and executive function); 2) Short Physical Performance Battery: composed of 3 assessments and each assessment score between 0 and 4. A final summary performance score out of 12 is calculated, with higher scores indicating superior lower extremity function [28]. The SPPB has also been validated and has demonstrated good internal consistency [28]; 3) Any other physical performance measure; 4) Treatment cost; 5) Quality of Life; 6) Any Adverse outcome.

Study selection: Using a standard form the eligibility assessment of title and abstract of citations obtained from the search will be performed by two independent reviewers unblinded to author, journal and country. The study form will be pilot-tested by the review team. Any disagreements will be resolved through consensus or with assistance from a third author if necessary. After title

and abstract screening for potentially eligible studies, two reviewers will use a standard form to check the full text articles for eligibility independently and any disagreements will be resolved through consensus or with assistance from a third author if necessary. The agreement between the two reviewers (on the title and abstract and full text selection) will be assessed by examining raw agreement and unweighted kappa (k). The agreement between reviewers will be interpreted using the following thresholds: ≤0 as poor agreement, .01–0.20 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement and >0.80 as almost perfect agreement [27].

Data extraction and management: A data extraction form will be developed for this review and pilot tested independently on two randomly selected studies by two reviewers to ensure consistency in extraction. The extraction form will be refined accordingly and data will be extracted in duplicate. The extracted information will include: the characteristics of participants (age, gender, frailty severity and method of diagnosis), types and characteristics of intervention (frequency, descriptions, durations) and all reported outcome measures, baseline data, post-treatment data points. At each data point, we will extract: 1) Mean or mean change from the baseline and standard deviations (SDs) or the information from which SD could be derived, such as standard error or confidence interval (CI) for continuous outcomes; 2) Number of events and total number of patients per arm or odds ratio with a measure of uncertainty such as a standard error, 95% CI or an exact P value for dichotomous data; and 3) Counts and total number of patients per arm or rate ratio with a measure of uncertainty such as a standard error, 95% CI or an exact P value for count outcomes. If a trial presents outcomes at more than one time point, data for all time points will be extracted; however, only data acquired immediately post-treatment and one year follow up (or the closest time point) will be used in the meta-analysis.

Assessment of risk of bias in included studies: The risk of bias of included trials will be assessed using the modified version of the Cochrane's tool for assessing risk of bias [29, 30]. The following domains are assessed according to this tool:

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias);
5. Incomplete outcome data (attrition bias)
6. Selective outcome reporting (reporting bias)
7. Other potential sources of bias (including For-profit bias)

Each of the domains will be judged as "definitely yes", "probably yes", "probably no", and "definitely no" for each of the domains, with "definitely yes" and "probably yes" ultimately assigned low risk of bias and "definitely no" and "probably no" assigned high risk of bias [29, 30]. We will summarize the risk of bias judgments across different studies for each of the domains listed. Any disagreements regarding risk of bias will be resolved by consensus or with assistance from a third author if necessary.

Data Synthesis

Network Geometry: Qualitative description of network geometry will be provided and accompanied by a network plot [31]. We will obtain a network plot to assess if the trials treatments are connected. We will evaluate the quantitative metrics assessing features of network geometry such as diversity (number of treatments and how frequently they are examined) and co-occurrence (whether certain treatment comparisons are more or less common and the extent of

comparisons between different treatments) [31].

Measures of treatment effect: For dichotomous outcomes, we will calculate the odds ratio with a 95% credible interval [32]. For continuous outcomes, we will calculate the mean difference with a 95% credible interval. We will use the standardized mean difference with a 95% credible interval if the included trials use different scales for a continuous outcome. In case the same outcome is described by both dichotomous and continuous data from different studies, we will convert mean differences or standardized mean differences to odds ratio estimates [29]. For count outcomes, such as the number of adverse events, we will calculate the rate ratio with a 95% credible interval. For multi-arm studies, we will use the data from all reported comparisons.

Dealing with missing data: We will contact study authors to obtain missing data. Where this is not possible or missing data could lead to serious biases, we will explore the impact of including these studies in the overall assessment of results by a sensitivity analysis for continuous and binary data. If numerical outcome data such as SDs or correlation coefficients are missing and they cannot be obtained from the study authors we will calculate them from other available statistics such as P values, according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [29]. In case outcome values are reported without a measure of variance, SDs will be imputed according to the method suggested by Furukawa et al [33]. We will report information regarding loss to follow-up and we will assess this as a potential risk of bias. We will perform an intention-to-treat analysis whenever possible. Otherwise, we will use the data that are available to us (e.g. a trial may have reported only ’per-protocol’ analysis results).

Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers (which include1) baseline frailty level; 2) age; 3) sex and 4) trials with low risk of bias compared to trials with high risk of bias, across the different pairwise comparisons) to ensure that they are on average balanced. Control groups (e.g., standard care or placebo) will be assessed for their similarity across treatment comparisons [34].

Methods for direct and indirect or mixed treatment comparisons

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. We will perform a network meta-analysis of trials in which participants will be reasonably similar (i.e. there will be no major concerns about transitivity assumption). We will conduct a network meta-analysis using a Bayesian hierarchical model, implemented by the gemtc package in R [35]. We will model the treatment contrast (i.e. mean difference or standardized mean difference for continuous outcomes, log-odds ratio for dichotomous outcomes, rate ratio for count outcomes) for any two interventions as a function of comparisons between each individual intervention. The reference group will be usual care or control [36]. We will use a hierarchical Bayesian model using a non-informative prior for the treatment effects parameter and between-trial variance due to lack of previous evidence of frailty intervention [37, 38]. Considering the expected heterogeneity of the included studies, we will use a random-effects model. Model convergence will be assessed using established methods including Gelman-Rubin diagnostics and inspection of Monte Carlo errors [36].

Relative treatment ranking: We will also estimate the ranking probabilities for all treatments at each possible rank for each intervention. Then, we will obtain the treatment hierarchy using the surface under the cumulative ranking (SUCRA) curve and mean ranks [39]. SUCRA can also be

expressed as a percentage of a treatment that can be ranked first without uncertainty. We will use the rank-heat plot to visually present the treatment hierarchy across the multiple outcomes of this review [40].

Assessment of statistical heterogeneity and inconsistency

In each network meta-analysis we will assume a common estimate for the heterogeneity variance across the different comparisons [41] since we expect that the heterogeneity will be similar across treatment comparisons. The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter estimated from the network meta-analysis models.

To check the assumption of consistency in the entire network we will use the design-by-treatment interaction model [29, 42]. This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results and when there is disagreement between direct and indirect evidence. Using this approach, we will make inferences about the presence of inconsistency from any source in the entire network based on a Chi^2 test. If the design-by-treatment interaction model shows evidence of inconsistency, we will use the loop-specific approach [43] (if we have a network with at least one closed loop) to detect the paths of the network that are responsible of inconsistency locally. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor) [34]. Then, the magnitude of the inconsistency factors and their 95% CIs can be used to make inferences about inconsistency in each loop and its statistical significance. We will assume common heterogeneity estimate within each loop, and the restricted maximum likelihood method will be used [44].

Subgroup and meta-regression analysis: If sufficient studies are available, we will perform subgroup analyses using possible sources of inconsistency or heterogeneity between studies such as: age, gender, educational level and comorbidity. Our a priori hypothesis will be; older, female, lower educational level and more comorbidities subgroups may show less improvement in the primary and secondary outcomes. We will conduct additional meta-regression analyses using random effects network meta-regression models to examine potential effect moderators such as the mean age of participants, baseline frailty level, adherence level to treatment and the frailty measure.

Sensitivity analysis: If sufficient studies are available, we will assess the effect of excluding 1) Studies with high risk of bias; 2) Studies with missing data; and 3) Studies with imputed data (to ensure that our imputations do not bias our network meta-analysis results) from the analyses.

Certainty of the evidence and Summary of findings table

We will use the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach of network meta-analysis [45] to assess the certainty of direct, indirect and mixed network meta-analysis effect estimates for each outcome. The certainty of evidence of direct effect estimates for each outcome will be rated as high, moderate, low or very low using the GRADE rating system [46]. In the GRADE system, RCTs start as high quality evidence, but may be rated down due to limitation in study design, inconsistency, imprecision, indirectness and publication bias [30, 47].

The indirect effect estimate will be calculated from the available loops of evidence (including loops with a single common comparator (first order) or more than one intervening treatment

(higher orders) connecting the two interventions of the comparison of interest). The quality of indirect evidence will focus on the dominant first order loop (loops with a single common comparator connecting the two interventions of the comparison of interest). The quality of evidence rating for indirect comparisons will be the lower of the ratings of quality for the two direct estimates that contribute to the first order loop of the indirect comparison. For instance, if one of the direct comparisons will be rated as low and other will be rated as moderate evidence, we will rate the quality of indirect evidence as low [45]. We will rate down the quality of the indirect comparison one further level for violation of the transitivity assumption (similarity of trials in terms of population, intervention (type and dosing frequency), settings and trial methodology) [45].

If both direct and indirect evidence are available, the network meta-analysis mixed estimate quality rating will come from the higher quality of the two. We will consider similarity between direct and indirect effect estimates (coherence) in our final quality rating. We will rate down the quality of the mixed network meta-analysis effect if there is incoherence between direct and indirect effect estimates (measured by the difference of point estimates and the extent of overlap of CIs, of direct and indirect effect estimates).

Assessment of publication biases

For each treatment comparison, we will visually assess publication bias and small-study effects using funnel plots (using study's effect estimates for the primary outcomes against their standard errors) [48, 49]. In the network, we will use a comparison-adjusted funnel plot to assess network-wide publication bias. We will chronologically order the treatments (from the oldest to the

newest) [50]. Funnel plots will be drawn only when the number of studies is ≥10 (27). Funnel plots asymmetry might be due to publication bias but other reasons such as true heterogeneity are also possible.

Two authors will assess the quality criteria independently. Disagreements will be arbitrated by a third author until we reach consensus. The main results of the review will be presented in a summary of findings (SoF) table [51]. The SoF table will include an overall grading of the quality of evidence related to each of the comparisons, using the GRADE approach [52].

2.4 Discussion

Given the established high prevalence and socio-economic burden of frailty in aging population, and the paucity of evidence on the comparative effectiveness of treatment options, there is a critical need for a high-quality systematic review to inform evidence-based management of frailty.

To the best of our knowledge to date, there is no systematic review and network meta-analysis considering the direct and indirect effect of interventions targeting frailty prevention or treatment. This analysis will include a comparison of several different prevention /treatment options including singular (e.g. physical activity or nutrition) and multi-faceted interventions. Methodologically our review has several strengths including: 1) Covering articles up to the present date which is an important consideration given the recent focus on interventions for frailty; 2) Exploring a wider range of literature databases than previous reviews and include eligible articles in all languages; 3) Determining trial eligibility and collecting data will be made in teams of reviewers, independently and in duplicate; 4) Using GRADE approach to evaluate

our confidence in treatment effects and present our findings with GRADE SoF tables; and 5) Meta-regression and subgroup analyses will be conducted, consistent with best current practices.

Potential challenges and limitations of the proposed review include: high heterogeneity, poor quality of reporting and/or methodological rigor in included trials and difficulty in interpreting measures of effect when the pooled estimates come from trials that measured the outcome using different frailty tools. Intervening to prevent or treat frailty is a relatively new field and whether the breadth of articles will be available to conduct comparisons is not known. Interpreting measures of effect when the pooled estimates come from trials that measured the outcome using different frailty tools and physical performance measures. Another likely limitation, unique to network meta-analyses, will be lack of available treatment comparisons to build robust networks for our analyses.

The findings of our review will inform clinicians and policy makers about evidence-based components, doses and duration of interventions to prevent or alleviate frailty. There is currently consensus regarding the importance of screening for frailty and its adverse effects [14], but research evidence regarding how we treat or prevent frailty is lacking. This review will facilitate updating clinical practice guidelines of frailty management.

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2.6 Additional file 1: The PRISMA-P checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including	☒	☐	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis			
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	

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2.7 Additional file 2: Proposed search strategy for databases

HealthStar

1. frail elderly.mp. or Frail Elderly/
2. frail*.ti,ab.
3. frailty.mp.
4. 1 or 2 or 3
5. limit 4 to (randomized controlled trial or "review")
6. random*.mp.
7. systematic review*.mp.
8. 6 or 7
9. 4 and 8
10. 5 or 9

PsychInfo

1. frail elderly.mp. or Frail Elderly/
2. frail*.ti,ab.
3. frailty.mp.
4. 1 or 2 or 3
5. random*.mp.
6. systematic review*.mp.
7. 5 or 6
8. 4 and 7

AMID

1. frail elderly.mp. or Frail Elderly/

2. frail*.ti,ab.

3. frailty.mp.

4. 1 or 2 or 3

5. random*.mp.

6. systematic review*.mp.

7. 5 or 6

8. 4 and 7

Embase

1. frail elderly.mp. or Frail Elderly/

2. frail*.ti,ab.

3. frailty.mp.

4. 1 or 2 or 3

5. limit 4 to randomized controlled trial

6. random*.mp.

7. systematic review*.mp.

8. 6 or 7

9. 4 and 8

10. 5 or 9

MiDLine

1. frail elderly.mp. or Frail Elderly/

2. frail*.ti,ab.

3. frailty.mp.

4. 1 or 2 or 3

5. limit 4 to (randomized controlled trial or systematic reviews)

6. random*.mp.

7. systematic review*.mp.

8. 6 or 7

9. 4 and 8

10. 5 or 9

CENTRAL

#1 Frail Elderly

#2 frail

#3 frailty

#4 random

#5 systematic review

#6 #4 or #5

#7 #1 or #2 or #3

#8 #6 and #7

CHAPTER 3

MANAGEMENT OF FRAILTY: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

PREFACE TO CHAPTER 3

Authors: Ahmed Negm, Courtney Kennedy, Lehana Thabane, Areti-Angeliki Veroniki, Johnathan Adachi, Julie Richardson, Ian Cameron, Aidan Giangregorio, Maria Petropoulou, Saad Alsaad, Jamaan Alzahrani, Maaz Muhammad, Muneen Ahmed, Eileen Kim, Hadi Tehfe, Robert Dima, Kalyani Sabanayagam, Patricia Hewston, Hajar abu alrob, Alexandra Papaioannou.

Publication status: This manuscript will be submitted to the British Medical Journal.

3.1 Abstract

Objective: To analyse and determine the comparative effectiveness of interventions targeting frailty prevention or treatment on frailty as a primary outcome and quality of life; short physical performance battery (SPPB); cognition; depression, and adverse events as secondary outcomes.

Design: Systematic review and network meta-analysis (NMA).

Data sources: Relevant RCTs were identified by a systematic search of several electronic databases including MEDLINE, EMBASE, CINAHL, and AMED. Duplicate title and abstract and full-text screening, data extraction and risk of bias assessment were performed.

Data extraction: All RCTs examining frailty interventions aimed to decrease frailty or improve physical performance were included. Comparators were standard care, placebo or another intervention.

Data synthesis: We performed both standard pairwise meta-analysis and Bayesian NMA. Dichotomous outcome data were pooled using the odds ratio effect size, whereas continuous outcome data were pooled using the standardized mean difference (SMD) effect size. The quality of evidence was evaluated using the GRADE approach.

Results: A total of 89 RCTs were included after screening of 7090 citations and 749 full-text articles. Network meta-analysis (including 20 RCTs, 4838 participants, 8 interventions) suggested that the physical activity intervention, when compared to placebo/standard care, were associated with reductions in frailty (SMD, -0.83 (-1.46, -0.18). Pairwise meta-analyses for depression (9 RCTs; 1519 participants) showed significant association between medication management and decrease in depression relative to placebo/standard care (SMD, -1.64 (-2.02, -1.27). Physical activity was probably the most effective or the second most effective interventions for all included outcomes except for SPPB.

Conclusion: Physical activity and physical activity with nutritional supplementation and medication management are the most effective frailty interventions. Safe exercise programs are required to decrease the number of adverse events.

Systematic review registration: PROSPERO 2016 CRD42016037465.

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3.2 Introduction

The world's fastest growing population is older adults ≥85years. In Canada, it is expected that 5.7% of the population will be 85 or older by 2051 (1), while older adults will represent 12% of the European union population by 2060 (2). Prevention and management of age-related frailty is becoming a public health issue due to its increasing prevalence (3-6). Frailty is defined as a clinical condition with increased vulnerability, which results from aging-related degeneration across psychological, physical and social functioning (7, 8). Frailty is also recognized by cumulative decline in many physiological systems including inflammation, neuromuscular dysfunction, endocrine dysregulation, immune dysfunction, abnormalities in energy metabolism and central nervous system failure (9-12). However, poor muscle strength and low physical performance are the most prevalent frailty markers in older adults (13).

Adverse outcomes associated with frailty include increased risk for functional disability, hospitalization, fractures (14), admission to long-term care, and increased mortality (9, 15-18). Similarly, age related decline in muscle strength, power, balance, and functional performance (19) leads to unfavourable health outcomes (20) such as reduced quality of life, increased risk of cardiovascular disease, all-cause mortality (21), poor daily activities performance, (22, 23) and increased risk of falls and fractures (24-26). Due to the epidemiologic trend of frailty burden and the global rise in life expectancy, maintaining physical performance and preventing frailty in advanced age are among the major clinical and public health challenges and priorities worldwide (27, 28)

Frailty and age-related physical performance decline is reversible (29). Several interventions were examined to determine whether they reduced frailty and improved physical performance in frail older adults such as physical training programs (different exercise interventions) (30-36), nutritional (37-41), physical training and nutrition (42-47), multicomponent (29, 48-51), geriatric comprehensive assessment (52, 53), pharmacologic (54-56), and whole body vibration (57, 58). Despite the variety of the intervention used to prevent or decrease frailty and improve physical performance, the most effective intervention is yet to be determined. Due to the rising burden of frailty and physical performance decline, determining the ideal intervention for these two health issues is critical for healthcare providers, public health and policy makers.

The key elements of an effective frailty prevention program need to be specified to facilitate standardized implementation of effective interventions (59). Previous systematic reviews with or without meta-analysis have selectively examined interventions targeting frailty and improved physical performance (60-69). However, directly comparing more than 2 interventions using conventional meta-analysis has major limitations. Network meta-analysis (NMA) synthesizes both direct and indirect evidence aiming to compare treatments that have not been compared head to head before. NMA can provide the ranking of all available interventions targeting frailty and physical performance. We conducted a systematic review and NMA of randomised controlled trials (RCTs) comparing interventions aimed to prevent/manage frailty and improve physical performance in older adults.

3.3 Method

The methods of systematic review and NMA have been described in our published protocol (59). Therefore, the methods are described briefly here. For reporting the methods and results of this systematic review and network meta-analysis, we followed the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions (70). We also followed the International Society for Pharmaco-economics and Outcomes Research (ISPOR) recommendations in conducting statistical analyses (71). This review is registered in PROSPERO, systematic review registration: PROSPERO 2016 CRD42016037465.

Data Sources and selection

To identify relevant studies, we searched MEDLINE, EMBASE, CINAHL, AMED, the Cochrane Central Registry of Controlled Trials (CENTRAL), HealthSTAR, DARE, PsychINFO, PEDro, SCOPUS, and Scielo from inception until May 3, 2016 (see protocol for search strategies (59)). We scanned relevant systematic reviews for any additional RCTs. An experienced librarian (LB) was involved in designing our search strategies in each individual database. An updated search was conducted on February 15, 2018, which involved screening, abstraction, and risk-of-bias assessment, by 2 reviewers working independently without additional reference scanning. Any disagreement was resolved through consensus or by a third reviewer (AN).

Eligibility Criteria

All RCTs examining one or more interventions aimed to decrease frailty or improve physical performance were included. Comparators were standard care, placebo or another intervention. Any RCT reporting on frailty or physical performance outcome was considered eligible.

Outcomes

In the protocol of this review, a large number of outcomes have been mentioned (59). However, this report will focus on frailty and its related outcomes including quality of life; short physical performance battery (SPPB); cognition; depression, and adverse events due to space limitations. The remaining outcomes will be reported in a subsequent paper. The primary outcome was frailty measured by any frailty outcome measure. The secondary outcomes included short physical performance battery, cognition, depression, quality of life, mental and physical domains of quality of life (if quality of life was reported by domains and not a global score), adverse events and serious adverse events.

Study Selection

After pilot-testing eligibility criteria for citations and full-text articles, the eligibility assessment of title and abstract of citations obtained from the search was performed by two independent reviewers unblinded to authors, journals and countries of the citations. After title and abstract screening for potentially eligible studies, two reviewers checked the full text articles for eligibility independently. Any disagreement was resolved through consensus or by a third reviewer (AN). The agreement between the two reviewers was assessed by examining raw agreement and unweighted kappa (72).

Data Extraction

A data extraction form was developed and pilot-tested for this review by two reviewers (CK, AG, SA, JA, MM, MA, EK, HT, RD, KS, PH, HA) to ensure consistency in extraction. The extraction form was refined accordingly and data were extracted in duplicate and independently. Any conflict was resolved by a third reviewer (AN). If needed, study authors were contacted for further information about included studies. The extracted information included the participants' characteristics, types and characteristics of intervention and all baseline and post-treatment data points of reported outcome measures. Included interventions were classified into the following categories: placebo/standard care, physical activity, nutritional supplementation, psychosocial/cognitive training, vibration waves or sound waves, medication management, pharmacotherapy, physical activity with nutritional supplementation, comprehensive geriatric assessments and multifaceted intervention.

Risk of Bias Assessment

The modified version of Cochrane's tool for assessing risk of bias was used to assess the risk of bias of included trials (73, 74). The studies' overall risk of bias was determined to be high if one of the risk of bias domains was determined to be high. The risk of bias assessment was conducted by two independent reviewers and any disagreements were resolved by consensus or with assistance from a third reviewer (AN) if necessary. When the number of studies was at least 10, a comparison-adjusted funnel plot was drawn to assess for publication bias and small study-effects (75, 76).

Data synthesis and statistical analysis

For meta-analysis, dichotomous outcome data were pooled and the odds ratio (OR) and its 95% confidence interval were reported, whereas continuous outcome data were pooled and the standardized mean difference (SMD) and its 95% confidence interval were reported for study-specific follow-up mean values. We used the follow-up means instead of change means, since we could not mix them up using SMD. Studies reported change means only were included in the systematic review, but we had to exclude them from the analysis. Missing standard deviations (SDs) in follow-up means were assumed to be equal with SDs in baseline mean values. In case a study did not report a measure of variance that could be transformed to a follow-up SD, then SD was imputed according to the method suggested by Furukawa et al (77). Studies including multiple doses of the same treatment were combined in the same node, as this information was not reported consistently across the studies.

We initially performed standard pairwise meta-analysis using the random-effects model (78). The random-effects model was selected as we expected that studies would differ both methodologically and clinically (between-study variability). Between-study variability (heterogeneity) of the treatment effects within each treatment comparison was assessed by I2 (79) and its 95% confidence interval, and the magnitude of the between-study variance (τ^2) and its 95% confidence interval, as estimated using the restricted maximum likelihood estimator and the Q-profile approach (80, 81).

We included the following interventions: placebo/standard care, physical activity, nutritional supplementation, psychosocial/cognitive training, vibration waves or sound waves, medication management, pharmacotherapy, physical activity with nutritional supplementation,

comprehensive geriatric assessments and multifaceted intervention. (Appendix, eTable 1 summarizes the interventions' descriptions). When the included trials formed a connected network in a studied outcome, we additionally conducted a Bayesian random-effects network meta-analysis using Markov chain Monte Carlo (MCMC) simulation. We assumed a common within-network between-study variance 〖(τ〗^2) across treatment comparisons, since clinically we expected no important differences in the heterogeneity magnitude across treatment comparisons, as well as there were many treatment comparisons informed by a single study, where τ^2 was not estimable.

For each NMA, we assessed a priori the transitivity and consistency assumptions (82, 83). Statistical assessment of the transitivity assumption implies that the distribution of potential treatment effect modifiers is balanced across the available direct comparisons. We assessed the plausibility of the transitivity assumption using the average age, BMI, and percentage male as potential treatment effect modifiers and present the mean values across comparisons in each outcome in tables (84). We checked for the plausibility of consistency (i.e., that direct and indirect evidence agree) as a whole in each network using a random-effects design-by-treatment interaction model (82, 85). Similar to the NMA model, in each design-by-treatment interaction model we assumed common within-network between-study variance across intervention comparisons. If the global test suggested inconsistency, we assessed inconsistency locally using the loop-specific approach (83, 86). When statistically significant inconsistency was detected, we checked the data for potential abstraction errors. If no data errors were identified we reported direct, indirect, and mixed estimates separately. We also explored significant inconsistency further by conducting meta-regression analysis using the potential effect modifiers.

Across all Bayesian models we assumed vague priors for all model parameters and a half-normal prior distribution for the between-study standard deviation ($\tau \sim N(0,1), \tau > 0$). The models were run for 100,000 iterations to ensure model convergence, which was checked by visual inspection of the mixing of two chains or by using Gelman-Rubin convergence diagnostics (87), after discarding the first 10,000 iterations and thinning of 10. We report the posterior median values along with their 95% credible intervals (CrIs) for the relevant model parameters, including treatment effects, between-study variance, and SUCRAs (88). Each NMA effect estimate is presented along with a 95% predictive interval (PrI), which captures the magnitude of the between-study variance and presents the interval within which we would expect the treatment effect of a future study to lie (89). Interventions of each outcome were ranked using the surface under the cumulative ranking curve (SUCRA) (90, 91) and presented in a rank-heat plot (http://rh.ktss.ca/) (92). A study with a markedly different intervention effect estimate compared to the remaining outcome data is defined as outlying (93). We monitored comparison-adjusted funnel plots for extreme study effects (outlying studies). When obvious outliers were detected, these were excluded in a sensitivity analysis to assess the robustness of results.

Network meta-regression and sensitivity network meta-analyses were conducted for the primary outcome with consideration of potential treatment effect modifiers such as age, sex, and overall risk of bias. Network meta-regression was performed assuming a common fixed coefficient across comparisons. For the primary outcome, we combined binary and continuous data in a shared parameter model, but we also conducted a sensitivity analysis restricting to continuous data only, since most studies reported frailty as a continuous outcome.

Standard pairwise meta-analyses were conducted in R statistical software (version 3.5.0) (94) using the metafor package (95). We ran Bayesian NMA models through the Jags program for Bayesian framework (96). Analyses of Bayesian NMAs were conducted within R (94) using rjags package (97). The shared parameter model was conducted within OpenBUGS (98). The design-by-treatment interaction model was performed in Stata using the network command (99). Comparison-adjusted funnel plots were performed in Stata using the netfunnel command (100).

Grading of evidence

We graded the strength of the body of evidence that emerged from this review using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (101).

3.4 Results

After removing duplicate articles, 7090 title and abstract were screened for eligibility. After title and abstract screening, 749 studies were retrieved for full text review. 185 studies met the eligibility criteria and 94 studies reported the frailty and frailty related outcomes and were included in this report. Figure 1 shows the flow diagram for identification of eligible trials. There was fair agreement between the reviewers in title and abstract screening with raw agreement of 86% and unweighted kappa = 0.38 (0.34, 0.42) and moderate agreement in full- text screening with raw agreement of 77% and unweighted kappa = 0.53 (0.46, 0.59). Seven authors were contacted, and a response was received from one author, which allowed inclusion of one additional study.

Study and Participant Characteristics

Most of the participants included in the RCTs of this systematic review were female (62.5%), had mean age between 75 and 85 years and Body mass index between 25 and 30. Table 1 demonstrates participants' characteristics and more details are provided in Appendix, eTable 2. The number of the included publications was consistently increasing between 2000 and 2018 and most of the included studies were published between 2011 and 2018 (70.2%). The majority of studies were conducted in Europe (43.6%), followed by North America (29.8%), Asia (13.8%) and Australia or New Zealand (10.6%). Of the included studies, 69.1% were conducted in a single centre. 38 RCTs were at home, 20 in the community and 16 in a hospital. RCTs sample size ranged from 15 to 1456 participants with the majority between 50 and 100 participants. 37 RCTs had intervention duration of 3 months or less and 29 RCTs had duration of 3 to 6 months. Table 2 summarizes the study characteristics, whereas additional details of the included studies are reported in Appendix, eTable 3.

Risk of Bias

Most of RCTs had high risk of bias of participants' and the blinding of study personnel was ((66%) and (63.8%) respectively). However, most RCTs had low risk of bias of Sequence generation (86.2%), allocation concealment (76.6%), outcome assessors blinding (60.6%), data analysts blinding (61.7%), incomplete outcome data (86.2%), selective outcome reporting (89.4%), and other sources of bias (89.4%). Of the included RCTs, 77.7% had overall high risk of bias. Figure 2 shows Cochrane risk of bias assessment and detailed risk of bias assessment are presented in Appendix, eTable 4. The agreement between the two reviewers on risk of bias assessment was fair with raw agreement of 74.5% and kappa of 0.21 (95% CI, 0 to 0.42). All

comparison-adjusted funnel plots suggested no evidence of publication bias (shown in Appendix, eFigure 1). Visual assessment of funnel plots for frailty, quality of life physical and mental domains indicates that there were markedly different study effects (outlying studies) and sensitivity analyses were conducted by excluding these outliers to check the robustness of results. Appendix, eTable 5 shows the results of these sensitivity analyses.

Analysis of the outcomes

The design-by-treatment interaction model showed no evidence of statistically significant inconsistency in the network meta-analysis for six outcomes (frailty, short physical performance battery, quality of life- physical function domain, quality of life- mental domain, cognition, adverse events), but we could not evaluate consistency in the network meta-analysis for three outcomes (quality of life, depression, adverse events) as they were star-shaped networks.

Due to the large number of interventions' comparisons, we present and discuss the overall results of each outcome with a focus on statistically significant intervention effects relative to placebo/standard care. All pairwise comparison results estimated in a meta-analysis model are reported in Appendix, eTable 6, as well all pairwise comparison results estimated in a network meta-analysis model are available in Appendix, eTable 7. The forest plots of interventions compared to placebo/standard care for each outcome are presented in Appendix, eFigure 2. The rank-heat plot using the SUCRA values, presented in Appendix eFigure 3, indicates that exercise is likely the most effective intervention for all the reported outcomes.

Primary Outcome: Frailty

Network meta-analysis for frailty included 20 RCTs (16 two-arm and 4 multiple-arm) with 4838 participants and 8 interventions (Figure 3). There was no significant heterogeneity in this network meta-analysis (Heterogeneity = 0.19, $P = 0.13$). Across all the relevant treatment effects from NMA, only one treatment comparison (physical activity intervention versus placebo/standard care) was statistically significant (3.6%) (Appendix, eTable 7). Of the 8 included interventions, physical activity intervention was associated with decrease in frailty compared to placebo/standard care (SMD, -0.93 (95% CI, -1.57 to -0.27) (Figure 4). According to SUCRA, physical activity intervention and physical activity and nutritional supplementation were probably the most effective interventions (100% and 71% likelihood, respectively) to reduce frailty.

Meta-regression was used to determine if the participant's age and gender modified the effect of the included interventions. We conducted two meta-regression analyses and results are provided in Appendix eTable8. The meta-regression for participants' age included 19 studies (4723 participants) with 8 interventions. As eTable8 provides, there was no significant difference in the intervention effect across all the comparisons ((regression coefficient reported on SMD scale 0.05 (95%CI, -0.05 to 0.14). The meta-regression for participants' gender included 17 studies (4449 participants) with 8 interventions. Gender did not significantly modify the interventions' effect across treatment comparisons (regression coefficient on SMD scale 1.7 (95%CI, -3.55 to 6.86)).

Sensitivity analysis was conducted restricting from the 17 included RCTs in NMA to 3 RCTs that have a low risk of bias (410 participants; 4 interventions); no intervention was associated with a lower frailty and the results were not different from the primary analyses (Appendix, eTable 5). After excluding the outlier study from the rest of the data in frailty, quality of life physical and mental domains, (Appendix, eTable 5), the most effective interventions were similar for the three outcomes. When restricting to studies with reporting a continuous frailty outcome the effect estimates and intervention ranking did not significantly change.

SPPB

For the short physical performance battery (SPPB), 36 RCTs (4568 participants) with 9 interventions were included in the network meta-analysis (Figure 5). There were 36 relevant mixed treatment effects from NMA and 8 treatment comparisons (22.2%) were statistically significant (Appendix, eTable 7). Of the included interventions, physical activity (SMD, 0.90 (95% CI, 0.20, 1.61), physical activity and nutritional supplementation (SMD, 2.41 (95% CI, 1.21 to 3.63), medication management (SMD, 3.94 (95% CI, 0.93 to 6.98), and nutritional supplementation (SMD, 1.62 (95% CI, 0.34 to 2.90) were different than placebo/standard care in SPPB outcome (Appendix eFigure 2). Of the 11 pairwise meta-analyses comparisons, 8 comparisons were significant (Appendix eTable 6). According to the SUCRA value, medication management interventions, physical activity with nutritional supplementation, and psychosocial/cognitive training were probably the most effective intervention (100%, 88%, and 75% respectively) to improve SPPB score.

Quality of life

Quality of life was reported in the included RCTs as a global score (such as EQ-5D) or domain specific scores (such as SF-36 domains). We conducted three analyses for quality of life outcome for global score, physical domain, and mental domain of quality of life.

For global quality of life analyses, the network meta-analysis included 16 RCTs (3259 participants) with 6 interventions (Figure 6). There were no important differences between all the relevant treatment effects from NMA (Appendix, eTable 7). Also, the included interventions did not show an important effect when compared to placebo/standard care (Appendix, eFigure 2) or between the 5 pairwise comparisons (Appendix eTable 6). Physical activity, and multifaceted interventions were probably the most effective interventions (100% and 63% respectively) to improve quality of life. For the physical and mental domains of the quality of life, the network included 15 RCTs (2293 participants) with 7 interventions (Figure 7) and 12 RCTs (2053 participants) with 7 interventions (Figure 8) respectively. The 21 treatment effects from NMA for the physical and mental domains were not different, except the comparison between medication management and placebo/standard care (Appendix, eTable 7). Also, there was no important differences between any of the included interventions and placebo/standard care except physical activity intervention (SMD, 1.33 (95% CI, 0.09 to 2.55) (Appendix, eFigure 2). Out of 9 pairwise comparisons, only the effect of physical activity was different than placebo/standard care (Appendix, eTable 6). The SUCRA ranking indicated that the most effective intervention was physical activity (83%), followed by medication management (67%) for the physical domain and physical activity (83%) and physical activity with nutritional supplementation (67%) for the mental domain.

Cognition

The network meta-analysis of the cognition outcome included 13 RCTs (1664 participants) with 8 interventions (Figure 9). The 28 treatment effects from NMA were not different and there were no differences in the 9 pairwise comparisons for the cognition outcome (Appendix, eTable 7). Also, there were no important differences between any of the interventions and placebo/standard care (Appendix, eFigure 2). According to the SUCRA values, medication management and physical activity were probably the most effective interventions (100% and 71% respectively) to improve cognition.

Depression

For the depression outcome, the network meta-analysis included 9 studies (1519 participants) with 5 interventions (Figure 10). 4 of 10 (40%) treatment effects from NMA were statistically significant (Appendix, eTable 7). All 4 significant comparisons showed superior effect of medication management compared to other interventions on depression. Medication management also was associated with lower depression compared to placebo/standard care (SMD, -1.64 (95% CI, -2.02, -1.27)) (Appendix, eFigure 2). Of the 4 pairwise comparisons, 2 comparisons showed differences (Physical activity and medication management versus placebo/standard care) (Appendix, eTable 6). According to the SUCRA results, medication management and physical activity were probably the most effective interventions (100% and 75% respectively) to decrease depression.

Adverse events

Of the included studies, 22 RCTs reported no intervention-related adverse events in any study group and another 30 RCTs reported 1 or more adverse events and/or serious adverse events. For adverse events, 28 RCTs (4013 participants) with 7 interventions were included in the network meta-analysis (Figure 11). Appendix, eTable 7 and eFigure 2 show that physical activity intervention versus placebo/standard care and multifaceted intervention versus placebo/standard care were the only significant treatment comparison (OR, 0.32 (95% CI, 0.12 to 0.76 and OR, 0.15 (95% CI, 0.02 to 0.88, respectively)). There were 11 pairwise comparisons and there were important differences in 5 of these comparisons (Appendix, eTable 6). The psychosocial/cognitive training intervention, placebo/standard care and nutritional supplementation interventions were associated with the least number of adverse events (100%, 83% and 67% respectively).

The network meta-analysis of serious adverse events included 10 RCTs (1644 participants) with 5 interventions (Figure 12). The network meta-analysis had 10 comparisons and 4 comparisons were significant (40%) (Appendix, eTable 7). One of the four pairwise comparisons shows differences (Multifaceted intervention versus placebo/standard care) (Appendix, eTable 6) and all the comparisons between the interventions and placebo/standard care showed no differences (Appendix, eFigure 2). Multifaceted intervention and physical activity were associated with the least number of serious adverse events (100% and75% respectively).

Quality of evidence

We used the recently updated GRADE approach methods to assess the quality of the evidence of this network meta-analysis (102). We judged the quality of evidence to be low or very low for all

outcomes after rating down for risk of bias, inconsistency and imprecision and incoherence between direct and indirect estimates. Appendix, eTable 9 shows the GRADE evidence profile for each outcome and Appendix, eTable 10 shows the summary of finding tables for the primary outcome (Frailty).

3.5 Discussion

This is the first systematic review and network meta-analysis to combine the direct and indirect effect of 10 interventions and compare their effect on frailty in older adults. Physical activity was probably the most effective intervention in decreasing frailty followed by physical activity with nutritional supplementation. Other interventions showed benefit in managing frailty and should be considered, including psychosocial/cognitive training and pharmacotherapy. Physical activity was probably the most effective or the second most effective intervention for all the reported outcomes except for the SPPB outcome. Physical activity with nutritional supplementation was among the most effective interventions on frailty, SPPB, and quality of life-physical and mental domains. Similarly, medication management was the most effective treatment on 3 outcomes (SPPB, cognition, depression). The most effective interventions on cognition and depression outcomes were physical activity and medication management. These results suggest that several components could be effective in frailty management and prevention, increasing SPPB scores and improving quality of life of older adults. These intervention components include physical activity, nutritional supplementation, psychosocial/cognitive training, pharmacotherapy and medication management. Physical activity, physical activity with nutritional supplementation and multifaceted interventions were associated with higher adverse events than the other interventions. However, physical activity and multicomponent interventions were associated

with lower serious adverse events. These results indicate that safe physical activity and exercise programs are required to minimize the number of adverse events in older adults.

As the quality of evidence of this review was low or very low, the estimates of interventions' effect are likely to change after including future studies. Future RCTs with adequate allocation concealment, blinding of participants, outcome assessor, study personnel and data analyst are needed. Most RCTs were completed within 6 months (69.7%), but longer-term follow-up and confirmation of the sustainability of these interventions' effect are required. In addition, the short duration of interventions could explain the lack of effectiveness of some of the included interventions. Most studies were conducted in the home and community setting (61.7%); more studies in retirement homes or long-term care setting are needed. In this review, we showed the rapid increase in the frailty interventional studies. Between 1990 and 2000, there were only 2 RCTs, however, there was 61 RCTs between 2011 and 2018. Due to the importance of this topic, we expect the number of frailty RCTs to continue to rise (103). Until more evidences of direct comparisons are reported, our network meta-analysis provides a useful and complete picture of frailty interventions among older adults. The network meta-analysis statistical technique not only includes the results of direct comparisons but also incorporates indirect comparisons.

Consistent with the results of this review, other studies showed the effectiveness of physical activity and exercise interventions. A recent systematic review and network meta-analysis concluded that the exercise alone was associated with lower risk of injurious falls compared to placebo/standard care, however, the effect of exercise on frailty, cognition or depression was not examined. A scoping review of frailty interventions in community dwelling older adults included

14 studies (12 RCTs) (104). The included interventions were physical activity; physical activity with nutrition; physical activity plus nutrition plus memory training; home modifications; prehabilitation (physical therapy plus exercise plus home modifications) and comprehensive geriatric assessment. The authors of this scoping review did not conduct meta-analysis due to the variability of the interventions' description without testing the statistical heterogeneity of the intervention effect. Another recent systematic review qualitatively summarized interventions aimed to prevent pre-frailty or frailty and included 21 RCTs (5275 participants) with 33 interventions (105). This review found that group exercise studies were effective in reducing or preventing frailty and other interventions components showed favourable effect on frailty such as supplementations and cognitive training (105).

Strengths of the review process include reviewers working in pairs across all levels of screening, data abstraction, and risk-of-bias appraisal; we assessed the quality of evidence and degree of confidence in the results of this review using the updated GRADE approach and our search was comprehensive and included a rigorous grey literature search for unpublished studies. This review has its own limitations such as the high risk of bias and small sample size (most of the RCTs included less than 100 participants (57.3%)) of most of the included RCTs. Also, there was a considerable variability of the interventions of some of the individual nodes. For example the physical activity included different types of exercise and physical activities (such as strength, endurance, walking, etc.) and the nutritional supplementation included different kinds of supplementations (such as vitamin D, calcium, protein, etc.). Thus, this review did not aim to determine the most effective exercise type or nutritional supplementation, but identified a number of effective frailty intervention components to be recommended by policy makers or

clinicians based on the patients' needs and preferences. Despite the variability of the included interventions, we found no significant heterogeneity in most of our traditional meta-analyses and no substantial inconsistency in our network meta-analyses.

The published protocol mentioned examining the potential confounder effect of participants' educational level and comorbidities by conduction subgroup analyses. We could not conduct those analyses because most of the included studies did not report these characteristics. As well, another outcome, depression, was added. Because most of the studies (78%) were assessed as having a high risk of bias, the power of the sensitivity analysis of including only RCTs with low risk of bias was limited by the lower number of studies. This limitation suggests that improvements in reporting are required. Some of the included interventions were examined in small number of studies such as medication management and pharmacotherapy. Therefore, more RCT with rigorous methodology and adequate sample size are needed to increase the confidence of the effect estimate of these interventions. Because of the large number of comparisons in the network meta-analyses, multiplicity may have elevated the rate of false positives in the statistically significant results (type I error) (106). Although SUCRA values are based on the treatment effect estimates and their associated CIs, it is recommended that the P score values be interpreted along with the network meta-analysis point estimates and their precision (90).

3.6 Conclusions

Physical activity and physical activity with nutritional supplementation and medication management are the most effective frailty interventions. To minimize the number of adverse events associated with physical activity and exercise programs, safe exercise programs are

required. The quality of evidence of the current review is low and very low. More robust RCTs are needed to increase the confidence of our NMA results and the quality of evidence.

Table 1. Summary of Patient Characteristics

Characteristic	No. (%) of Randomized Clinical Trials (N=89)
Age, mean, y	
55-64.9	2 (2.2)
65-74.9	24 (27)
75-84.9	57 (64)
85-95	5 (5.6)
Not reported	1 (1.1)
% Male	
0-49.9%	64 (71.9)
50-100%	16 (18)
Not reported	9 (10.1)
BMI	
20-24.9	14 (15.7)
25-29.9	32 (36)
30-34.9	2 (2.2)
35-40	5 (5.6)
Not reported	36 (40.4)

Table 2. Summary of Study Characteristics

Study characteristic	**No. (%) of RCT (N=89)**
Year of Publication	
1990 - 1995	1 (1.1%)
1996 - 2000	1 (1.1%)
2001 - 2005	10 (11.2%)
2006 - 2010	16 (18%)
2011 - 2015	30 (33.7%)
2016 - 2018	31 (34.8%)
Continent	
Europe	40 (44.9%)
Australia / New Zealand	8 (9%)
North America	26 (29.2%)
Asia	13 (14.6%)
South America	1 (1.1%)
Multi-continent	1 (1.1%)
Site	
Multicenter	22 (24.7%)
Single Centre	61 (68.5%)
Not Reported	6 (6.7%)
Settings	
Home	36 (40.4%)
Therapist office	1 (1.1%)
Community	19 (21.3%)
Hospital	15 (16.9%)

Long-term care facility	7 (7.9%)
Retirement Home	4 (4.5%)
Research Centre	2 (2.2%)
Not Reported	5 (5.6%)
Sample Size (No. Of Participants)	
10-50	18 (20.2%)
51-100	33 (37.1%)
101-150	13 (14.6%)
≥ 151	25 (28.1%)
Duration of Intervention, wk	
<1-12 (3 months and under)	34 (38.2%)
13-24 (up to 6 months)	28 (31.5%)
24-52 (up to 12 months)	24 (27%)
52-104 (up to 24 months)	1 (1.1%)
Not Reported	2 (2.2%)

Figure 3-1: Study flow diagram

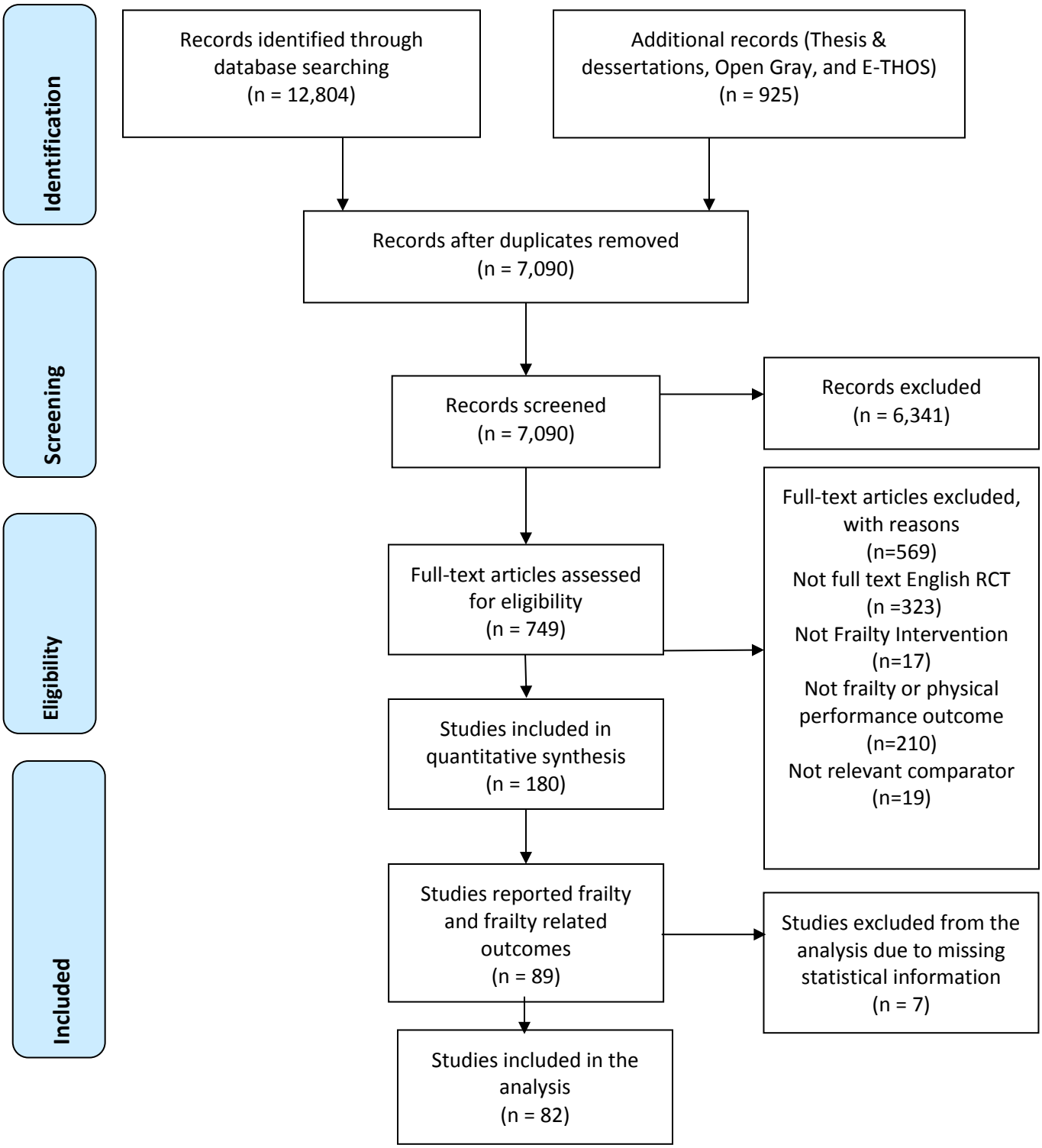


Figure 3-2: Cochrane Risk of Bias Assessment

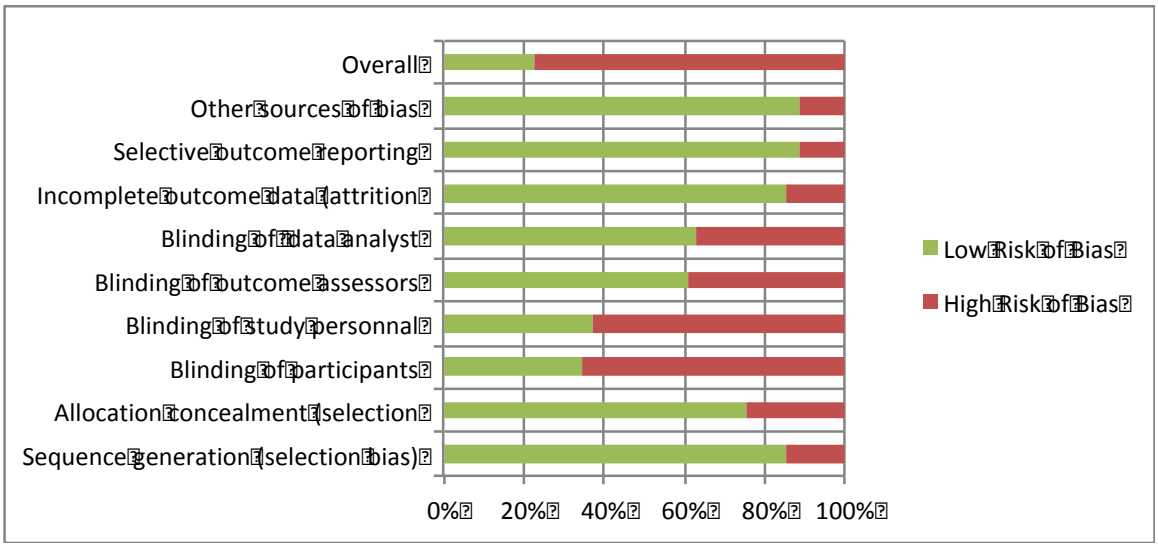
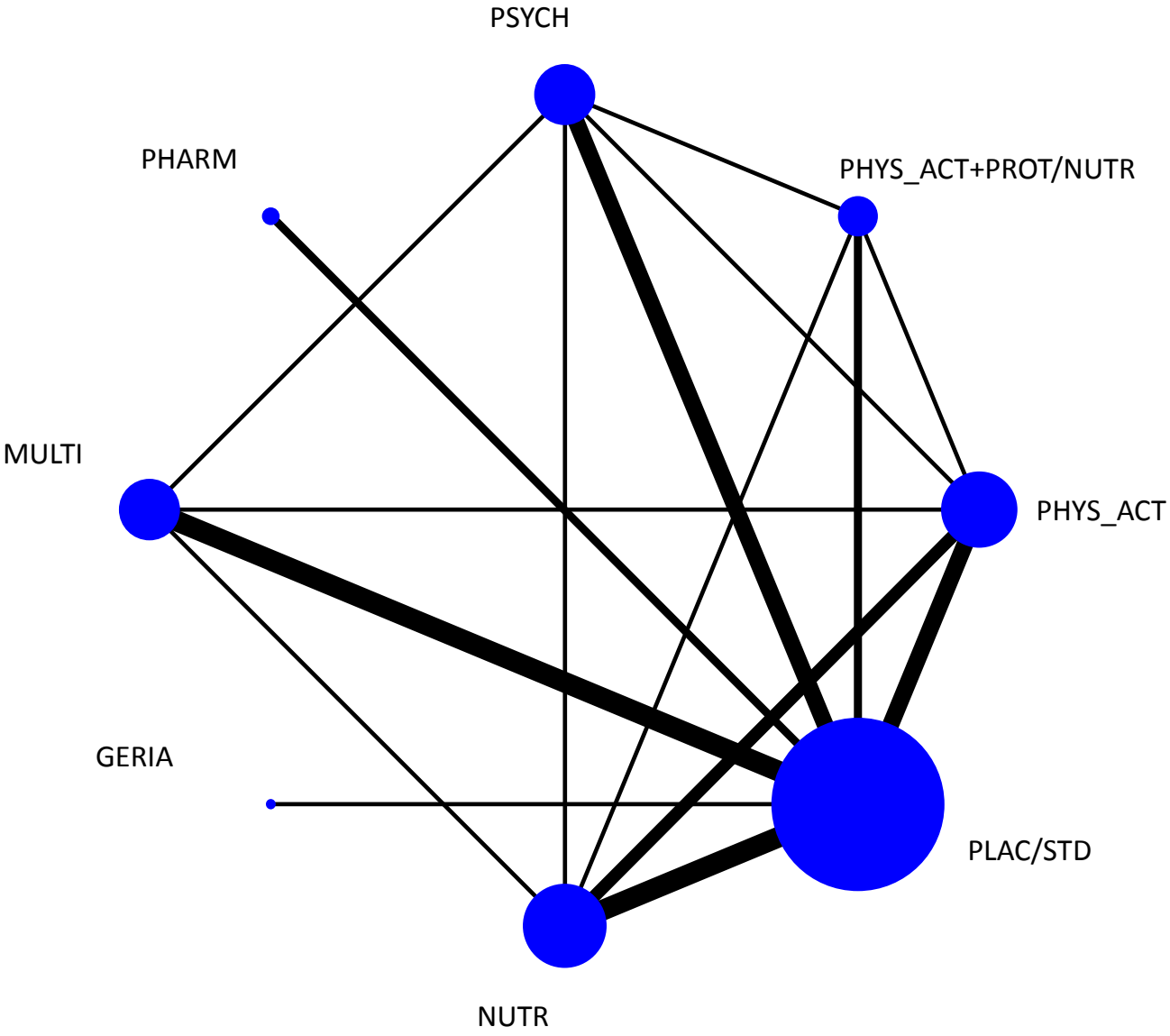
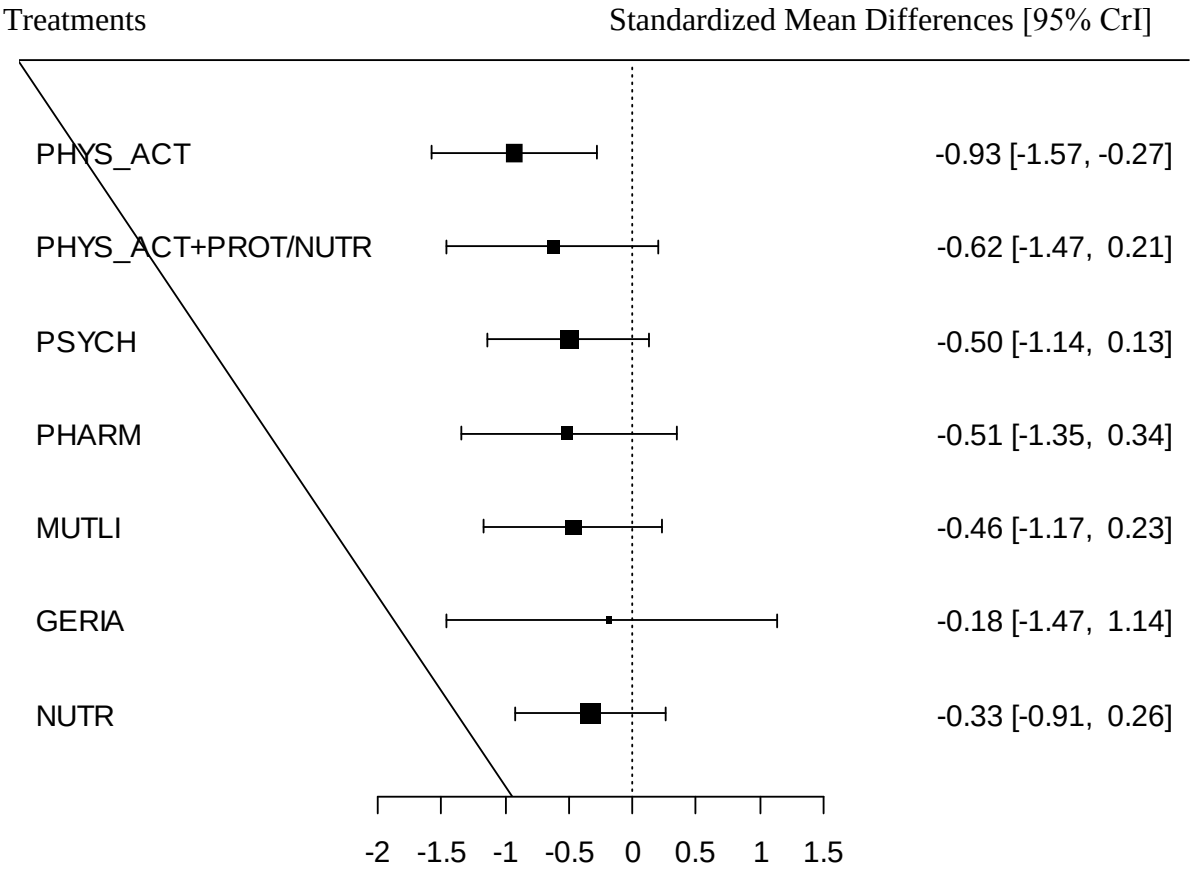


Figure 3-3: Network geometry for frailty



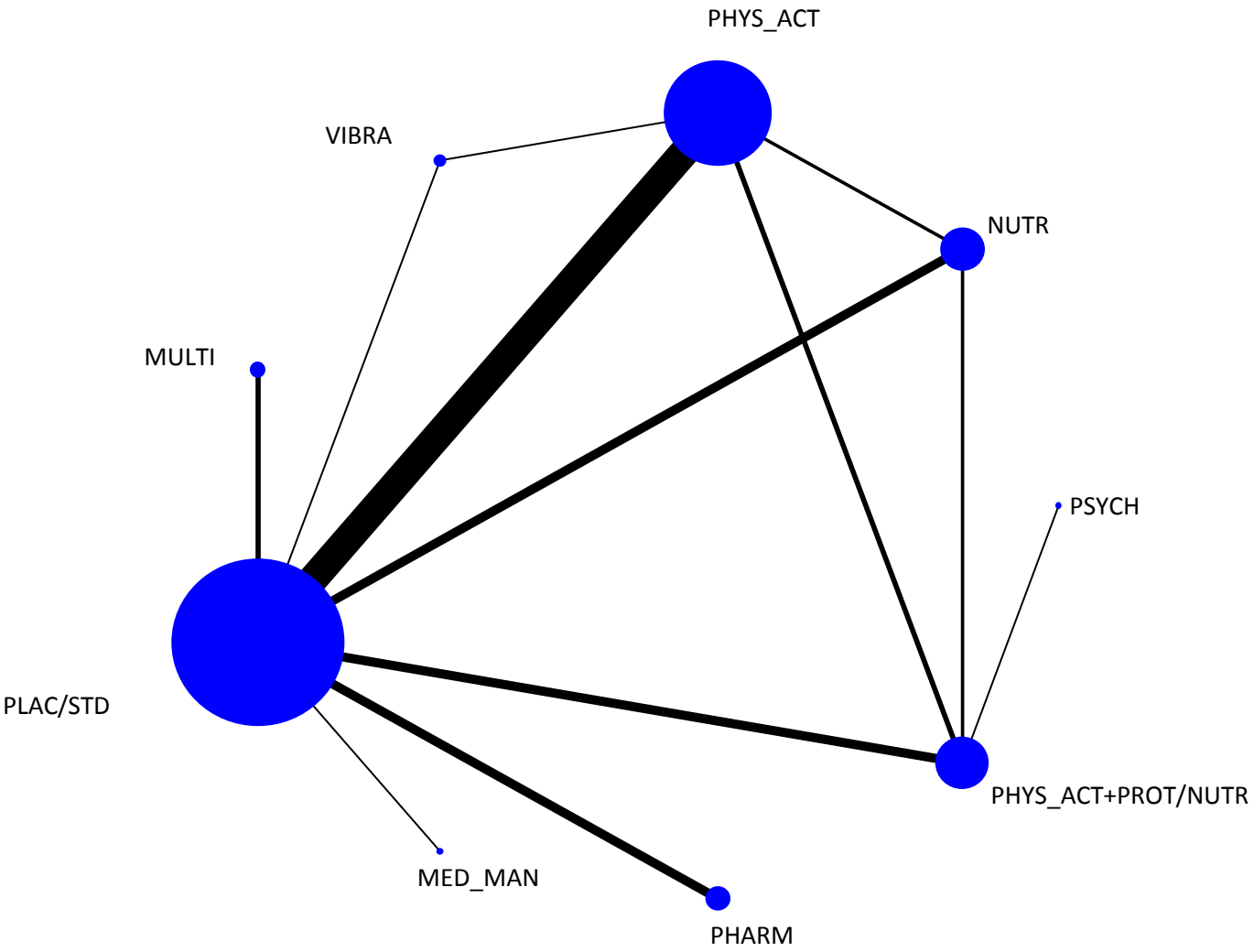
Network geometry for 20 randomized clinical trials (4838 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-4: Frailty outcome of pairwise comparison of included interventions versus placebo/standard care



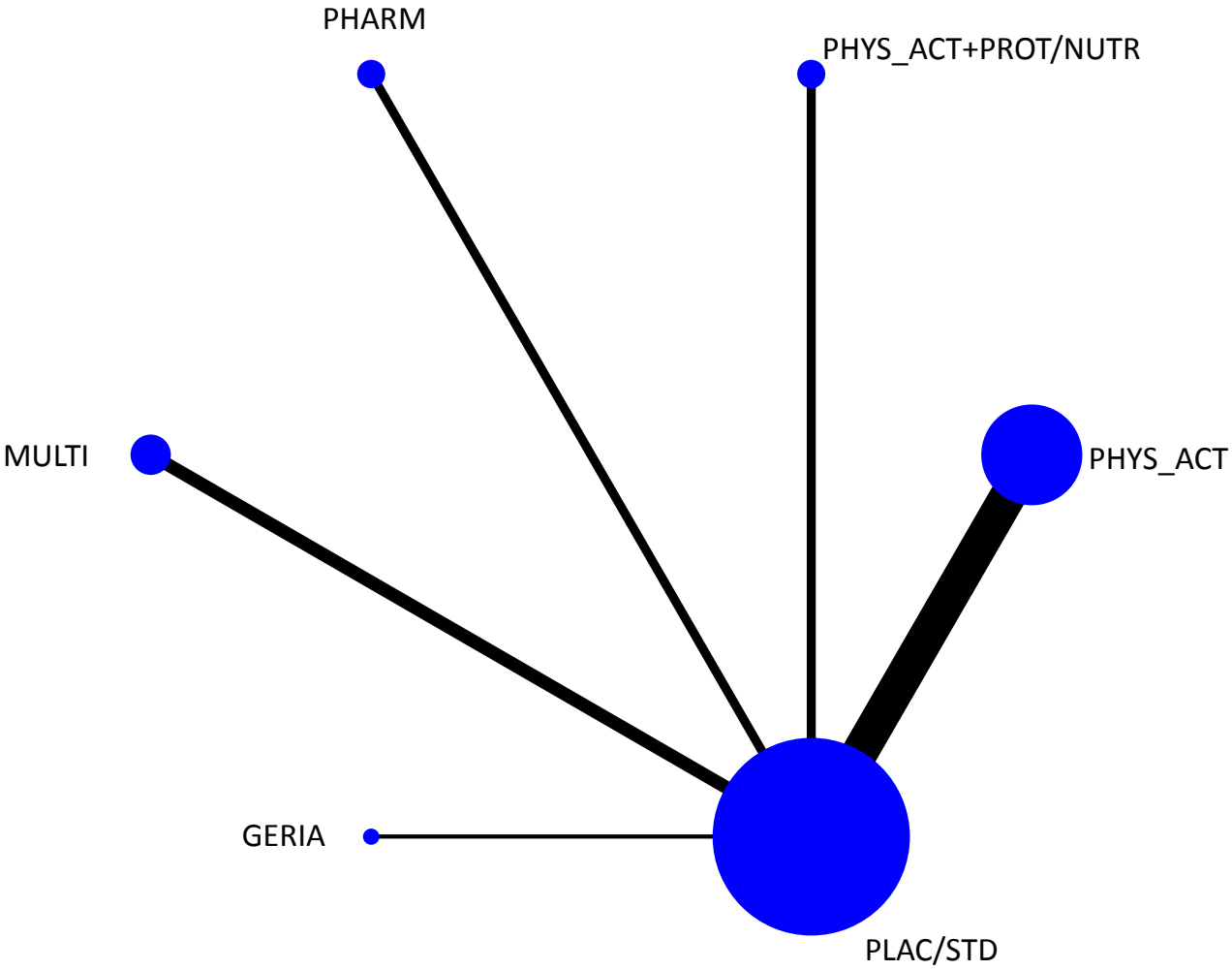
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-5: Network geometry for short physical performance battery



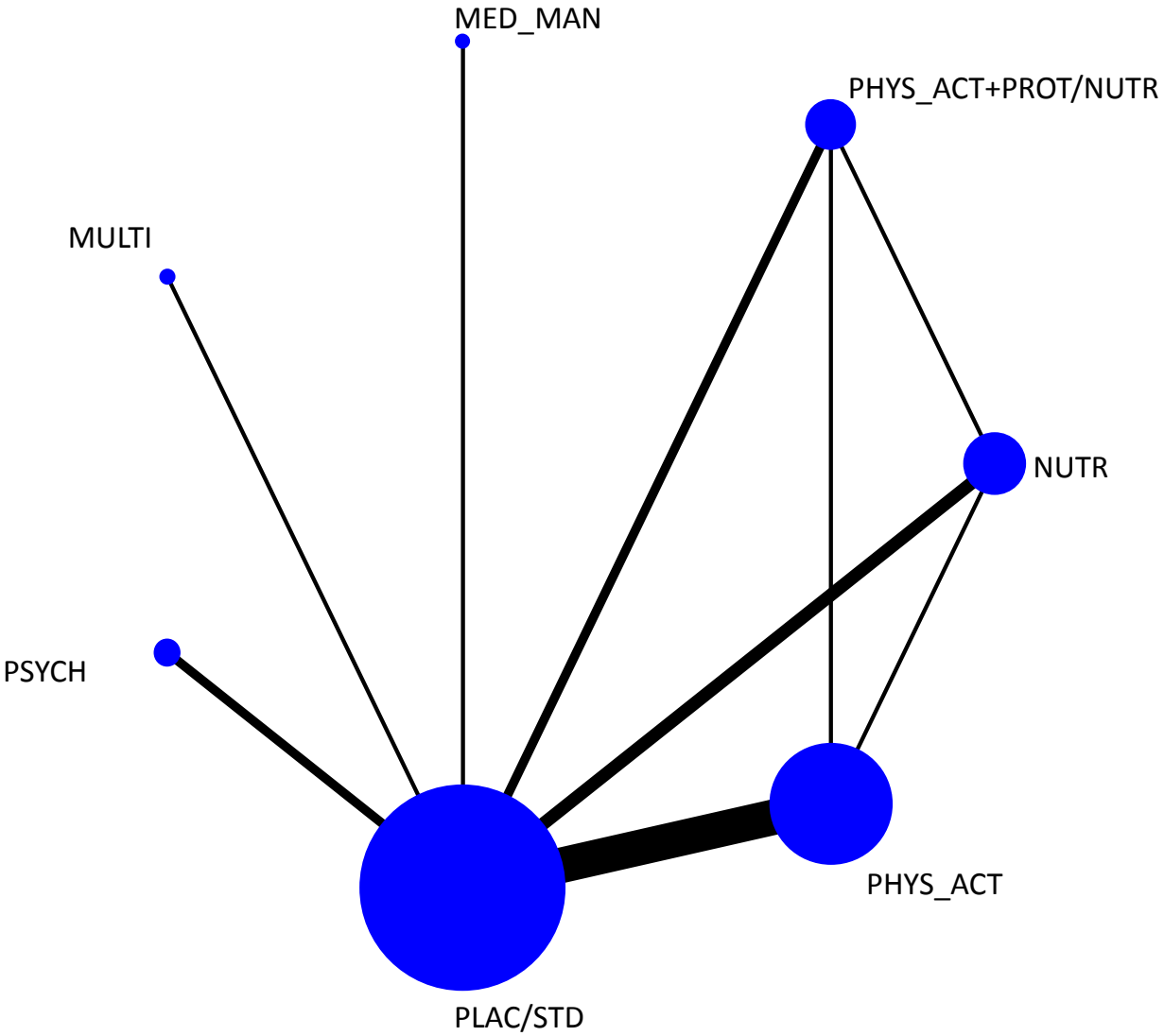
Network geometry for 36 randomized clinical trials (4568 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-6: Network geometry for quality of life



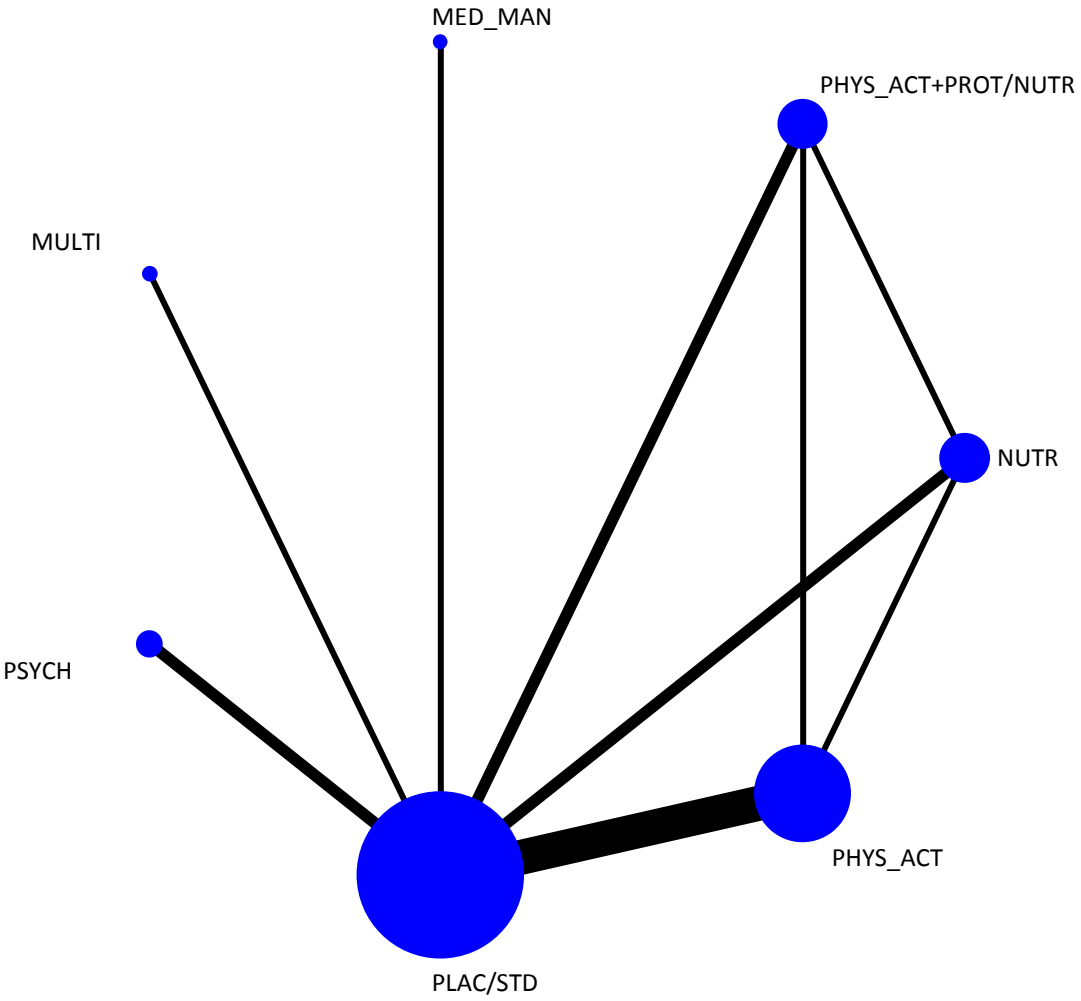
Network geometry for 16 randomized clinical trials (3259 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-7: Network geometry for quality of life- physical function domain



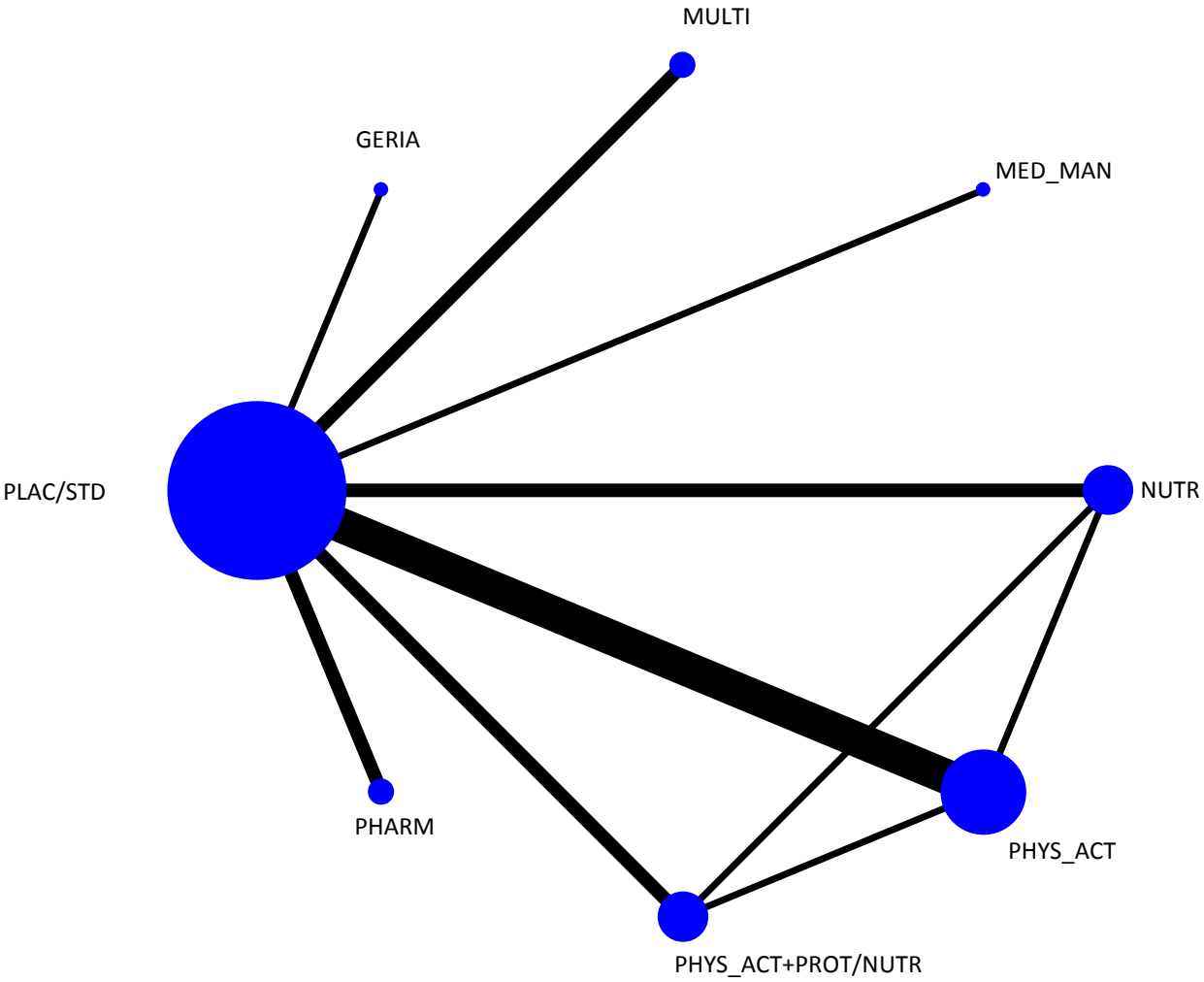
Network geometry for 15 randomized clinical trials (2293 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-8: Network geometry for quality of life- mental domain



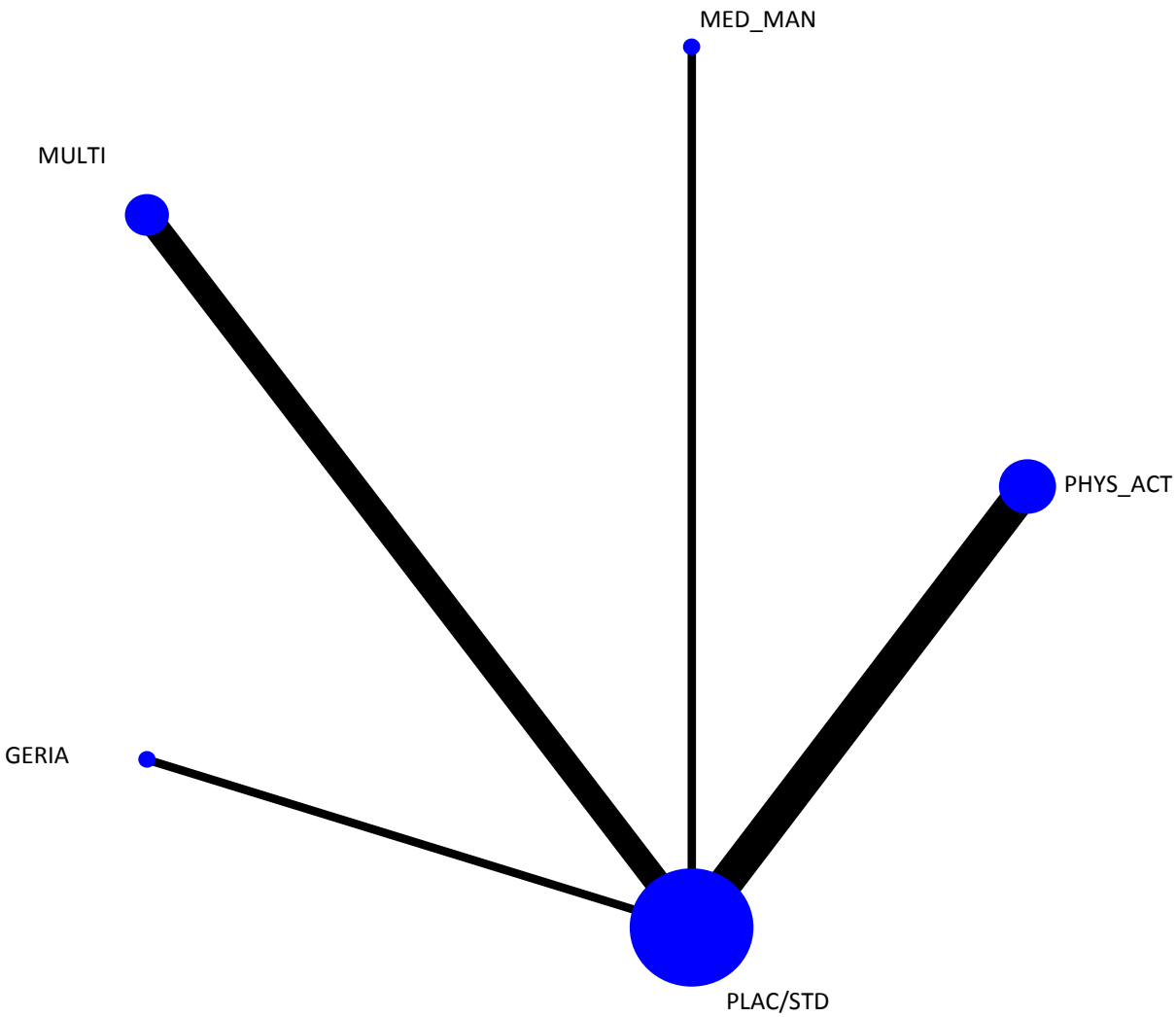
Network geometry for 12 randomized clinical trials (2053 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-9: Network geometry for cognition



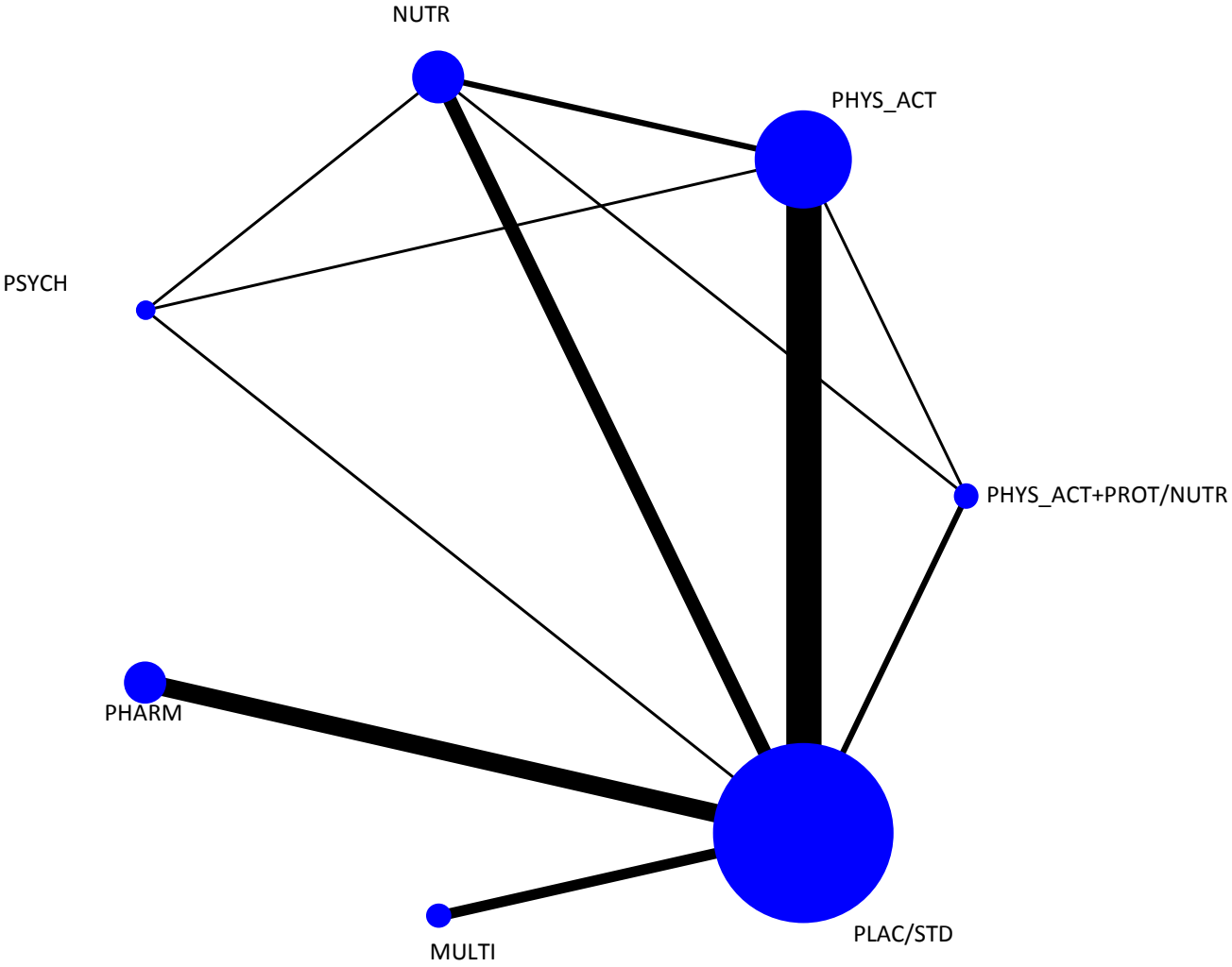
Network geometry for 13 randomized clinical trials (1664 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-10: Network geometry for depression



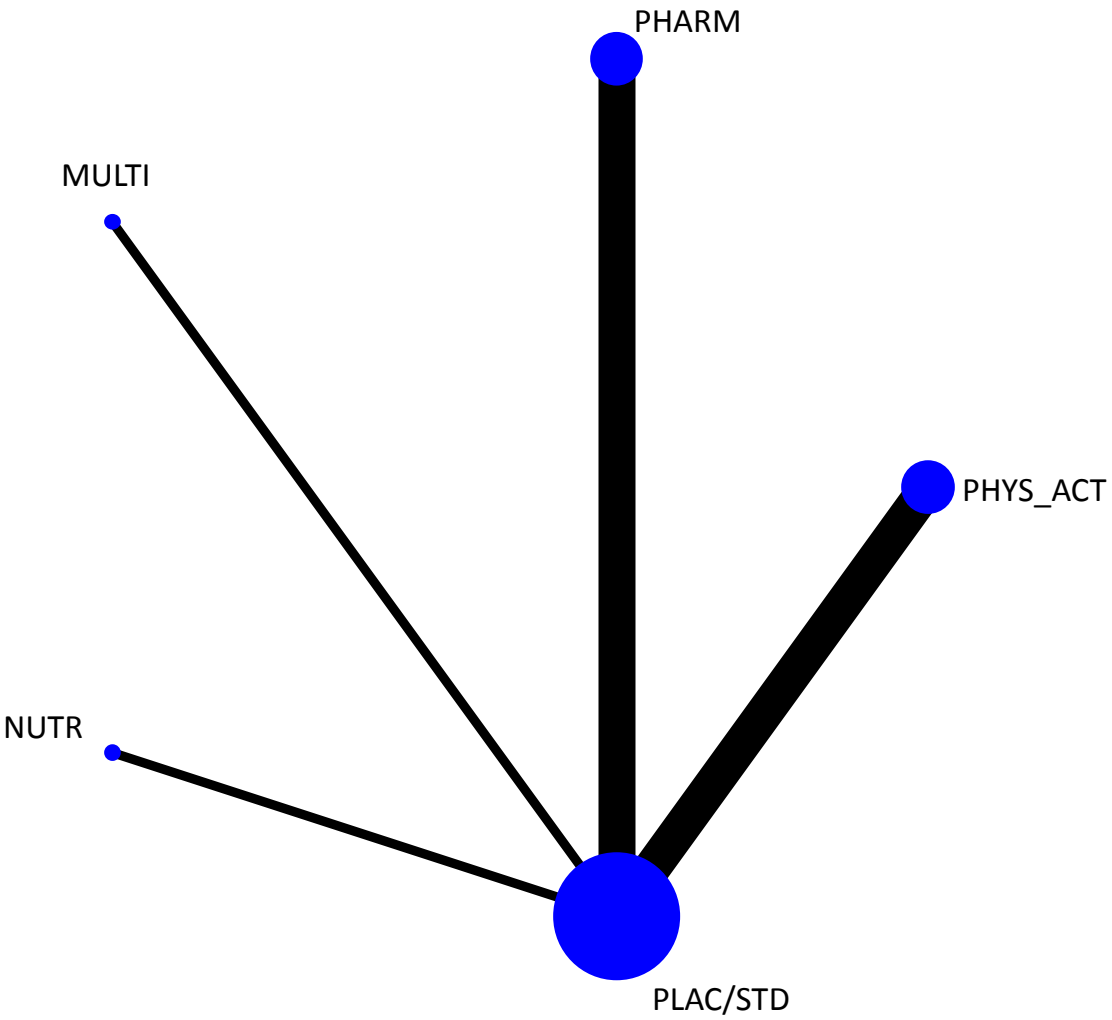
Network geometry for 9 randomized clinical trials (1519 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-11: Network geometry for adverse events



Network geometry for 28 randomized clinical trials (4013 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

Figure 3-12: Network geometry for serious adverse events



Network geometry for 10 randomized clinical trials (1644 participants). Each treatment node indicates an intervention and is weighted according to the number of participants who received the particular intervention. Each edge (line connecting the nodes) is weighted according to the number of studies and directly compares the treatments it connects.
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

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3.8 Appendix

List of contents

eTable 1. Coding Guide and description of frailty Interventions

	Abbreviation	***Treatments***	***Description***
1	PHYS_ACT	Physical activity	Any form of exercise including walking, strength, endurance, flexibility, balance exercise, elastic bands, yoga, tai chi, etc.
2	PHYS_ACT+PROT/NUTR	Physical activity and Protein or Nutrition supplementation	Any form of exercise with nutritional supplementation (such as calcium/vitamin D, protein, etc.) or weight management program or nutritional recommendation
3	PSYCH	Psychosocial or cognitive training	Any psychosocial intervention, (such as home visits, meetings, etc.) or cognitive training including cognitive visual training, cognitive games, etc.)
4	MED_MAN	Medication management	This intervention includes medication review or reconciliation that aim to optimize participant medications
5	PHARM	Pharmacotherapy	Pharmacotherapy included any medication such as testosterone, prebiotic, quinapril, selective Androgen Receptor Modulator, etc.
6	MULTI	Multifaceted	This intervention included any combination of intervention (other than Physical activity and Protein or Nutrition supplementation)
7	GERIA	Geriatric Comprehensive Assessments	Any geriatric comprehensive assessment interventions
8	NUTR	Nutrition Only	Any nutritional supplementation (such as calcium/vitamin D, protein, etc.) or weight management program or nutritional recommendation
9	PLAC/STD	Placebo/standard care	Usual/routine care, no treatment, placebo
10	VIBRA	Vibration wave or sound waves	Any intervention includes whole body vibration or sound waves

eTable 2. Individual Patient Characteristics

Study ID	Author	Year	Country	Sample size	Mean age	Male %	BMI	Sites
2223	McMurdo (1)	1993	Scotland	49.0	80.8	17.9	26.3	4
2102	Sih (2)	1997	United States of America	32.0	66.5	100.0	28.2	Not reported
4632	Worm (3)	2001	Denmark	46.0	81.2	41.3	Not reported	1
1771	Zi (4)	2003	United Kingdom	74.0	77.5	35.2	Not reported	2
1790	Wittert (5)	2003	Australia	76.0	68.5	Not reported	28.0	1
1825	Toulotte (6)	2003	France	20.0	81.5	Not reported	Not reported	1
10700	Baum (7)	2003	United States of America	20.0	88.0	25.8	Not reported	1
8914	Gill (8)	2004	United States of America	188.0	83.2	20.2	Not reported	6
1601	Sullivan (9)	2005	United States of America	71.0	78.2	Not reported	Not reported	1
1605	Thomas (10)	2005	United States of America	19.0	83.4	42.8	21.8	1
6041	Witham (11)	2005	United Kingdom	82.0	80.5	54.9	Not reported	1
8843	Binder (12)	2005	United States of America	119.0	83.0	29.8	26.5	1
1549	Villareal (13)	2006	United States of America	27.0	70.3	64.1	38.8	1
4317	Muller (14)	2006	Netherlands	100.0	78.5	Not reported	24.8	1
5806	Faber (15)	2006	Netherlands	278.0	84.9	21.0	27.9	15
6011	Miller (16)	2006	Australia	100.0	83.5	21.1	22.2	1
1355	Peterson (17)	2007	United States of America	81.0	79.3	100.0	28.0	1
1468	Kircher (18)	2007	Germany	315.0	78.1	33.7	Not reported	5
1476	Sullivan (19)	2007	United States of America	29.0	79.5	78.6	20.9	1
128	Donaldson (20)	2008	Canada	74.0	82.5	28.3	Not reported	1
1273	Vestergaard (21)	2008	Denmark	61.0	81.9	0.0	Not reported	1
1281	Smoliner (22)	2008	Germany	65.0	83.1	26.4	22.1	3
1352	Robinson (23)	2008	New Zealand	149.0	85.8	15.4	Not reported	5
1060	Kenny (24)	2010	United States of America	99.0	76.7	0.0	27.8	1

1071	Kenny (25)	2010	United States of America	131.0	75.6	100.0	26.9	1
1098	Monteserin (26)	2010	Spain	1070.0	80.3	39.7	Not reported	1
1132	Li (27)	2010	Netherlands	310.0	78.9	52.3	Not reported	1
1135	Srinivas-Shankar (28)	2010	United Kingdom	274.0	73.8	100.0	27.8	1
998	Neelemaat (29)	2011	Netherlands	210.0	74.5	31.1	Not reported	1
1007	Villareal (30)	2011	United States of America	107.0	69.8	37.3	37.2	1
1015	O'Connell (31)	2011	United Kingdom	274.0	73.8	100.0	27.8	1
719	Zech (32)	2012	Germany	69.0	77.0	Not reported	28.6	1
761	Tieland (33)	2012	Netherlands	65.0	79.5	44.8	26.6	1
833	Witham (34)	2012	Scotland	107.0	80.0	67.3	Not reported	1
3406	Drey (35)	2012	Germany	69.0	77.0	30.3	28.7	1
7349	Chan (36)	2012	Taiwan	117.0	71.4	41.0	25.4	1
7485	Gustafsson (37)	2012	Sweden	459.0	85.7	35.9	Not reported	2
182	Tsang (38)	2013	Hong Kong	134.0	84.1	25.1	Not reported	1
184	Upatising (39)	2013	United States of America	205.0	80.4	46.3	Not reported	1
605	Molino-Lova (40)	2013	Italy	140.0	74.3	66.4	25.5	1
642	Marek (41)	2013	United States of America	414.0	79.1	34.0	Not reported	3
656	Papanicolaou (42)	2013	Colombia, Peru, South Africa, Brazil, Sweden, Finland, Denmark, France, Spain, Mexico, Israel, Chile, New Zealand, United Kingdom, Hong Kong	170.0	75.9	0.0	22.6	28
702	Kim (43)	2013	South Korea	87.0	78.7	20.7	Not reported	Not reported
3258	Favela (44)	2013	Mexico	133.0	76.3	45.2	27.4	1
6876	Boxer (45)	2013	United States of America	64.0	65.9	51.5	33.1	1
7195	Cameron (46)	2013	Australia	241.0	83.3	32.4	26.3	1
151	Saravanakumar (47)	2014	Australia	33.0	83.8	27.3	Not reported	1
430	Kessler (48)	2014	Switzerland	27.0	87.3	33.3	26.5	1

2873	Sherrington (49)	2014	Australia	340.0	81.2	26.2	Not reported	9
2885	Manor (50)	2014	United States of America	66.0	86.5	18.4	28.0	2
2933	Ota (51)	2014	Japan	66.0	82.8	21.3	22.9	5
5408	Sievnen (52)	2014	Finland	15.0	84.0	20.5	Not reported	1
6020	Clegg (53)	2014	United Kingdom	84.0	78.7	28.7	Not reported	1
273	Kim (54)	2015	Japan	131.0	80.9	Not reported	Not reported	1
315	Prestmo (55)	2015	Norway	397.0	83.3	26.2	Not reported	1
2449	Nyunt (56)	2015	Singapore	246.0	70.0	38.6	23.6	Not reported
6127	Cesari (57)	2015	United States of America	424.0	76.8	31.1	30.2	4
9090	El-Khoury (58)	2015	France	706.0	79.7	0.0	27.1	20
73	Strike (59)	2016	United Kingdom	29.0	66.7	0.0	24.9	1
573	Tse (60)	2016	United States of America	115.0	Not reported	Not reported	Not reported	1
586	de Vries (61)	2016	Netherlands	139.0	78.5	27.9	Not reported	13
606	Ramirez-Campillo (62)	2016	Chile	24.0	70.3	0.0	28.3	1
613	Badrasawi (63)	2016	Malaysia	58.0	68.5	45.7	Not reported	Not reported
617	Freitag (64)	2016	Germany	210.0	75.1	Not reported	Not reported	1
637	Luger (65)	2016	Austria	80.0	82.8	16.2	27.2	1
639	Tarazona-Santabalbina (66)	2016	Spain	100.0	80.0	46.1	Not reported	2
693	Peel (67)	2016	Australia	255.0	81.5	39.6	25.1	3
730	Buigues (68)	2016	Spain	60.0	73.8	29.7	26.0	Not reported
785	Armamento-Villareal (69)	2016	United States of America	40.0	69.3	100.0	36.9	1
801	Porter (70)	2016	United States of America	67.0	68.3	21.3	36.8	1
1895	Parsons (71)	2016	New Zealand	56.0	81.9	19.6	Not reported	1
2054	Imaoka (72)	2016	Japan	91.0	84.3	22.0	20.5	1
5017	Shah (73)	2016	United States of America	67.0	55.4	61.0	26.9	1
906	Walters (74)	2017	United Kingdom	51.0	80.0	41.2	Not reported	1
917	Seino (75)	2017	Japan	77.0	74.6	68.8	23.5	1
1041	Dirks (76)	2017	Netherlands	34.0	76.5	35.3	29.1	1

1066	Serra-Prat (77)	2017	Spain	172.0	78.4	43.9	27.8	3
1080	Lamberti (78)	2017	Italy	35.0	68.0	77.1	26.5	1
1084	Yoon (79)	2017	South Korea	70.0	76.3	0.0	24.1	1
1089	Oh (80)	2017	South Korea	80.0	74.2	0.0	24.9	1
1090	van Schijndel-Speet (81)	2017	Netherlands	151.0	58.0	45.1	27.7	10
1097	Laksmi (82)	2017	Indonesia	120.0	68.9	37.4	25.7	1
1167	Villareal (83)	2017	United States of America	160.0	70.0	47.5	36.3	1
1195	Talley (84)	2017	United States of America	42.0	84.9	Not reported	Not reported	1
1220	Haider (85)	2017	Austria	80.0	82.8	16.3	27.4	1
1238	Bellumori (86)	2017	United States of America	26.0	69.6	35.7	26.5	1
1243	Bo (87)	2018	China	81.0	74.0	45.0	20.5	Not reported
1253	Romera-Liebana (88)	2018	Spain	352.0	77.3	24.7	Not reported	8
1271	Spoorenberg (89)	2018	Netherlands	1456.0	80.7	45.1	Not reported	3

eTable 3. Individual Study Characteristics

Study ID	Author	Year	Intervention class	Intervention duration	Construct measured	Outcome included in the analysis	Setting	Funding
2223	McMurdo (1)	1993	Physical Activity	12 months	Cognition, Depression	Mini- Mental State Examination, Depression Scale	Community	Government
2102	Sih (2)	1997	Pharmacotherapy	24 weeks	Adverse Events	Number of Events	Home	Government
4632	Worm (3)	2001	Physical activity	20 weeks	Quality of Life	SF-36	Home	Government
1771	Zi (4)	2003	Pharmacotherapy	16 weeks	Serious Adverse Events, Adverse Events, Quality of Life	Number of Events, McMaster quality of life questionnaire	Home	Government
1790	Wittert (5)	2003	Pharmacotherapy	Up to 6 months (depending on discharge)	Adverse events and serious adverse events	Number of events	Hospital	Government
1825	Toulotte (6)	2003	Physical Activity	12 months	Cognition	Mini- Mental State Examination	Long term-care	Government
10700	Baum (7)	2003	Physical activity	4 weeks	Cognition	Mini- Mental State Examination	Home	Government
8914	Gill (8)	2004	Physical activity	26 weeks	Mobility	Physical Performance Test	University research centre	Government
1601	Sullivan (9)	2005	Physical Activity	12 months	Mobility	Physical performance test	Home	Private
1605	Thomas (10)	2005	Nutritional supplementation	12 weeks	Adverse Events	Number of events	Not Specified	Industry
6041	Witham (11)	2005	Physical Activity	12 months	Quality of Life; Depression;	Philadelphia Geriatric Morale Score, Hospital Anxiety and Depression Score	Home and community	Government
8843	Binder (12)	2005	Physical activity	12 months	Adverse Events	Number Of Events	Long term-care	Not reported
1549	Villareal (13)	2006	Physical Activity and Nutritional Supplementation	6 months	Quality of life, adverse events, Quality of Life-	McMaster Quality of life	Home	Industry

					Physical Domain, SF-test	questionnaire, Number of Events, Physical Performance Test, SF-36		
4317	Muller (14)	2006	Pharmacotherapy	2.5 months	Cognition, Mobility	Mini- Mental State Examination, Physical Performance Test	Community	Government
5806	Faber (15)	2006	Physical activity	12 weeks	Mobility	Physical Performance Scale	Community	Private
6011	Miller (16)	2006	Nutritional supplementation	12 months	Quality of Life-Physical Domain, SF-test	SF-12	Home and community	Government
1355	Peterson (17)	2007	Psychosocial or Cognitive Training	26 weeks	Frailty	Fried Frailty Model	Not reported	Government
1468	Kircher (18)	2007	Comprehensive Geriatric Assessments	3 months	Quality of life, depression	Quality of Life Philadelphia Geriatric Centre Morale Scale, Geriatric Depression Scale	Hospital	Industry and private
1476	Sullivan (19)	2007	Physical Activity	15.8±6.7 days	Mobility	Physical Performance Test	Hospital	Not reported
128	Donaldson (20)	2008	Physical activity	6 months	Adverse events	Number of events	Home	Not reported
1273	Vestergaard (21)	2008	Physical Activity	6 months	Quality of Life, Mobility	EQ-5D, Physical Performance Test	Home	Government
1281	Smoliner (22)	2008	Nutritional supplementation	12 months	Quality of Life-Physical Domain	SF-36 Physical Functioning Component	Hospital	Private
1352	Robinson (23)	2008	Physical activity	3 months	Adverse Events	Number of events	Hospital	Industry and private
1060	Kenny (24)	2010	Physical activity and nutritional supplementation	12 months	Mobility	SPPB	Home	Government
1071	Kenny (25)	2010	Pharmacotherapy	8 weeks	Mobility	Physical Performance Scale	Community	Private

1098	Monteserin (26)	2010	Comprehensive geriatric assessment	Not reported	Frailty	Fried frailty phenotype	Hospital	Government
1132	Li (27)	2010	Comprehensive Geriatric assessment	6 months	Frailty	Fried frailty criteria	Long term-care	Industry
1135	Srinivas-Shankar (28)	2010	Pharmacotherapy	12 weeks	Serious Adverse Events, Adverse Events, Mobility	Number of events, Physical Performance Scale	Home	Industry and Private
998	Neelemaat (29)	2011	Nutritional supplementation	12 months	Mobility	Physical Performance Test	Not reported	Government and Hospital
1007	Villareal (30)	2011	Nutritional supplementation	6 months	Mobility, adverse events	Physical Performance Test	Home	Industry and private
1015	O'Connell (31)	2011	Pharmacotherapy	6 months	Mobility	Physical Performance Test	University research centre	Industry
719	Zech (32)	2012	Physical activity	13 weeks	Mobility	SPPB	Long term-care	Industry
761	Tieland (33)	2012	Nutritional supplementation	12 months	Mobility	SPPB	Home	Government
833	Witham (34)	2012	Physical activity	6 months	adverse events, serious adverse events	number of events	Home	Industry
3406	Drey (35)	2012	Physical Activity	3 months	Mobility, Adverse Events	SPPB, number of events	Long term-care	Government
7349	Chan (36)	2012	Physical activity and nutritional supplementation	6 months	Quality Of Life, Cognition	EQ-5D, Mini Mental State Examination	Home	Government
7485	Gustafsson (37)	2012	Psychosocial or Cognitive Training	Two Years	Frailty	Six Frailty Indicators	Community	Government
182	Tsang (38)	2013	Physical activity	12 weeks	Depression	Geriatric depression scale	Community	Government
184	Upatising (39)	2013	Multifaceted intervention	12 months	Frailty	Fried frailty criteria from the Cardiovascular Health Study	Home	Industry
605	Molino-Lova (40)	2013	Physical activity	12 weeks	Mobility	Physical Performance Test	Hospital	Industry
642	Marek (41)	2013	Medication	6 months	Cognition,	Mini- Mental	Community	Government

			Management		Depression, Mobility,Quality of Life- Physical Domain, SF-test	State Examination, Geriatric Depression Scale, SPPB, Physical Summary, Mental Summary		
656	Papanicolaou (42)	2013	Pharmacotherapy	4 weeks	Mobility, Adverse Events	SPPB, number of events	Hospital	Government
702	Kim (43)	2013	Nutritional supplementation	12 weeks	Mobility	SPPB	Home	Private
3258	Favela (44)	2013	Comprehensive Geriatric Assessments	12 weeks	Frailty	Fried frailty phenotype	Community	Industry
6876	Boxer (45)	2013	Nutritional supplementation	One or 4 home visits	Serious Adverse Events, Adverse Events	Number of events	Home	Not reported
7195	Cameron (46)	2013	Multifaceted	9 months	Adverse events, Quality of Life, Depression, Mobility, Frailty	Number of events, EQ-5D, Geriatric Depression Scale, SPPB, Frailty phenotype as specified using Cardiovascular Health Study criteria	Home	Government and Private
151	Saravanakumar (47)	2014	Physical Activity	3.5 months	Quality of life, adverse events	Dementia quality of life, number of events	Retirement home	Government
430	Kessler (48)	2014	Physical Activity	8 weeks	Mobility	SPPB	Not reported	Industry
2873	Sherrington (49)	2014	Physical activity	9 months	Adverse Events, Quality Of Life, Mobility	Number of events, EQ-5D Utility Score, Physical Performance Scale (PPS)	Home	Government
2885	Manor (50)	2014	Physical activity	12 weeks	Mobility, Frailty	SPPB, fried frailty phenotype	Community	Government
2933	Ota (51)	2014	Physical activity	9 months	Quality of Life-Physical Domain, SF-test	8-item Short Form Health Survey (SF-8)	Community	Government

5408	Sievnen (52)	2014	Vibration Wave or Sound Waves	6 weeks	Mobility	SPPB	Community	Private
6020	Clegg (53)	2014	Physical activity	6 months	Adverse events, serious adverse events, Quality of Life, Depression	Number of events, EQ-5D, Geriatric Depression Scale	Home	Government and Private
273	Kim (54)	2015	Physical activity and nutritional supplementation	3 months	Frailty	Fried frailty phenotype	Home	Government
315	Prestmo (55)	2015	Comprehensive Geriatric assessment	12 months	Mobility, Quality Of Life, Cognition	SPPB, EQ-5D, Mini-mental state examination	Hospital	Government and private
2449	Nyunt (56)	2015	Nutritional supplementation	12 weeks	Frailty, Adverse Events	Frailty index, Number Of Events	Home	Government
6127	Cesari (57)	2015	Physical Activity	3 months	Frailty	Fried frailty phenotype	Hospital	Government
9090	El-Khoury (58)	2015	Physical activity	6 months	Serious Adverse events, adverse events, SF-test, Quality of Life-Physical Domain	Number of events, SF-36	Residential Care Homes	Private
73	Strike (59)	2016	Nutritional supplementation	6 months	Cognition	Verbal recognition memory immediate free recall	Home	Industry and Private
573	Tse (60)	2016	Psychosocial or Cognitive Training	6 months	Frailty, SF-test, Quality of Life-Physical Domain	Frailty index, Physical Component Summary, Mental Component Summary	Therapist Office	Government
586	de Vries (61)	2016	Physical activity	12 months	Serious Adverse Events, Frailty, Quality of Life-Physical Domain	Number of Events, Fried Frailty Phenotype,SF-36	Community	Government
606	Ramirez-Campillo (62)	2016	Physical Activity	10 weeks	Quality of Life	The menopause-speci c quality of life questionnair e (MenQOl)	Home	Government
613	Badrasawi (63)	2016	Nutritional Supplementation	6 weeks	Frailty	Frailty Index Score	Community	Government

617	Freitag (64)	2016	Psychosocial or cognitive training	12 weeks	Frailty, SF-test, Quality of Life-Physical Domain	Frailty-status, SF-12	Community	Government
637	Luger (65)	2016	Physical Activity and Nutritional Supplementation	6 months	Frailty	Fried frailty phenotype	Community	Government and Industry
639	Tarazona-Santabalbina (66)	2016	Physical Activity	12 months	Frailty, Quality Of Life, Mobility	Fried Frailty Criteria,EQ-5D, SPPB	Home	Government
693	Peel (67)	2016	Physical activity	12 weeks	Cognition, Mobility	InterRAI Cognitive Function Score, SPPB	Home	Government
730	Buigues (68)	2016	Pharmacotherapy	24 Weeks	Frailty, Cognition	Frailty Phenotype, Mini Mental State Examination	Home	Not reported
785	Armamento-Villareal (69)	2016	Nutritional supplementation	6 months	Mobility	Physical Performance Test	Home	Government and Industry
801	Porter (70)	2016	Physical Activity	24 weeks	Mobility	SPPB	Hospital (8 weeks)then Home (16 weeks)	Government
1895	Parsons (71)	2016	Physical activity	7 months	Adverse Events	Number of events	Hospital	Government
2054	Imaoka (72)	2016	Physical activity	6 months	Cognition	Mini- Mental State Examination	Home	Government
5017	Shah (73)	2016	Physical activity	12 months	Depression, Quality of Life-Physical Domain, Mobility	Depression Scale, SF-36, Physical Performance Test	Home	Industry
906	Walters (74)	2017	Multifaceted intervention	3 months	Quality of life, cognition, adverse events, serious adverse events,	EQ-5D, MoCA, number of events	Community	Government
917	Seino (75)	2017	Multifaceted Intervention	3 months	Depression, Quality of Life-Physical Domain, SF-test	Depression Scale Score, Mental Component Summary, Physical Function	Community	Private

1041	Dirks (76)	2017	Physical activity and nutritional supplementation	6 months	Mobility	SPPB	Home	Government
1066	Serra-Prat (77)	2017	Physical activity and nutritional supplementation	12 months	Frailty, Quality of Life	Fried Criteria,Visual Analogue Scale For Quality Of Life	Medical Institutions	Other Sources of Funding
1080	Lamberti (78)	2017	Physical activity	3 months	SF-test, Quality of Life- Physical Domain	SF-36	Hospital	Government
1084	Yoon (79)	2017	Physical Activity	18 weeks	Cognition, Mobility	Mini- Mental State Examination, SPPB	Retirement Home	Industry
1089	Oh (80)	2017	Multifaceted intervention	8 months	Adverse Events, Mobility	Number of events, SPPB	Day Activity Centers	Government and Private
1090	van Schijndel-Speet (81)	2017	Multifaceted intervention	16 weeks	Depression, Cognition	Signalizing Depression List for people with Intellectual Disabilities,Dementia Questionnaire for Persons with Mental Retardation	Hospital	Not reported
1097	Laksmi (82)	2017	Pharmacotherapy	not reported	Quality of life, serious adverse events, adverse event	EQ-5D, Number of Events	Not reported	Private
1167	Villareal (83)	2017	Physical Activity	12 weeks	Adverse Events, Mobility, Quality of Life-Physical Domain, SF-Test	Number of events, Physical Performance Test, SF-36	Home	Private
1195	Talley (84)	2017	Physical activity	6 weeks	Mobility	SPPB	Long term-care	Government
1220	Haider (85)	2017	Physical Activity and Nutritional Supplementation	6 months	Mobility	SPPB	Hospital	Industry
1238	Bellumori (86)	2017	Physical activity	3 months	Quality of Life	SF-36	Long term-care	Government
1243	Bo (87)	2018	Nutritional Supplementation	12 months	Adverse Events, Quality of Life-Physical Domain, SF-test	Number of events, SF-36 Mental and Physical	Community	Government and private

						Component Score		
1253	Romera-Liebana (88)	2018	Multifaceted intervention	5 months	Mobility	SPPB	Home	Government
1271	Spoorenberg (89)	2018	Multifaceted intervention	3 months	Frailty, Quality of life	Fried frailty criteria, EQ-5D	Retirement home	Industry
SPPB: Short physical performance battery, EQ5D: EuroQol-5, SF-36: The Short Form (36) Health Survey, MoCA: Montreal Cognitive Assessment								

eTable 4. Risk of Bias Results

	Author	Year	sequence_generation	allocation_concealment	Blinding_participants	healthcare_blind	assessor_blind	analyst_blind	incomplete_outcome	selective_outcome	other_bias	Overall risk of bias
2223	McMurdo (1)	1993	Low	Low	High	High	High	Low	Low	Low	Low	High
2102	Sih (2)	1997	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
4632	Worm (3)	2001	High	Low	Low	High	High	High	Low	Low	Low	High
1771	Zi (4)	2003	High	High	Low	Low	Low	High	Low	Low	High	High
1790	Wittert (5)	2003	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1825	Toulotte (6)	2003	High	Low	High	High	High	High	Low	Low	High	High
10700	Baum (7)	2003	Low	Low	High	Low	Low	Low	High	High	Low	High
8914	Gill (8)	2004	High	Low	High	High	Low	Low	Low	High	Low	High
6041	Witham (11)	2005	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1605	Thomas (10)	2005	High	High	High	High	High	High	High	Low	High	High
1601	Sullivan (9)	2005	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
8843	Binder (12)	2005	Low	High	High	High	Low	High	Low	Low	Low	High
1549	Villareal (13)	2006	Low	High	High	High	High	High	High	Low	Low	High
4317	Muller (14)	2006	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
6011	Miller (16)	2006	Low	Low	High	High	Low	High	Low	Low	High	High
5806	Faber (15)	2006	Low	Low	High	High	Low	High	Low	Low	Low	High

1476	Sullivan (19)	2007	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1355	Peterson (17)	2007	Low	Low	Low	High	Low	Low	High	High	Low	High
1468	Kircher (18)	2007	Low	High	High	High	High	High	Low	High	Low	High
1273	Vestergaard (21)	2008	High	High	High	High	High	High	Low	Low	Low	High
1281	Smoliner (22)	2008	High	Low	Low	High	High	High	Low	Low	High	High
1352	Robinson (23)	2008	Low	Low	High	High	High	Low	Low	Low	Low	High
128	Donaldson (20)	2008	Low	Low	High	High	Low	High	Low	Low	Low	High
1135	Srinivas-Shankar (28)	2010	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1098	Montesserin (26)	2010	Low	Low	Low	High	Low	Low	High	Low	Low	High
1132	Li (27)	2010	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1071	Kenny (24)	2010	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1060	Kenny (25)	2010	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1007	Villareal (30)	2011	High	High	High	High	High	High	Low	Low	Low	High
1015	O'Connell (31)	2011	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
998	Neelemaat (29)	2011	Low	Low	High	High	Low	Low	Low	Low	Low	High
719	Zech (32)	2012	Low	Low	High	Low	Low	Low	Low	High	Low	High
833	Witham	201	Low	High	Low	High	High	High	High	Low	Low	High

	(34)	2										
761	Tieland (33)	2012	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
7485	Gustafsson (37)	2012	High	Low	High	High	Low	Low	Low	High	Low	High
3406	Drey (35)	2012	Low	Low	High	Low	Low	High	Low	Low	Low	High
7349	Chan (36)	2012	Low	Low	High	High	Low	Low	Low	Low	Low	High
184	Upatising (39)	2013	Low	Low	High	High	High	Low	High	Low	High	High
182	Tsang (38)	2013	Low	High	High	High	High	Low	Low	Low	Low	High
656	Papanicolaou (42)	2013	High	High	Low	Low	High	High	Low	Low	High	High
605	Molino-Lova (40)	2013	Low	Low	Low	Low	Low	High	Low	Low	Low	High
642	Marek (41)	2013	Low	High	High	High	High	High	High	Low	Low	High
702	Kim (43)	2013	Low	Low	High	Low	Low	Low	Low	High	Low	High
3258	Favela (44)	2013	Low	High	High	High	Low	Low	Low	Low	Low	High
7195	Cameron (46)	2013	Low	Low	High	High	Low	Low	Low	Low	Low	High
6876	Boxer (45)	2013	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
5408	Sievnen (52)	2014	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
2873	Sherrington (49)	2014	Low	Low	High	Low	Low	Low	Low	Low	Low	High
151	Saravanakumar (47)	2014	Low	Low	High	High	High	High	Low	Low	Low	High

2933	Ota (51)	2014	High	High	High	High	High	High	Low	Low	Low	High
2885	Manor (50)	2014	High	Low	High	High	High	High	Low	Low	Low	High
430	Kessler (48)	2014	Low	High	High	High	High	Low	Low	Low	Low	High
6020	Clegg (53)	2014	Low	Low	Low	High	High	Low	Low	Low	Low	High
315	Prestmo (55)	2015	Low	High	High	High	High	Low	Low	Low	Low	High
2449	Nyunt (56)	2015	Low	Low	High	Low	Low	Low	Low	Low	Low	High
273	Kim (54)	2015	Low	Low	High	High	Low	Low	Low	Low	Low	High
9090	El-Khoury (58)	2015	Low	Low	Low	High	Low	High	Low	Low	Low	High
6127	Cesari (57)	2015	Low	High	High	High	High	High	Low	Low	High	High
73	Strike (59)	2016	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
5017	Shah (73)	2016	Low	Low	High	High	High	High	Low	Low	High	High
785	Armamento-Villareal (69)	2016	Low	Low	High	Low	Low	Low	Low	Low	Low	High
613	Badrasawi (63)	2016	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
730	Buigues (68)	2016	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
586	de Vries (61)	2016	Low	Low	Low	High	Low	Low	Low	Low	Low	High
617	Freitag (64)	2016	Low	High	High	High	High	High	Low	Low	Low	High
637	Luger	201	Low	Low	High	High	High	Low	Low	Low	Low	High

	(65)	6										
693	Peel (67)	2016	Low	Low	High	High	Low	Low	Low	Low	Low	High
801	Porter (70)	2016	Low	Low	High	High	Low	Low	Low	Low	Low	High
606	Ramirez-Campillo (62)	2016	Low	High	High	Low	Low	Low	Low	Low	Low	High
639	Tarazona-Santabalbina (66)	2016	Low	Low	High	High	High	Low	Low	Low	Low	High
573	Tse (60)	2016	High	High	High	High	High	High	High	High	High	High
1895	Parsons (71)	2016	Low	Low	High	High	High	Low	Low	Low	Low	High
2054	Imaoka (72)	2016	Low	Low	High	High	High	High	Low	Low	Low	High
1238	Bellumori (86)	2017	Low	High	High	High	High	High	Low	Low	Low	High
1041	Dirks (76)	2017	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1220	Haider (85)	2017	Low	High	High	High	High	High	Low	Low	Low	High
1097	Laksmi (82)	2017	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1080	Lamberti (78)	2017	Low	Low	High	High	High	High	Low	Low	Low	High
1089	Oh (80)	2017	Low	Low	High	High	High	High	High	High	Low	High
917	Seino (75)	2017	Low	Low	High	Low	Low	Low	Low	Low	Low	High

1066	Serra-Prat (77)	2017	Low	Low	High	High	High	High	Low	Low	Low	High
1195	Talley (84)	2017	Low	Low	High	Low	Low	Low	Low	Low	Low	High
1090	van Schijndel-Speet (81)	2017	Low	Low	High	High	Low	Low	High	Low	Low	High
1167	Villareal (83)	2017	Low	Low	High	High	Low	Low	Low	Low	Low	High
906	Walters (74)	2017	Low	Low	High	High	Low	Low	Low	Low	Low	High
1084	Yoon (79)	2017	Low	High	High	High	High	High	High	High	Low	High
1243	Bo (87)	2018	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
1253	Romera-Liebana (88)	2018	Low	Low	High	High	Low	Low	Low	Low	Low	High
1271	Spooren berg (89)	2018	Low	Low	High	High	Low	Low	High	Low	Low	High

eTable 5. Sensitivity Analyses

Frailty outcome						
Excluding studies with High Risk of Bias (3 studies, 4 treatments, 410 patients)						
Treatment Comparison	**Coded Trt Comparison**	**Median SMD**	**Low CrI**	**High CrI**	**Low PrI**	**High PrI**
PHARM vs GERIA	1 vs 2	-0.1053	-3.127	2.960	-3.878	3.670
PHARM vs NUTR	1 vs 3	0.2243	-2.916	3.320	-3.585	4.042
PHARM vs PLAC/STD	1 vs 4	-0.3456	-2.502	1.857	-3.414	2.689
GERIA vs NUTR	2 vs 3	0.3338	-2.767	3.453	-3.536	3.946
GERIA vs PLAC/STD	2 vs 4	-0.2469	-2.394	1.883	-3.330	2.679
NUTR vs PLAC/STD	3 vs 4	-0.5721	-2.765	1.682	-3.673	2.561
Excluding an outlying study (19 studies, 8 treatments, 4738 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.066	-0.272	0.425	-0.388	0.546
PHYS_ACT vs PSYCH	1 vs 3	-0.010	-0.298	0.291	-0.413	0.432
PHYS_ACT vs PHARM	1 vs 4	0.021	-0.346	0.404	-0.452	0.513
PHYS_ACT vs MUTLI	1 vs 5	-0.069	-0.350	0.249	-0.468	0.389
PHYS_ACT vs GERIA	1 vs 6	-0.520	-1.121	0.039	-1.175	0.121
PHYS_ACT vs NUTR	1 vs 7	-0.244	-0.513	0.045	-0.635	0.185
PHYS_ACT vs PLAC/STD	1 vs 8	-0.254	-0.531	0.005	-0.670	0.138
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	-0.079	-0.389	0.240	-0.502	0.369
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 4	-0.050	-0.455	0.364	-0.550	0.473
PHYS_ACT+PROT/NUTR vs MUTLI	2 vs 5	-0.136	-0.460	0.213	-0.577	0.333
PHYS_ACT+PROT/NUTR vs GERIA	2 vs 6	-0.591	-1.196	-0.018	-1.256	0.049
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	-0.314	-0.626	0.014	-0.752	0.136
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	-0.323	-0.636	-0.040	-0.768	0.079
PSYCH vs PHARM	3 vs 4	0.030	-0.308	0.367	-0.433	0.493
PSYCH vs MUTLI	3 vs 5	-0.055	-0.305	0.201	-0.448	0.355
PSYCH vs GERIA	3 vs 6	-0.512	-1.122	0.060	-1.192	0.134
PSYCH vs NUTR	3 vs 7	-0.234	-0.449	-0.016	-0.603	0.154
PSYCH vs PLAC/STD	3 vs 8	-0.245	-0.491	-0.030	-0.654	0.108
PHARM vs MUTLI	4 vs 5	-0.087	-0.409	0.247	-0.526	0.358
PHARM vs GERIA	4 vs 6	-0.541	-1.202	0.067	-1.271	0.135
PHARM vs NUTR	4 vs 7	-0.266	-0.540	0.019	-0.684	0.162
PHARM vs PLAC/STD	4 vs 8	-0.275	-0.615	0.037	-0.743	0.143
MUTLI vs GERIA	5 vs 6	-0.456	-1.063	0.108	-1.132	0.179

MUTLI vs NUTR	5 vs 7	-0.179	-0.371	0.015	-0.544	0.195
MUTLI vs PLAC/STD	5 vs 8	-0.184	-0.441	0.003	-0.608	0.163
GERIA vs NUTR	6 vs 7	0.278	-0.270	0.872	-0.341	0.950
GERIA vs PLAC/STD	6 vs 8	0.265	-0.305	0.863	-0.379	0.932
NUTR vs PLAC/STD	7 vs 8	-0.009	-0.245	0.195	-0.420	0.331
Excluding studies with binary data (10 studies, 7 treatments, 2542 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.827	-3.047	1.375	-4.061	2.460
PHYS_ACT vs PSYCH	1 vs 3	-0.761	-2.416	0.909	-3.641	2.205
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	0.068	-1.758	1.912	-2.985	3.112
PHYS_ACT vs PHARM	1 vs 4	-0.811	-3.702	1.960	-4.617	2.937
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 4	0.021	-3.113	3.100	-3.881	3.967
PSYCH vs PHARM	3 vs 4	-0.057	-2.841	2.758	-3.818	3.656
PHYS_ACT vs MULTI	1 vs 5	-0.862	-2.732	1.043	-3.961	2.237
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 5	-0.022	-2.390	2.355	-3.425	3.326
PSYCH vs MULTI	3 vs 5	-0.101	-1.939	1.754	-3.242	2.930
PHARM vs MULTI	4 vs 5	-0.064	-3.003	2.926	-3.847	3.759
PHYS_ACT vs NUTR	1 vs 6	-0.679	-2.596	1.170	-3.847	2.344
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	0.147	-2.233	2.449	-3.222	3.470
PSYCH vs NUTR	3 vs 6	0.087	-1.777	1.908	-2.969	3.146
PHARM vs NUTR	4 vs 6	0.134	-2.789	3.061	-3.665	3.908
MULTI vs NUTR	5 vs 6	0.172	-1.824	2.186	-2.906	3.358
PHYS_ACT vs PLAC/STD	1 vs 7	-1.182	-2.526	0.157	-3.989	1.637
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	-0.355	-2.208	1.475	-3.440	2.689
PSYCH vs PLAC/STD	3 vs 7	-0.419	-1.670	0.805	-3.141	2.333
PHARM vs PLAC/STD	4 vs 7	-0.380	-2.824	2.146	-3.852	3.151
MULTI vs PLAC/STD	5 vs 7	-0.319	-1.906	1.247	-3.253	2.558
NUTR vs PLAC/STD	6 vs 7	-0.499	-2.098	1.076	-3.405	2.490
Quality of life- Mental domain						
Excluding an outlying study (10 studies, 7 treatments, 1744 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.119	-0.748	0.531	-1.020	0.832
PHYS_ACT vs PSYCH	1 vs 3	-0.210	-0.821	0.538	-1.078	0.828
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	-0.086	-0.855	0.788	-1.086	1.035
PHYS_ACT vs MED_MAN	1 vs 4	0.034	-0.700	0.901	-0.937	1.128
PHYS_ACT+PROT/NUTR vs MED_MAN	2 vs 4	0.163	-0.725	1.121	-0.911	1.340

PSYCH vs MED_MAN	3 vs 4	0.252	-0.663	1.134	-0.887	1.375
PHYS_ACT vs MULTI	1 vs 5	0.092	-0.729	1.030	-0.962	1.261
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 5	0.213	-0.736	1.254	-0.943	1.451
PSYCH vs MULTI	3 vs 5	0.297	-0.661	1.245	-0.885	1.452
MED_MAN vs MULTI	4 vs 5	0.049	-0.987	1.102	-1.173	1.311
PHYS_ACT vs NUTR	1 vs 6	-0.306	-0.869	0.340	-1.166	0.642
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	-0.185	-0.878	0.555	-1.155	0.828
PSYCH vs NUTR	3 vs 6	-0.099	-0.883	0.643	-1.161	0.908
MED_MAN vs NUTR	4 vs 6	-0.350	-1.240	0.532	-1.465	0.750
MULTI vs NUTR	5 vs 6	-0.398	-1.363	0.542	-1.593	0.741
PHYS_ACT vs PLAC/STD	1 vs 7	0.121	-0.211	0.556	-0.605	0.967
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	0.245	-0.338	0.887	-0.601	1.194
PSYCH vs PLAC/STD	3 vs 7	0.331	-0.234	0.869	-0.574	1.191
MED_MAN vs PLAC/STD	4 vs 7	0.080	-0.619	0.794	-0.913	1.042
MULTI vs PLAC/STD	5 vs 7	0.030	-0.751	0.820	-1.009	1.043
NUTR vs PLAC/STD	6 vs 7	0.432	-0.099	0.986	-0.436	1.306
Quality of life- Physical domain						
Excluding An outlying study (12 studies, 7 treatments, 1925 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.015	-0.906	0.875	-1.376	1.322
PHYS_ACT vs PSYCH	1 vs 3	0.019	-0.901	0.939	-1.350	1.438
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	0.040	-1.100	1.190	-1.461	1.584
PHYS_ACT vs MED_MAN	1 vs 4	-0.839	-1.991	0.294	-2.356	0.695
PHYS_ACT+PROT/NUTR vs MED_MAN	2 vs 4	-0.819	-2.132	0.500	-2.470	0.802
PSYCH vs MED_MAN	3 vs 4	-0.863	-2.192	0.459	-2.538	0.762
PHYS_ACT vs MULTI	1 vs 5	0.455	-0.738	1.698	-1.112	2.036
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 5	0.480	-0.863	1.898	-1.212	2.229
PSYCH vs MULTI	3 vs 5	0.442	-0.931	1.809	-1.290	2.166
MED_MAN vs MULTI	4 vs 5	1.303	-0.226	2.835	-0.520	3.125
PHYS_ACT vs NUTR	1 vs 6	-0.098	-0.822	0.627	-1.373	1.170
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	-0.083	-0.987	0.857	-1.447	1.321
PSYCH vs NUTR	3 vs 6	-0.118	-1.134	0.879	-1.568	1.311
MED_MAN vs NUTR	4 vs 6	0.744	-0.473	1.949	-0.822	2.297
MULTI vs NUTR	5 vs 6	-0.558	-1.841	0.708	-2.226	1.107
PHYS_ACT vs PLAC/STD	1 vs 7	0.263	-0.211	0.768	-0.829	1.426

PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	0.281	-0.523	1.113	-1.001	1.575
PSYCH vs PLAC/STD	3 vs 7	0.244	-0.560	1.038	-1.044	1.546
MED_MAN vs PLAC/STD	4 vs 7	1.102	0.092	2.146	-0.326	2.601
MULTI vs PLAC/STD	5 vs 7	-0.194	-1.314	0.915	-1.719	1.291
NUTR vs PLAC/STD	6 vs 7	0.363	-0.249	0.980	-0.807	1.532
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.						

eTable 6. Meta-analyses

Treatment Comparison	Coded Treatment Comparison	Odds Ratio	Low CI	High CI	between-study variance [95% CI]	I-square [95% CI]	Number of studies	Number of patients	Risk of bias	Age	Body mass index	Percent of males
Frailty (20 studies, 8 treatments, 4838 patients)												
NUTR vs PLAC/STD	7 vs 8	-0.260	-0.438	-0.082	0.009 [0, 0.528]	20.503 [0, 93.93]	5	1143	2	75.70	23.72	0.58
PSYCH vs PLAC/STD	3 vs 8	-0.315	-0.557	-0.073	0.015 [0, 0.762]	24.507 [0, 94.287]	4	440	2	74.51	25.86	0.98
MULTI vs PLAC/STD	5 vs 8	-0.086	-0.215	0.043	0.004 [0, 0.215]	14.02 [0, 89.635]	5	2052	2	78.89	24.98	0.54
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.135	-0.400	0.670	0 [0, 0]	0 [0, 0]	1	66	2	80.85	N/A	N/A
PHYS_ACT vs NUTR	1 vs 7	-0.187	-0.509	0.134	0.01 [0, 4.78]	12.001 [0, 98.42]	3	228	2	79.13	25.84	0.58
PHYS_ACT vs PLAC/STD	1 vs 8	-1.034	-2.454	0.386	2.038 [0.605, 29.662]	97.416 [91.798, 99.818]	4	392	2	77.35	23.72	0.57
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	-0.686	-1.256	-0.115	0 [0, 0]	0 [0, 0]	1	65	2	80.85	N/A	N/A
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	-0.335	-0.680	0.010	0.021 [0, 74.768]	28.254 [0, 99.93]	2	237	2	79.60	27.80	0.44
GERIA vs PLAC/STD	6 vs 8	-0.315	-0.718	0.089	0 [0, 0]	0 [0, 0]	1	133	2	76.33	27.40	0.45
PHARM vs PLAC/STD	4 vs 8	-0.086	-0.669	0.496	0.086 [0, 100]	48.324 [0, 99.909]	2	509	2	79.73	25.95	0.33
PHYS_ACT vs PSYCH	1 vs 3	-0.113	-0.510	0.283	0 [0, 0]	0 [0, 0]	1	98	2	70.04	23.72	0.97

PHYS_ACT vs MULTI	1 vs 5	-0.113	-0.512	0.285	0 [0, 0]	0 [0, 0]	1	97	2	70.04	23.72	0.98
PSYCH vs MULTI	3 vs 5	0.000	-0.394	0.394	0 [0, 0]	0 [0, 0]	1	99	2	70.04	23.72	0.96
PSYCH vs NUTR	3 vs 7	0.000	-0.394	0.394	0 [0, 0]	0 [0, 0]	1	99	2	70.04	23.72	0.96
MULTI vs NUTR	5 vs 7	0.000	-0.396	0.396	0 [0, 0]	0 [0, 0]	1	98	2	70.04	23.72	0.97
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	-0.079	-0.518	0.360	0 [0, 0]	0 [0, 0]	1	80	2	82.75	27.15	0.16
Short physical performance battery (36 studies, 9 treatments, 4568 patients)												
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.455	-2.278	1.368	2.427 [0.519, 100]	94.234 [77.75, 99.852]	3	110	N/A	72	34	0.59
PHYS_ACT vs NUTR	1 vs 7	-0.245	-0.714	0.225	0 [0, 100]	0 [0, 99.85]	2	71	N/A	70	37	0.68
PHYS_ACT vs PLAC/STD	1 vs 8	0.708	0.287	1.130	0.695 [0.395, 2.551]	94.19 [90.196, 98.347]	17	1823	2	79	29	0.32
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	0.876	0.055	1.697	0.207 [0, 100]	55.608 [0, 99.835]	2	75	N/A	70	37	0.69
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	3.184	0.373	5.996	9.948 [3.359, 84.83]	98.654 [96.115, 99.84]	5	362	2	71	35	0.45
NUTR vs PLAC/STD	7 vs 8	1.859	0.236	3.481	3.187 [0.965, 31.578]	96.957 [90.611, 99.684]	5	290	2	73	34	0.44
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	0.395	-0.048	0.838	N/A	N/A	1	80	2	83	27	0.16
MULTI vs PLAC/STD	6 vs 8	0.471	0.306	0.635	0.002 [0, 0.867]	9.575 [0, 97.651]	3	673	2	78	25.570	0.260
VIBRA vs PLAC/STD	9 vs 8	0.860	0.014	1.706	N/A	N/A	1	24	2	87	26.450	0.330
PHARM vs PLAC/STD	5 vs 8	0.180	0.014	0.345	0.012 [0, 0.208]	33.627 [0, 89.88]	5	925	1	76	25.970	0.750
PHYS_ACT vs VIBRA	1 vs 9	-0.245	-1.265	0.774	N/A	N/A	1	15	N/A	84	N/A	0.210

MED_MAN vs PLAC/STD	4 vs 8	3.966	3.623	4.309	N/A	N/A	1	414	2	79	N/A	0.280
Quality of life (16 studies, 7 treatments, 3259 patients)												
PHYS_ACT vs PLAC/STD	1 vs 6	0.172	-0.089	0.433	0.072 [0, 0.81]	57.727 [0, 93.852]	8	742	2	78	27	0.27
GERIA vs PLAC/STD	5 vs 6	-0.033	-0.267	0.201	0 [0, 0]	0 [0, 0]	1	315	2	78	N/A	0.29
PHARM vs PLAC/STD	3 vs 6	-0.025	-0.330	0.281	0 [0, 24.223]	0 [0, 99.797]	2	165	2	73	26	0.36
MULTI vs PLAC/STD	4 vs 6	0.054	-0.040	0.148	0 [0, 0.233]	0 [0, 93.574]	3	1748	2	81	26	0.47
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 6	-0.011	-0.242	0.220	0 [0, 18.458]	0 [0, 99.844]	2	289	2	75	27	0.40
Quality of life-Physical domain (15 studies, 7 treatments, 2293 patients)												
PHYS_ACT vs PLAC/STD	1 vs 7	1.315	0.040	2.590	3.315 [1.405, 14.21]	98.771 [97.149, 99.711]	8	1355	2	75	27	0.3
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.203	-0.359	0.765	N/A	N/A	1	49	N/A	84	22	0.25
PHYS_ACT vs NUTR	1 vs 6	-0.004	-0.559	0.550	N/A	N/A	1	50	N/A	84	22	0.18
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	-0.207	-0.769	0.354	N/A	N/A	1	49	N/A	84	22	0.23
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	0.263	-0.622	1.148	0.287 [0, 100]	69.504 [0, 99.874]	2	77	2	77	30	0.44
NUTR vs PLAC/STD	6 vs 7	0.318	-0.445	1.082	0.377 [0.045, 17.876]	82.819 [36.729, 99.564]	3	163	2	80	22	0.3
PSYCH vs PLAC/STD	3 vs 7	0.237	-0.045	0.519	0 [0, 26.228]	0 [0, 99.837]	2	259	2	75	N/A	N/A
MED_MAN vs PLAC/STD	4 vs 7	1.100	0.877	1.323	N/A	N/A	1	414	2	79	N/A	0.28
MULTI vs PLAC/STD	5 vs 7	-0.196	-0.643	0.252	N/A	N/A	1	77	2	75	24	0.69
Quality of life-Mental domain (12 studies, 7 treatments, 2053 patients)												

PSYCH vs PLAC/STD	3 vs 7	0.328	-0.045	0.700	0.03 [0, 74.121]	40.769 [0, 99.942]	2	259	2	75	N/A	N/A
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.775	-0.090	1.639	1.109 [0.399, 6.908]	96.779 [91.521, 99.468]	6	1167	2	78	27	0.26
PHYS_ACT vs NUTR	1 vs 6	0.069	-0.491	0.630	N/A	N/A	1	49	N/A	84	22	0.25
PHYS_ACT vs PLAC/STD	1 vs 7	-0.005	-0.559	0.550	N/A	N/A	1	50	N/A	84	22	0.18
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	-0.074	-0.634	0.486	N/A	N/A	1	49	N/A	84	22	0.23
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	0.241	-0.329	0.812	0.056 [0, 100]	31.312 [0, 99.877]	2	77	2	77	30	0.44
NUTR vs PLAC/STD	6 vs 7	0.432	-0.233	1.098	0.155 [0, 100]	67.37 [0, 99.925]	2	111	2	79	21	0.31
MED_MAN vs PLAC/STD	4 vs 7	0.083	-0.127	0.293	N/A	N/A	1	414	2	79	N/A	0.28
MULTI vs PLAC/STD	5 vs 7	0.032	-0.414	0.479	N/A	N/A	1	77	2	75	24	0.69
Cognition (13 studies, 8 treatments, 1664 patients)												
PHYS_ACT vs PLAC/STD	1 vs 8	0.398	-0.364	1.161	0.639 [0.158, 5.936]	88.456 [65.402, 98.614]	5	413	2	82.32	23.21	0.24
NUTR vs PLAC/STD	7 vs 8	-0.169	-1.149	0.810	0.379 [0, 100]	75.606 [0, 99.878]	2	73	1	75.51	22.66	0.12
PHARM vs PLAC/STD	4 vs 8	-0.028	-0.469	0.413	0.035 [0, 100]	33.59 [0, 99.932]	2	150	1	76.14	25.35	0.30
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	-0.052	-0.497	0.393	0.048 [0, 100]	44.053 [0, 99.939]	2	163	2	77.87	22.94	0.32
MULTI vs PLAC/STD	5 vs 8	0.217	-0.082	0.515	0.002 [0, 57.452]	3.153 [0, 99.905]	2	182	2	69.01	27.70	0.43
GERIA vs PLAC/STD	6 vs 8	0.018	-0.216	0.252	N/A	N/A	1	315	2	78.10	N/A	0.33

PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.320	-0.908	0.269	N/A	N/A	1	45	2	84.33	20.48	0.25
PHYS_ACT vs NUTR	1 vs 7	-0.024	-0.608	0.561	N/A	N/A	1	45	2	84.33	20.48	0.20
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	0.296	-0.285	0.878	N/A	N/A	1	46	N/A	84.33	20.48	0.17
MED_MAN vs PLAC/STD	3 vs 8	1.350	1.121	1.580	N/A	N/A	1	414	N/A	79.10	N/A	0.27
Depression (9 studies, 5 treatments, 1519 patients)												
PHYS_ACT vs PLAC/STD	1 vs 5	-0.249	-0.463	-0.036	0 [0, 0.2]	0 [0, 80.465]	4	341	2	75	26	0.47
MED_MAN vs PLAC/STD	2 vs 5	-1.637	-1.875	-1.400	0 [0, 0]	0 [0, 0]	1	414	2	79	N/A	0.28
MULTI vs PLAC/STD	3 vs 5	-0.040	-0.225	0.145	0 [0, 0.292]	0 [0, 90.728]	3	449	2	72	26	0.56
GERIA vs PLAC/STD	4 vs 5	0.191	-0.044	0.426	0 [0, 0]	0 [0, 0]	1	315	2	78	N/A	0.29
Adverse Events (28 studies, 7 treatments, 4013 patients)												
PHYS_ACT vs PLAC/STD	1 vs 7	3	1.039	7.799	1.963 [0.413, 8.178]	71.975 [35.093, 91.452]	13	2020	2	78.73	29.87	0.31
PHARM vs PLAC/STD	4 vs 7	1.776	0.883	3.572	0.496 [0.061, 3.582]	65.108 [18.614, 93.091]	7	983	1	72.13	26.67	0.61
NUTR vs PLAC/STD	6 vs 7	1.870	0.585	5.983	0.581 [0, 10.52]	39.339 [0, 92.154]	4	479	2	72.65	27.21	0.36
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	7.852	1.273	48.447	0.039 [0, 100]	1.923 [0, 98.031]	2	82	2	70.12	37.95	0.51
PHYS_ACT vs PSYCH	1 vs 3	5.430	0.254	116.087	N/A	N/A	1	98	N/A	69.95	23.55	0.34
PHYS_ACT vs NUTR	1 vs 6	5.567	1.521	20.382	0 [0, 0.039]	0 [0, 2.562]	2	149	N/A	69.97	30.35	0.38
MULTI vs PLAC/STD	5 vs 7	4.185	1.208	14.494	0 [0, 5.983]	0 [0, 77.15]	4	503	2	73.88	26.28	0.35
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	1.320	0.441	3.953	N/A	N/A	1	54	N/A	70	37.15	0.41

PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	4.259	1.019	17.799	N/A	N/A	1	54	N/A	70	37.15	0.39
Serious Adverse Events (10 studies, 5 treatments, 1644 patients)												
PHARM vs PLAC/STD	2 vs 5	1.227	0.543	2.777	0.278 [0.000, 25.866]	41.696 [0.000, 98.518]	4	503	Low	72.18	27.15	0.58
PHYS_ACT vs PLAC/STD	1 vs 5	0.726	0.264	2.002	0.504 [0.000, 14.895]	50.732 [0.000, 96.816]	4	1026	High	79.21	27.05	0.32
NUTR vs PLAC/STD	4 vs 5	3.429	0.337	34.864	0.000 [0.000, 0.000]	0.000 [0.000, 0.000]	1	64	Low	65.90	33.05	0.70
MULTI vs PLAC/STD	3 vs 5	0.039	0.002	0.717	0.000 [0.000, 0.000]	0.000 [0.000, 0.000]	1	51	High	80.03	N/A	0.41
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.												

eTable 7. Network meta-analysis

Frailty (20 studies, 8 treatments, 4838 patients)						
Treatment Comparison	**Coded Trt Comparison**	**Median Odds Ratio**	**Low CrI**	**High CrI**	**Low PrI**	**High PrI**
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.306	-1.191	0.621	-1.886	1.343
PHYS_ACT vs PSYCH	1 vs 3	-0.429	-1.207	0.350	-1.980	1.154
PHYS_ACT vs PHARM	1 vs 4	-0.412	-1.362	0.539	-2.048	1.249
PHYS_ACT vs MUTLI	1 vs 5	-0.460	-1.272	0.346	-2.040	1.109
PHYS_ACT vs GERIA	1 vs 6	-0.752	-2.031	0.511	-2.583	1.104
PHYS_ACT vs NUTR	1 vs 7	-0.599	-1.264	0.077	-2.098	0.922
PHYS_ACT vs PLAC/STD	1 vs 8	-0.927	-1.571	-0.274	-2.437	0.579
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	-0.124	-1.002	0.740	-1.708	1.475
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 4	-0.116	-1.212	0.968	-1.864	1.630
PHYS_ACT+PROT/NUTR vs MUTLI	2 vs 5	-0.163	-1.142	0.823	-1.832	1.517
PHYS_ACT+PROT/NUTR vs GERIA	2 vs 6	-0.446	-1.776	0.835	-2.346	1.411
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	-0.297	-1.156	0.557	-1.868	1.293
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	-0.624	-1.467	0.206	-2.200	0.937
PSYCH vs PHARM	3 vs 4	0.013	-0.913	0.936	-1.650	1.639
PSYCH vs MUTLI	3 vs 5	-0.035	-0.825	0.760	-1.612	1.519
PSYCH vs GERIA	3 vs 6	-0.318	-1.674	0.994	-2.263	1.551
PSYCH vs NUTR	3 vs 7	-0.169	-0.808	0.458	-1.643	1.296
PSYCH vs PLAC/STD	3 vs 8	-0.499	-1.145	0.132	-1.986	0.999
PHARM vs MUTLI	4 vs 5	-0.052	-0.963	0.895	-1.665	1.599
PHARM vs GERIA	4 vs 6	-0.338	-1.789	1.110	-2.313	1.632
PHARM vs NUTR	4 vs 7	-0.187	-0.906	0.553	-1.696	1.343
PHARM vs PLAC/STD	4 vs 8	-0.511	-1.347	0.344	-2.126	1.081
MUTLI vs GERIA	5 vs 6	-0.288	-1.661	1.088	-2.221	1.643
MUTLI vs NUTR	5 vs 7	-0.138	-0.744	0.481	-1.597	1.325
MUTLI vs PLAC/STD	5 vs 8	-0.462	-1.172	0.233	-1.987	1.052
GERIA vs NUTR	6 vs 7	0.148	-1.119	1.442	-1.727	2.005
GERIA vs PLAC/STD	6 vs 8	-0.181	-1.467	1.135	-2.044	1.720
NUTR vs PLAC/STD	7 vs 8	-0.329	-0.914	0.260	-1.790	1.158
Short physical performance battery (36 studies, 9 treatments, 4568 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-1.508	-2.796	-0.217	-4.944	1.850

PHYS_ACT vs PSYCH	1 vs 3	-1.111	-4.500	2.280	-5.703	3.436
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	0.405	-2.718	3.538	-3.928	4.666
PHYS_ACT vs MED_MAN	1 vs 4	-3.035	-6.147	0.018	-7.380	1.291
PHYS_ACT+PROT/NUTR vs MED_MAN	2 vs 4	-1.539	-4.789	1.677	-6.052	2.856
PSYCH vs MED_MAN	3 vs 4	-1.944	-6.489	2.528	-7.395	3.569
PHYS_ACT vs PHARM	1 vs 5	0.759	-0.776	2.314	-2.616	4.151
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 5	2.260	0.434	4.108	-1.287	5.781
PSYCH vs PHARM	3 vs 5	1.867	-1.802	5.474	-2.926	6.562
MED_MAN vs PHARM	4 vs 5	3.788	0.471	7.143	-0.660	8.310
PHYS_ACT vs MULTI	1 vs 6	0.497	-1.415	2.409	-3.099	4.007
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 6	1.995	-0.135	4.147	-1.695	5.785
PSYCH vs MULTI	3 vs 6	1.609	-2.190	5.384	-3.289	6.443
MED_MAN vs MULTI	4 vs 6	3.534	0.012	7.115	-1.030	8.306
PHARM vs MULTI	5 vs 6	-0.260	-2.515	1.956	-3.980	3.502
PHYS_ACT vs NUTR	1 vs 7	-0.719	-2.106	0.674	-4.041	2.597
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	0.782	-0.819	2.412	-2.653	4.204
PSYCH vs NUTR	3 vs 7	0.387	-3.156	3.948	-4.343	5.083
MED_MAN vs NUTR	4 vs 7	2.314	-0.959	5.605	-2.125	6.821
PHARM vs NUTR	5 vs 7	-1.472	-3.369	0.366	-5.099	2.123
MULTI vs NUTR	6 vs 7	-1.211	-3.377	0.970	-5.024	2.545
PHYS_ACT vs PLAC/STD	1 vs 8	0.899	0.202	1.612	-2.218	4.070
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	2.409	1.209	3.626	-0.876	5.679
PSYCH vs PLAC/STD	3 vs 8	2.013	-1.352	5.354	-2.516	6.536
MED_MAN vs PLAC/STD	4 vs 8	3.944	0.929	6.982	-0.298	8.180
PHARM vs PLAC/STD	5 vs 8	0.146	-1.221	1.506	-3.195	3.523
MULTI vs PLAC/STD	6 vs 8	0.403	-1.349	2.154	-3.100	3.905
NUTR vs PLAC/STD	7 vs 8	1.623	0.344	2.905	-1.648	4.961
PHYS_ACT vs VIBRA	1 vs 9	-0.094	-2.347	2.174	-3.899	3.722
PHYS_ACT+PROT/NUTR vs VIBRA	2 vs 9	1.414	-1.150	3.961	-2.579	5.350
PSYCH vs VIBRA	3 vs 9	1.014	-3.067	5.032	-3.997	6.106
MED_MAN vs VIBRA	4 vs 9	2.948	-0.759	6.748	-1.822	7.844
PHARM vs VIBRA	5 vs 9	-0.858	-3.485	1.797	-4.923	3.248
MULTI vs VIBRA	6 vs 9	-0.585	-3.491	2.296	-4.778	3.660
NUTR vs VIBRA	7 vs 9	0.626	-1.927	3.224	-3.350	4.602
VIBRA vs PLAC/STD	9 vs 8	0.993	-1.260	3.242	-2.880	4.724

Quality of life (16 studies, 6 treatments, 3259 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.190	-0.284	0.646	-0.496	0.847
PHYS_ACT vs PHARM	1 vs 3	0.198	-0.317	0.690	-0.510	0.885
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 3	0.008	-0.591	0.609	-0.757	0.781
PHYS_ACT vs MULTI	1 vs 4	0.117	-0.292	0.498	-0.534	0.720
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 4	-0.073	-0.590	0.434	-0.781	0.620
PHARM vs MULTI	3 vs 4	-0.080	-0.628	0.456	-0.832	0.632
PHYS_ACT vs GERIA	1 vs 5	0.204	-0.382	0.779	-0.552	0.949
PHYS_ACT+PROT/NUTR vs GERIA	2 vs 5	0.012	-0.651	0.676	-0.815	0.843
PHARM vs GERIA	3 vs 5	0.006	-0.684	0.691	-0.851	0.844
MULTI vs GERIA	4 vs 5	0.086	-0.524	0.728	-0.685	0.901
PHYS_ACT vs PLAC/STD	1 vs 6	0.169	-0.073	0.389	-0.382	0.694
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 6	-0.020	-0.428	0.374	-0.654	0.610
PHARM vs PLAC/STD	3 vs 6	-0.027	-0.472	0.416	-0.682	0.633
MULTI vs PLAC/STD	4 vs 6	0.053	-0.262	0.374	-0.526	0.614
GERIA vs PLAC/STD	5 vs 6	-0.036	-0.576	0.496	-0.760	0.662
Quality of life-Physical domain (15 studies, 7 treatments, 2293 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.771	-1.723	3.281	-3.529	5.017
PHYS_ACT vs PSYCH	1 vs 3	1.079	-1.656	3.835	-3.366	5.528
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	0.298	-3.118	3.687	-4.534	5.210
PHYS_ACT vs MED_MAN	1 vs 4	0.228	-3.504	3.965	-4.954	5.256
PHYS_ACT+PROT/NUTR vs MED_MAN	2 vs 4	-0.551	-4.826	3.628	-6.102	4.789
PSYCH vs MED_MAN	3 vs 4	-0.864	-5.208	3.435	-6.341	4.652
PHYS_ACT vs MULTI	1 vs 5	1.512	-2.225	5.276	-3.565	6.671
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 5	0.754	-3.452	5.045	-4.788	6.355
PSYCH vs MULTI	3 vs 5	0.440	-3.860	4.711	-5.006	5.991
MED_MAN vs MULTI	4 vs 5	1.326	-3.550	6.327	-4.665	7.364
PHYS_ACT vs NUTR	1 vs 6	0.767	-1.356	2.923	-3.520	4.886
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	-0.005	-2.769	2.740	-4.489	4.473
PSYCH vs NUTR	3 vs 6	-0.313	-3.462	2.779	-5.002	4.314
MED_MAN vs NUTR	4 vs 6	0.538	-3.455	4.563	-4.701	5.913
MULTI vs NUTR	5 vs 6	-0.745	-4.853	3.276	-6.238	4.564
PHYS_ACT vs PLAC/STD	1 vs 7	1.328	0.094	2.551	-2.312	5.098

PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	0.555	-1.784	2.884	-3.768	4.755
PSYCH vs PLAC/STD	3 vs 7	0.260	-2.195	2.706	-4.060	4.567
MED_MAN vs PLAC/STD	4 vs 7	1.106	-2.394	4.569	-3.752	6.000
MULTI vs PLAC/STD	5 vs 7	-0.197	-3.853	3.334	-5.161	4.785
NUTR vs PLAC/STD	6 vs 7	0.571	-1.350	2.460	-3.390	4.663
Quality of life-Mental domain (12 studies, 7 treatments, 2053 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.311	-1.341	1.943	-2.470	3.069
PHYS_ACT vs PSYCH	1 vs 3	0.501	-1.336	2.301	-2.366	3.371
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	0.190	-2.051	2.354	-2.887	3.289
PHYS_ACT vs MED_MAN	1 vs 4	0.722	-1.653	3.080	-2.449	3.847
PHYS_ACT+PROT/NUTR vs MED_MAN	2 vs 4	0.402	-2.289	3.069	-3.098	3.854
PSYCH vs MED_MAN	3 vs 4	0.223	-2.477	2.928	-3.296	3.709
PHYS_ACT vs MULTI	1 vs 5	0.781	-1.633	3.191	-2.486	4.072
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 5	0.472	-2.226	3.162	-3.009	3.866
PSYCH vs MULTI	3 vs 5	0.284	-2.455	3.050	-3.230	3.801
MED_MAN vs MULTI	4 vs 5	0.059	-3.072	3.191	-3.773	3.849
PHYS_ACT vs NUTR	1 vs 6	0.213	-1.351	1.787	-2.518	2.928
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	-0.108	-1.959	1.776	-2.918	2.818
PSYCH vs NUTR	3 vs 6	-0.291	-2.423	1.866	-3.330	2.822
MED_MAN vs NUTR	4 vs 6	-0.515	-3.135	2.160	-4.022	3.024
MULTI vs NUTR	5 vs 6	-0.570	-3.223	2.104	-3.994	2.824
PHYS_ACT vs PLAC/STD	1 vs 7	0.806	-0.088	1.715	-1.566	3.226
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	0.496	-1.041	2.007	-2.158	3.209
PSYCH vs PLAC/STD	3 vs 7	0.304	-1.238	1.904	-2.331	3.059
MED_MAN vs PLAC/STD	4 vs 7	0.086	-2.092	2.319	-3.004	3.170
MULTI vs PLAC/STD	5 vs 7	0.031	-2.211	2.228	-3.149	3.122
NUTR vs PLAC/STD	6 vs 7	0.595	-0.870	2.063	-2.063	3.239
Cognition (13 studies, 8 treatments, 1664 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	0.230	-0.915	1.354	-1.659	2.116
PHYS_ACT vs MED_MAN	1 vs 3	-0.918	-2.609	0.752	-3.185	1.334
PHYS_ACT+PROT/NUTR vs MED_MAN	2 vs 3	-1.144	-3.001	0.715	-3.538	1.253
PHYS_ACT vs PHARM	1 vs 4	0.455	-0.894	1.758	-1.519	2.433
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 4	0.215	-1.290	1.723	-1.916	2.311

MED_MAN vs PHARM	3 vs 4	1.367	-0.516	3.217	-1.095	3.752
PHYS_ACT vs MULTI	1 vs 5	0.294	-1.041	1.604	-1.707	2.294
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 5	0.059	-1.464	1.597	-2.066	2.225
MED_MAN vs MULTI	3 vs 5	1.206	-0.706	3.111	-1.236	3.605
PHARM vs MULTI	4 vs 5	-0.160	-1.720	1.450	-2.296	2.042
PHYS_ACT vs GERIA	1 vs 6	0.421	-1.259	2.095	-1.882	2.675
PHYS_ACT+PROT/NUTR vs GERIA	2 vs 6	0.183	-1.669	2.062	-2.218	2.595
MED_MAN vs GERIA	3 vs 6	1.340	-0.844	3.501	-1.237	3.960
PHARM vs GERIA	4 vs 6	-0.029	-1.904	1.917	-2.423	2.453
MULTI vs GERIA	5 vs 6	0.134	-1.763	1.995	-2.278	2.572
PHYS_ACT vs NUTR	1 vs 7	0.357	-0.834	1.545	-1.533	2.270
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	0.135	-1.202	1.461	-1.876	2.140
MED_MAN vs NUTR	3 vs 7	1.280	-0.598	3.140	-1.115	3.700
PHARM vs NUTR	4 vs 7	-0.089	-1.588	1.460	-2.261	2.091
MULTI vs NUTR	5 vs 7	0.085	-1.517	1.595	-2.116	2.202
GERIA vs NUTR	6 vs 7	-0.051	-1.962	1.807	-2.461	2.354
PHYS_ACT vs PLAC/STD	1 vs 8	0.436	-0.262	1.138	-1.153	2.100
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	0.205	-0.818	1.247	-1.627	2.022
MED_MAN vs PLAC/STD	3 vs 8	1.355	-0.164	2.866	-0.781	3.496
PHARM vs PLAC/STD	4 vs 8	-0.014	-1.130	1.101	-1.875	1.887
MULTI vs PLAC/STD	5 vs 8	0.149	-0.974	1.251	-1.722	2.041
GERIA vs PLAC/STD	6 vs 8	0.017	-1.504	1.550	-2.152	2.166
NUTR vs PLAC/STD	7 vs 8	0.069	-0.992	1.165	-1.800	1.904
Depression (9 studies, 5 treatments, 1519 patients)						
PHYS_ACT vs MED_MAN	1 vs 2	1.382	0.935	1.841	0.826	1.962
PHYS_ACT vs MULTI	1 vs 3	-0.223	-0.599	0.145	-0.716	0.256
MED_MAN vs MULTI	2 vs 3	-1.605	-2.079	-1.169	-2.207	-1.061
PHYS_ACT vs GERIA	1 vs 4	-0.448	-0.930	0.045	-1.024	0.164
MED_MAN vs GERIA	2 vs 4	-1.831	-2.394	-1.282	-2.478	-1.185
MULTI vs GERIA	3 vs 4	-0.228	-0.708	0.284	-0.808	0.392
PHYS_ACT vs PLAC/STD	1 vs 5	-0.254	-0.518	0.008	-0.670	0.154
MED_MAN vs PLAC/STD	2 vs 5	-1.637	-2.023	-1.272	-2.163	-1.129
MULTI vs PLAC/STD	3 vs 5	-0.033	-0.290	0.239	-0.451	0.406
GERIA vs PLAC/STD	4 vs 5	0.192	-0.230	0.600	-0.327	0.723
Adverse Events (28 studies, 7 treatments, 4013 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	1.559	0.173	14.390	0.053	49.450

PHYS_ACT vs PSYCH	1 vs 3	0.142	0.000	5.759	0.000	13.690
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	0.086	0.000	5.989	0.000	13.720
PHYS_ACT vs PHARM	1 vs 4	0.615	0.142	2.556	0.030	12.120
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 4	0.401	0.033	4.307	0.011	13.600
PSYCH vs PHARM	3 vs 4	4.476	0.088	2733.000	0.035	4395.000
PHYS_ACT vs MULTI	1 vs 5	2.136	0.279	18.480	0.076	63.550
PHYS_ACT+PROT/NUTR vs MULTI	2 vs 5	1.392	0.076	25.780	0.026	68.690
PSYCH vs MULTI	3 vs 5	16.180	0.223	12160.000	0.103	19660.000
PHARM vs MULTI	4 vs 5	3.469	0.410	34.870	0.119	113.900
PHYS_ACT vs NUTR	1 vs 6	0.494	0.106	2.283	0.024	10.340
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 6	0.318	0.030	3.215	0.010	11.080
PSYCH vs NUTR	3 vs 6	3.540	0.076	2176.000	0.033	3509.000
PHARM vs NUTR	4 vs 6	0.803	0.138	4.887	0.035	18.850
MULTI vs NUTR	5 vs 6	0.233	0.020	2.321	0.007	7.352
PHYS_ACT vs PLAC/STD	1 vs 7	0.318	0.121	0.757	0.019	4.798
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 7	0.205	0.022	1.655	0.006	5.540
PSYCH vs PLAC/STD	3 vs 7	2.206	0.052	1306.000	0.022	2284.000
PHARM vs PLAC/STD	4 vs 7	0.516	0.166	1.532	0.029	8.740
MULTI vs PLAC/STD	5 vs 7	0.149	0.019	0.881	0.006	3.615
NUTR vs PLAC/STD	6 vs 7	0.645	0.150	2.527	0.031	11.410
Serious Adverse Events (10 studies, 5 treatments, 1644 patients)						
PHYS_ACT vs PHARM	1 vs 2	0.504	0.087	2.396	0.036	5.817
PHYS_ACT vs MULTI	1 vs 3	45.413	1.337	27700.831	0.789	34281.796
PHARM vs MULTI	2 vs 3	92.851	2.842	57803.468	1.844	80450.523
PHYS_ACT vs NUTR	1 vs 4	0.163	0.003	4.294	0.002	6.766
PHARM vs NUTR	2 vs 4	0.326	0.006	8.547	0.004	13.392
MULTI vs NUTR	3 vs 4	0.003	0.000	0.329	0.000	0.456
PHYS_ACT vs PLAC/STD	1 vs 5	0.733	0.217	2.493	0.074	7.072
PHARM vs PLAC/STD	2 vs 5	1.459	0.51	5.139	0.170	15.202
MULTI vs PLAC/STD	3 vs 5	0.016	0.000	0.444	0.000	0.758
NUTR vs PLAC/STD	4 vs 5	4.448	0.212	204.918	0.132	300.752
PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments,						

NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

eTable 8. Network Meta-regression results for frailty outcome

Treatment Comparison	Coded Trt Comparison	median SMD	Low CrI	High CrI	*Low PrI*	*High PrI*
Network Meta-regression- Age (19 studies, 8 treatments, 4723 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.535	-1.604	0.534	-2.287	1.240
PHYS_ACT vs PSYCH	1 vs 3	-0.587	-1.493	0.342	-2.242	1.079
PHYS_ACT vs PHARM	1 vs 4	-0.482	-1.457	0.520	-2.204	1.234
PHYS_ACT vs MUTLI	1 vs 5	-0.615	-1.504	0.281	-2.287	1.065
PHYS_ACT vs GERIA	1 vs 6	-0.961	-2.344	0.425	-2.910	1.018
PHYS_ACT vs NUTR	1 vs 7	-0.705	-1.428	0.043	-2.275	0.869
PHYS_ACT vs PLAC/STD	1 vs 8	-1.154	-1.961	-0.343	-2.750	0.452
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	-0.049	-0.974	0.880	-1.710	1.601
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 4	0.058	-1.114	1.242	-1.768	1.896
PHYS_ACT+PROT/NUTR vs MUTLI	2 vs 5	-0.078	-1.104	0.967	-1.793	1.666
PHYS_ACT+PROT/NUTR vs GERIA	2 vs 6	-0.430	-1.772	0.927	-2.338	1.501
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	-0.168	-1.114	0.773	-1.839	1.497
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	-0.614	-1.515	0.283	-2.266	1.032
PSYCH vs PHARM	3 vs 4	0.103	-0.900	1.118	-1.616	1.828
PSYCH vs MUTLI	3 vs 5	-0.034	-0.859	0.822	-1.659	1.606
PSYCH vs GERIA	3 vs 6	-0.378	-1.753	0.993	-2.343	1.572
PSYCH vs NUTR	3 vs 7	-0.118	-0.824	0.588	-1.640	1.448
PSYCH vs PLAC/STD	3 vs 8	-0.571	-1.317	0.156	-2.157	0.999
PHARM vs MUTLI	4 vs 5	-0.138	-1.093	0.839	-1.841	1.547
PHARM vs GERIA	4 vs 6	-0.476	-1.993	1.019	-2.501	1.600
PHARM vs NUTR	4 vs 7	-0.225	-0.991	0.543	-1.818	1.373
PHARM vs PLAC/STD	4 vs 8	-0.675	-1.613	0.241	-2.316	1.005
MUTLI vs GERIA	5 vs 6	-0.344	-1.733	1.046	-2.313	1.605

MUTLI vs NUTR	5 vs 7	-0.085	-0.735	0.546	-1.629	1.422
MUTLI vs PLAC/STD	5 vs 8	-0.537	-1.291	0.190	-2.124	1.048
GERIA vs NUTR	6 vs 7	0.255	-1.059	1.580	-1.654	2.179
GERIA vs PLAC/STD	6 vs 8	-0.199	-1.538	1.143	-2.141	1.757
NUTR vs PLAC/STD	7 vs 8	-0.451	-1.112	0.200	-1.990	1.103
Regression coefficient (SMD scale)		0.047	-0.048	0.142		
Network Meta-regression- percent of males (17 studies, 8 treatments, 4449 patients)						
PHYS_ACT vs PHYS_ACT+PROT/NUTR	1 vs 2	-0.509	-1.930	0.931	-2.642	1.651
PHYS_ACT vs PSYCH	1 vs 3	-0.646	-1.778	0.523	-2.562	1.252
PHYS_ACT vs PHARM	1 vs 4	-0.460	-1.608	0.691	-2.357	1.467
PHYS_ACT vs MUTLI	1 vs 5	-0.617	-1.615	0.429	-2.491	1.253
PHYS_ACT vs GERIA	1 vs 6	1.330	-199.100	197.300	-199.000	197.900
PHYS_ACT vs NUTR	1 vs 7	-0.674	-1.551	0.230	-2.434	1.118
PHYS_ACT vs PLAC/STD	1 vs 8	-1.074	-1.909	-0.226	-2.884	0.761
PHYS_ACT+PROT/NUTR vs PSYCH	2 vs 3	-0.136	-1.590	1.314	-2.269	2.000
PHYS_ACT+PROT/NUTR vs PHARM	2 vs 4	0.052	-1.469	1.561	-2.187	2.220
PHYS_ACT+PROT/NUTR vs MUTLI	2 vs 5	-0.101	-1.649	1.401	-2.275	2.100
PHYS_ACT+PROT/NUTR vs GERIA	2 vs 6	1.737	-198.800	198.000	-199.000	198.400
PHYS_ACT+PROT/NUTR vs NUTR	2 vs 7	-0.170	-1.531	1.213	-2.242	1.910
PHYS_ACT+PROT/NUTR vs PLAC/STD	2 vs 8	-0.569	-1.911	0.767	-2.622	1.461
PSYCH vs PHARM	3 vs 4	0.185	-1.053	1.404	-1.805	2.170
PSYCH vs MUTLI	3 vs 5	0.035	-0.971	1.050	-1.858	1.894
PSYCH vs GERIA	3 vs 6	1.889	-198.300	197.900	-198.200	198.200
PSYCH vs NUTR	3 vs 7	-0.031	-0.933	0.872	-1.794	1.770
PSYCH vs PLAC/STD	3 vs 8	-0.431	-1.415	0.543	-2.281	1.380
PHARM vs MUTLI	4 vs 5	-0.155	-1.233	0.955	-2.087	1.778
PHARM vs GERIA	4 vs 6	1.781	-198.500	197.800	-198.600	198.000
PHARM vs NUTR	4 vs 7	-0.213	-1.060	0.648	-1.996	1.561
PHARM vs PLAC/STD	4 vs 8	-0.619	-1.612	0.405	-2.493	1.261
MUTLI vs GERIA	5 vs 6	1.833	-198.500	198.100	-198.500	198.000
MUTLI vs NUTR	5 vs 7	-0.061	-0.788	0.675	-1.758	1.669

MUTLI vs PLAC/STD	5 vs 8	-0.462	-1.316	0.373	-2.242	1.303
GERIA vs NUTR	6 vs 7	-1.978	-197.900	198.700	-198.100	198.900
GERIA vs PLAC/STD	6 vs 8	-2.322	-198.400	198.100	-198.500	198.000
NUTR vs PLAC/STD	7 vs 8	-0.406	-1.148	0.341	-2.094	1.306
Regression coefficient (SMD scale)		1.670	-3.548	6.860		

PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

eTable 9: Grading Evidence

A) Direct Evidence

DIRECT EVIDENCE								
Frailty								
	Risk of bias	Inconsistency	Indirectness	Publication bias	Preliminary rating	Contributes as much as indirect	Need to assess indirect	Final direct rating
PHYS_ACT vs PHARM	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHYS_ACT vs GERIA	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHYS_ACT+PROT/NUTR vs PHARM	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHYS_ACT+PROT/NUTR vs MUTLI	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHYS_ACT+PROT/NUTR vs GERIA	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PSYCH vs PHARM	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PSYCH vs GERIA	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHARM vs MUTLI	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHARM vs GERIA	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHARM vs NUTR	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
MUTLI vs GERIA	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
GERIA vs NUTR	N/A	N/A	N/A	N/A	N/A	No	yes	N/A
PHYS_ACT vs PHYS_ACT+PROT/NUTR	serious	not serious	not serious	not serious	mod	No	yes	mod
PHYS_ACT vs PSYCH	serious	not serious	not serious	not serious	mod	No	yes	mod
PHYS_ACT vs MUTLI	serious	not serious	not serious	not serious	mod	No	yes	mod
PHYS_ACT vs NUTR	serious	not serious	not serious	not serious	mod	No	yes	mod
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	yes	low
PHYS_ACT+PROT/NUTR vs PSYCH	serious	not serious	not serious	not serious	mod	No	yes	mod
PHYS_ACT+PROT/NUTR vs NUTR	serious	not serious	not serious	not serious	mod	No	yes	mod

PHYS_ACT+PROT/NUTR vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	yes	mod
PSYCH vs MUTLI	serious	not serious	not serious	not serious	mod	No	yes	mod
PSYCH vs NUTR	serious	not serious	not serious	not serious	mod	No	yes	mod
PSYCH vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	yes	mod
PHARM vs PLAC/STD	not serious	not serious	not serious	not serious	high	No	yes	high
MUTLI vs NUTR	serious	not serious	not serious	not serious	mod	No	yes	mod
MUTLI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	yes	mod
GERIA vs PLAC/STD	not serious	not serious	not serious	not serious	high	No	yes	high
NUTR vs PLAC/STD	not serious	not serious	not serious	not serious	high	No	yes	high
Short physical performance battery								
PHYS_ACT vs PHYS_ACT+PROT/NUTR	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT vs PSYCH	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs PSYCH	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A

MED_MAN vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT+PROT/NUTR vs NUTR	serious	serious	not serious	not serious	low	No	Yes	low
PSYCH vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT+PROT/NUTR vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PSYCH vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHARM vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MULTI vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
NUTR vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT vs VIBRA	not serious	not serious	not serious	not serious	high	No	Yes	high
PHYS_ACT+PROT/NUTR vs VIBRA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs VIBRA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs VIBRA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs VIBRA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs VIBRA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
NUTR vs VIBRA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PLAC/STD vs VIBRA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
Quality of life								
PHYS_ACT vs	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A

PHYS_ACT+PROT/NUTR								
PHYS_ACT vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT+PROT/NUTR vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHARM vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MULTI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
GERIA vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
Quality of life- Physical domain								
PHYS_ACT vs PHYS_ACT+PROT/NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT vs PSYCH	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs PSYCH	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A

vs MULTI								
PSYCH vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT+PROT/NUTR vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PSYCH vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT+PROT/NUTR vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PSYCH vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MED_MAN vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MULTI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
NUTR vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
Quality of life-Mental domain								
PHYS_ACT vs PHYS_ACT+PROT/NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT vs PSYCH	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs PSYCH	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A

MED_MAN vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT+PROT/NUTR vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PSYCH vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT+PROT/NUTR vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
PSYCH vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MED_MAN vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MULTI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
NUTR vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
Cognition								
PHYS_ACT vs PHYS_ACT+PROT/NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A

PHYS_ACT+PROT/NUTR vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT+PROT/NUTR vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
MED_MAN vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
GERIA vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT+PROT/NUTR vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MED_MAN vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHARM vs PLAC/STD	not serious	not serious	not serious	not serious	high	No	Yes	high
MULTI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
GERIA vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
NUTR vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
Depression								
PHYS_ACT vs MED_MAN	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MED_MAN vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs GERIA	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod

MED_MAN vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MULTI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
GERIA vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
Adverse events								
PHYS_ACT vs PHYS_ACT+PROT/NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT vs PSYCH	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT+PROT/NUTR vs PSYCH	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT+PROT/NUTR vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PSYCH vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PHYS_ACT+PROT/NUTR vs NUTR	serious	not serious	not serious	not serious	mod	No	Yes	mod
PSYCH vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHYS_ACT+PROT/NUTR vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
PSYCH vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
MULTI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod

NUTR vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
Serious adverse events								
PHYS_ACT vs PHARM	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs MULTI	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHARM vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
MULTI vs NUTR	N/A	N/A	N/A	N/A	N/A	No	Yes	N/A
PHYS_ACT vs PLAC/STD	serious	serious	not serious	not serious	low	No	Yes	low
PHARM vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
MULTI vs PLAC/STD	serious	not serious	not serious	not serious	mod	No	Yes	mod
NUTR vs PLAC/STD	not serious	not serious	not serious	not serious	high	No	Yes	high

B) Indirect and Network Evidence

	INDIRECT EVIDENCE						**NETWORK EVIDENCE**			
Frailty										
	Common comparator	Tmt1 vs. common comparator rating	Tmt2 vs. common comparator rating	Lowest of the two	Intransitivity	Final indirect rating	Highest between direct and indirect	Incoherence	Imprecision	Final network rating
PHYS_ACT vs PHARM	placebo	low	high	low	not serious	low	low	N/A	serious	very low
PHYS_ACT vs GERIA	placebo	low	high	low	not serious	low	low	N/A	serious	very low
PHYS_ACT+PROT/ NUTR vs PHARM	placebo	mod	high	mod	not serious	mod	mod	N/A	serious	low
PHYS_ACT+PROT/ NUTR vs MUTLI	placebo	mod	mod	mod	not serious	mod	mod	N/A	serious	low

PHYS_ACT+PROT/ NUTR vs GERIA	placebo	mod	high	mod	not serious	mod	mod	N/A	serious	low
PSYCH vs PHARM	placebo	mod	high	mod	not serious	mod	mod	N/A	serious	low
PSYCH vs GERIA	placebo	mod	high	mod	not serious	mod	mod	N/A	serious	low
PHARM vs MUTLI	placebo	high	mod	mod	not serious	mod	mod	N/A	serious	low
PHARM vs GERIA	placebo	high	high	high	not serious	high	high	N/A	very serious	low
PHARM vs NUTR	placebo	high	high	high	not serious	high	high	N/A	very serious	low
MUTLI vs GERIA	placebo	mod	high	mod	not serious	mod	mod	N/A	serious	low
GERIA vs NUTR	placebo	high	high	high	not serious	high	high	N/A	very serious	low
PHYS_ACT vs PHYS_ACT+PROT/ NUTR	placebo	low	mod	low	not serious	low	mod	not serious	serious	low
PHYS_ACT vs PSYCH	placebo	low	mod	low	not serious	low	mod	not serious	serious	low
PHYS_ACT vs MUTLI	placebo	low	mod	low	not serious	low	mod	serious	serious	very low
PHYS_ACT vs NUTR	placebo	low	high	low	not serious	low	mod	not serious	serious	low
PHYS_ACT vs PLAC/STD	psych	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT+PROT/ NUTR vs PSYCH	placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT+PROT/ NUTR vs NUTR	placebo	mod	high	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT+PROT/ NUTR vs PLAC/STD	psych	mod	mod	mod	not serious	mod	mod	serious	serious	very low
PSYCH vs MUTLI	placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PSYCH vs NUTR	placebo	mod	high	mod	not serious	mod	mod	not serious	serious	low
PSYCH vs	Phys_Act	mod	mod	mod	not serious	mod	mod	serious	not serious	low

PLAC/STD										
PHARM vs PLAC/STD	NA						high	N/A	very serious	low
MUTLI vs NUTR	placebo	mod	high	mod	not serious	mod	mod	not serious	serious	low
MUTLI vs PLAC/STD	psych	mod	mod	mod	not serious	mod	mod	serious	not serious	low
GERIA vs PLAC/STD	NA	NA	NA	NA	NA	N/A	high	N/A	very serious	low
NUTR vs PLAC/STD	Psych	mod	mod	mod	not serious	mod	high	serious	serious	low
Short physical performance battery										
PHYS_ACT vs PHYS_ACT+PROT/ NUTR	placebo	low	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs PSYCH	PHYS_ACT+PROT	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PSYCH	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
PHYS_ACT vs MED_MAN	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MED_MAN	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PSYCH vs MED_MAN	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PHYS_ACT vs PHARM	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PHARM	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PSYCH vs PHARM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MED_MAN vs PHARM	placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs MULTI	placebo	low	low	low	not serious	low	low	not serious	serious	very low

PHYS_ACT+PROT/ NUTR vs MULTI	placebo	low	low	low	not serious	low	low	not serious	serious	very low
PSYCH vs MULTI	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MED_MAN vs MULTI	placebo	mod	low	low	not serious	low	low	not serious	serious	very low
PHARM vs MULTI	placebo	mod	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs NUTR	placebo	low	low	low	not serious	low	mod	not serious	serious	low
PHYS_ACT+PROT/ NUTR vs NUTR	placebo	low	low	low	not serious	low	low	not serious	serious	very low
PSYCH vs NUTR	PHYS_ACT+P ROT/NUTR	mod	low	low	not serious	low	low	not serious	serious	very low
MED_MAN vs NUTR	placebo	mod	low	low	not serious	low	low	not serious	serious	very low
PHARM vs NUTR	placebo	mod	low	low	not serious	low	low	not serious	serious	very low
MULTI vs NUTR	placebo	low	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs PLAC/STD	Nutr	mod	low	low	not serious	low	low	serious	not serious	very low
PHYS_ACT+PROT/ NUTR vs PLAC/STD	Nutr	low	low	low	not serious	low	low	serious	serious	very low
PSYCH vs PLAC/STD	PHYS_ACT+P ROT/NUTR	mod	low	low	not serious	low	low	not serious	serious	very low
MED_MAN vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
PHARM vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	low	not serious	serious	low
NUTR vs PLAC/STD	PHYS_ACT	mod	low	low	not serious	low	low	serious	serious	very low
PHYS_ACT vs VIBRA	N/A	N/A	N/A	N/A	N/A	N/A	high	not serious	very serious	low
PHYS_ACT+PROT/ NUTR vs VIBRA	PHYS_ACT	low	high	low	not serious	low	low	not serious	serious	very low

PSYCH vs VIBRA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MED_MAN vs VIBRA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PHARM vs VIBRA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MULTI vs VIBRA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
NUTR vs VIBRA	PHYS_ACT	mod	high	mod	not serious	mod	mod	not serious	serious	low
PLAC/STD vs VIBRA	PHYS_ACT	low	high	low	not serious	low	low	not serious	serious	very low
Quality of life										
PHYS_ACT vs PHYS_ACT+PROT/ NUTR	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs PHARM	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PHARM	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs MULTI	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHARM vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs GERIA	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHARM vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MULTI vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
PHARM vs	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low

PLAC/STD										
MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
GERIA vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
Quality of life- Physical domain										
PHYS_ACT vs PHYS_ACT+PROT/ NUTR	Placebo	low	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs PSYCH	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PSYCH	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs MED_MAN	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MED_MAN	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PSYCH vs MED_MAN	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs MULTI	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MULTI	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PSYCH vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs NUTR	Placebo	low	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs NUTR	Placebo	low	low	low	not serious	low	mod	not serious	serious	low
PSYCH vs NUTR	Placebo	mod	low	low	not serious	low	low	not serious	serious	very low
MED_MAN vs NUTR	Placebo	mod	low	low	not serious	low	low	not serious	serious	very low

MULTI vs NUTR	Placebo	mod	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs PLAC/STD	Nutr	mod	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PLAC/STD	Nutr	mod	low	low	not serious	low	low	not serious	serious	very low
PSYCH vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MED_MAN vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
NUTR vs PLAC/STD	PHYS_ACT	mod	low	low	not serious	low	low	not serious	serious	very low
Quality of life-Mental domain										
PHYS_ACT vs PHYS_ACT+PROT/ NUTR	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs PSYCH	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PSYCH	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs MED_MAN	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MED_MAN	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PSYCH vs MED_MAN	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs MULTI	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PSYCH vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low

PHYS_ACT vs NUTR	Placebo	low	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs NUTR	Placebo	mod	low	low	not serious	low	mod	not serious	serious	low
PSYCH vs NUTR	Placebo	mod	low	low	not serious	low	low	not serious	serious	very low
MED_MAN vs NUTR	Placebo	mod	low	low	not serious	low	low	not serious	serious	very low
MULTI vs NUTR	Placebo	mod	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs PLAC/STD	Nutr	mod	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PLAC/STD	Nutr	mod	low	low	not serious	low	mod	not serious	serious	low
PSYCH vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MED_MAN vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
NUTR vs PLAC/STD	PHYS_ACT	mod	low	low	not serious	low	low	not serious	serious	very low
Cognition										
PHYS_ACT vs PHYS_ACT+PROT/ NUTR	Placebo	low	mod	low	not serious	low	mod	not serious	serious	low
PHYS_ACT vs MED_MAN	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MED_MAN	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs PHARM	Placebo	low	high	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PHARM	Placebo	mod	high	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs	Placebo	mod	high	mod	not serious	mod	mod	not serious	serious	low

PHARM										
PHYS_ACT vs MULTI	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHARM vs MULTI	Placebo	high	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs GERIA	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHARM vs GERIA	Placebo	high	mod	mod	not serious	mod	mod	not serious	serious	low
MULTI vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs NUTR	Placebo	low	mod	low	not serious	low	mod	not serious	serious	low
PHYS_ACT+PROT/ NUTR vs NUTR	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs NUTR	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHARM vs NUTR	Placebo	high	mod	mod	not serious	mod	mod	not serious	serious	low
MULTI vs NUTR	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
GERIA vs NUTR	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs PLAC/STD	Nutr	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT+PROT/ NUTR vs PLAC/STD	Nutr	mod	mod	mod	not serious	mod	mod	serious	serious	very low
MED_MAN vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
PHARM vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	high	not serious	very serious	low

MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
GERIA vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
NUTR vs PLAC/STD	PHYS-ACT	mod	low	low	not serious	low	mod	serious	serious	very low
Depression										
PHYS_ACT vs MED_MAN	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MED_MAN vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
MULTI vs GERIA	Placebo	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MED_MAN vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
GERIA vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
Adverse events										
PHYS_ACT vs PHYS_ACT+PROT/ NUTR	placebo	low	mod	low	not serious	low	mod	not serious	serious	low
PHYS_ACT vs PSYCH	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	very serious	very low
PHYS_ACT+PROT/ NUTR vs PSYCH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

PHYS_ACT vs PHARM	placebo	low	low	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs PHARM	placebo	mod	low	low	not serious	low	low	not serious	serious	very low
PSYCH vs PHARM	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A
PHYS_ACT vs MULTI	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs MULTI	placebo	mod	mod	mod	not serious	mod	mod	not serious	very serious	very low
PSYCH vs MULTI	N/A	N/A	N/A	N/A	N/A		N/A			
PHARM vs MULTI	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT vs NUTR	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
PHYS_ACT+PROT/ NUTR vs NUTR	placebo	low	mod	low	not serious	low	mod	not serious	very serious	very low
PSYCH vs NUTR	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PHARM vs NUTR	placebo	low	mod	low	not serious	low	low	not serious	serious	very low
MULTI vs NUTR	placebo	mod	mod	mod	not serious	mod	mod	not serious	very serious	very low
PHYS_ACT vs PLAC/STD	Nutr	mod	mod	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT+PROT/ NUTR vs PLAC/STD	Nutr	mod	mod	mod	not serious	mod	mod	not serious	very serious	very low
PSYCH vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PHARM vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	low	not serious	serious	very low
MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	very serious	very low
NUTR vs PLAC/STD	PHYS_ACT	mod	low	low	not serious	low	mod	not serious	serious	low
Serious adverse events										
PHYS_ACT vs PHARM	Placebo	low	mod	low	not serious	low	low	not serious	serious	very low

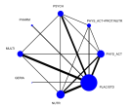
PHYS_ACT vs MULTI	Placebo	low	mod	low	not serious	low	low	not serious	very serious	very low
PHARM vs MULTI	Placebo	mod	mod	mod	not serious	mod	mod	not serious	very serious	very low
PHYS_ACT vs NUTR	Placebo	low	high	low	not serious	low	low	not serious	serious	very low
PHARM vs NUTR	Placebo	mod	high	mod	not serious	mod	mod	not serious	serious	low
MULTI vs NUTR	Placebo	mod	high	mod	not serious	mod	mod	not serious	serious	low
PHYS_ACT vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	low	not serious	serious	very low
PHARM vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
MULTI vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	mod	not serious	serious	low
NUTR vs PLAC/STD	N/A	N/A	N/A	N/A	N/A	N/A	high	not serious	very serious	low

PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

eTable 10: Summary of findings

Estimate of effects, credible intervals, and certainty of evidence for comparing frailty interventions

Patient or population: Older adults
Setting: Any setting
Intervention: Physical Activity, Nutritional Supplementation, Psychosocial/Cognitive Training, multi-faceted Intervention, Physical Activity with Nutritional Supplementation, Comprehensive Geriatric Assessment, Pharmacotherapy
Comparator (reference): Placebo/Standard Care


Network Geometry

Total studies: 19 RCTs Total Participants: 4361	Relative effect (95% CrI)	Certainty of the evidence (GRADE)	Ranking (95% CrI)*	Interpretation of Finding
Physical Activity	-0.93 (-1.57, -0.27)	⊕⊕◯◯ LOW [a,b]	1 (0.43, 1.00)	Probably superior
Physical Activity with nutritional supplementation	-0.62 (-1.47, 0.21)	⊕◯◯◯ VERY LOW [a,bd]	0.71 (0.14, 1.00)	Probably superior
Psychosocial/cognitive training	-0.50 (-1.14, 0.13)	⊕⊕◯◯ LOW [a,d]	0.57 (0.14, 1.00)	Probably superior
Pharmacotherapy	-0.51 (-1.35, 0.34)	⊕⊕◯◯ LOW [e]	0.57 (0.00, 1.00)	Probably superior
Comprehensive Geriatric Assessment	-0.18 (-1.47, 1.14)	⊕⊕◯◯ LOW [e]	0.14 (0.00, 1.00)	Probably inferior
Nutritional supplementation	-0.33 (-0.91, 0.26)	⊕⊕◯◯ LOW [cd]	0.43 (0.00, 0.71)	Probably inferior
Multifaceted Intervention	-0.46 (-1.17, 0.23)	⊕⊕◯◯ LOW [ad]	0.57 (0.00, 1.00)	Probably inferior

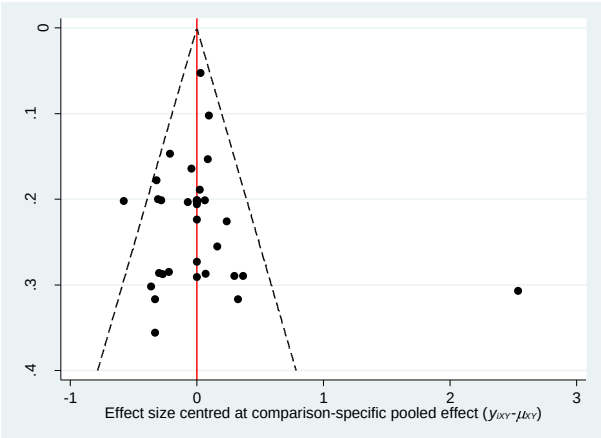
*Median and credible interval are presented. Rank statistics is defined as the probabilities that a treatment out of n treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

CrI: Confidence interval

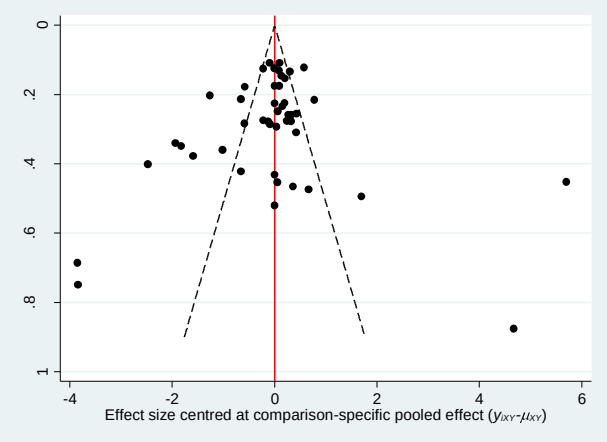
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Serious risk of bias: most of the included studies have high risk of bias
b. Serious inconsistency: significant heterogeneity of direct evidence
c. Serious imprecision: wide credible interval of the network estimate
d. Serious incoherence: The direct and indirect estimates are not sufficiently similar
e. Very serious imprecision: wide credible interval of the network estimate

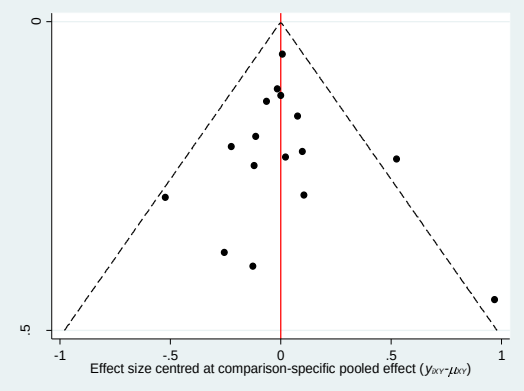
eFigure 1: Comparison-Adjusted Funnel Plots



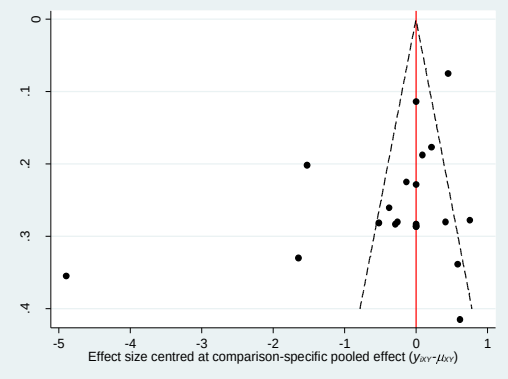
A- Frailty



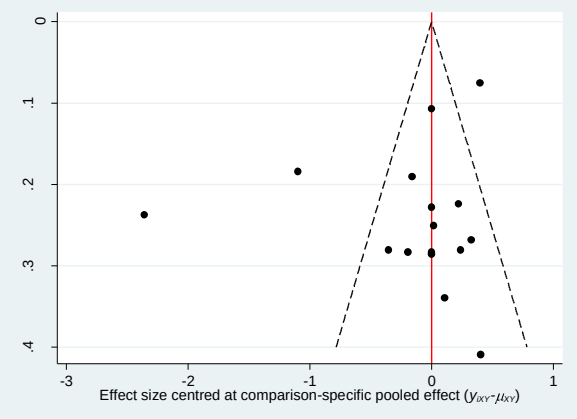
B- Short physical performance battery



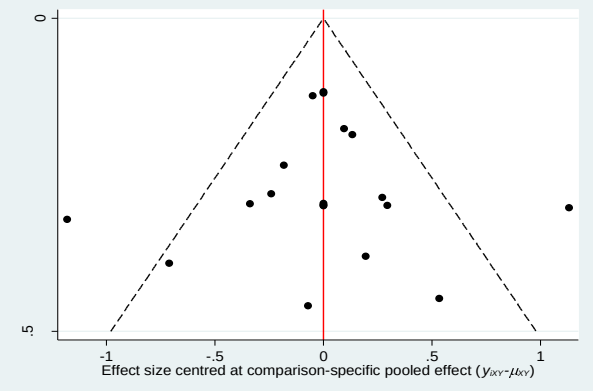
C- Quality of life



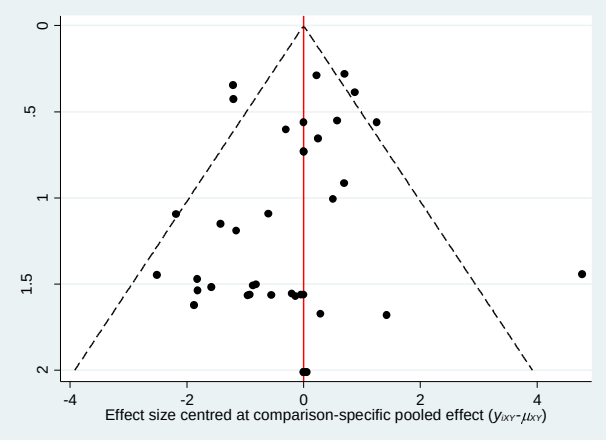
D- Quality of life- physical domain



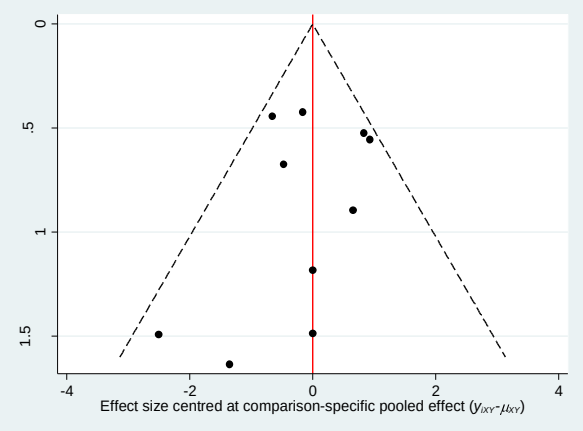
E- Quality of life- mental domain



F- Cognition



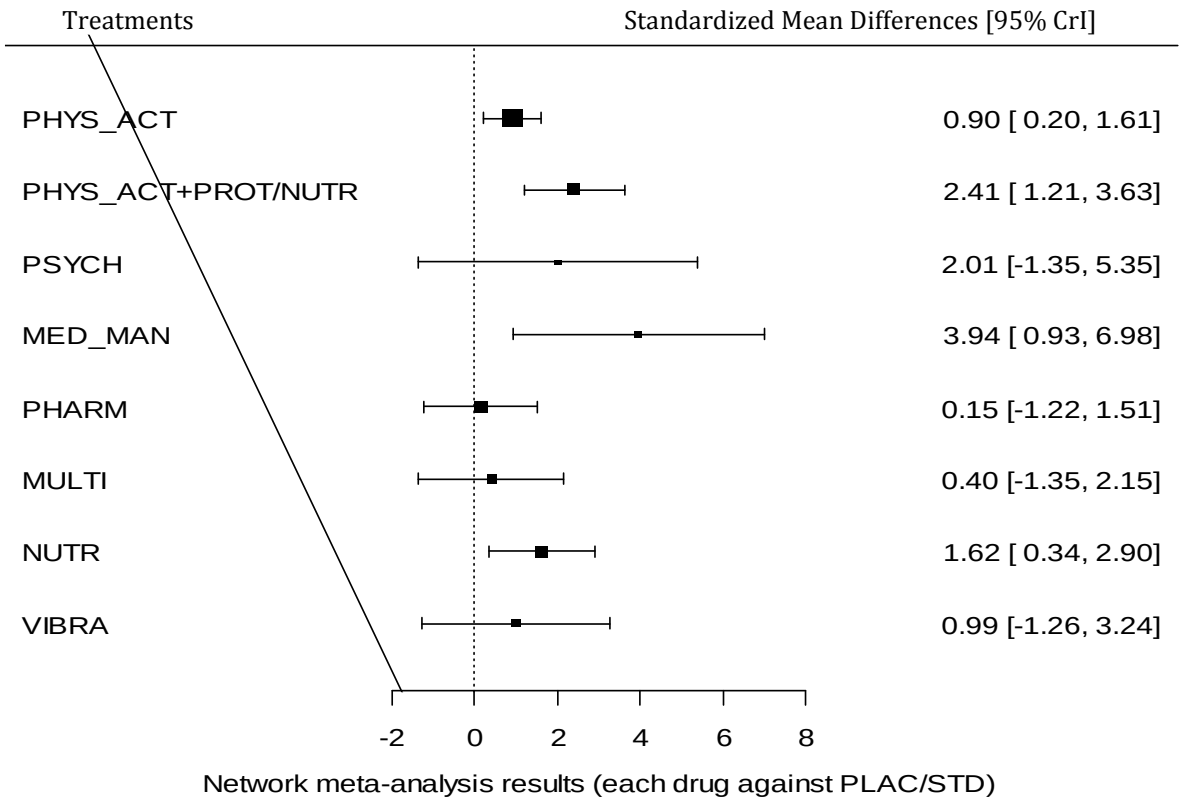
G- Adverse events



H- Serious adverse events

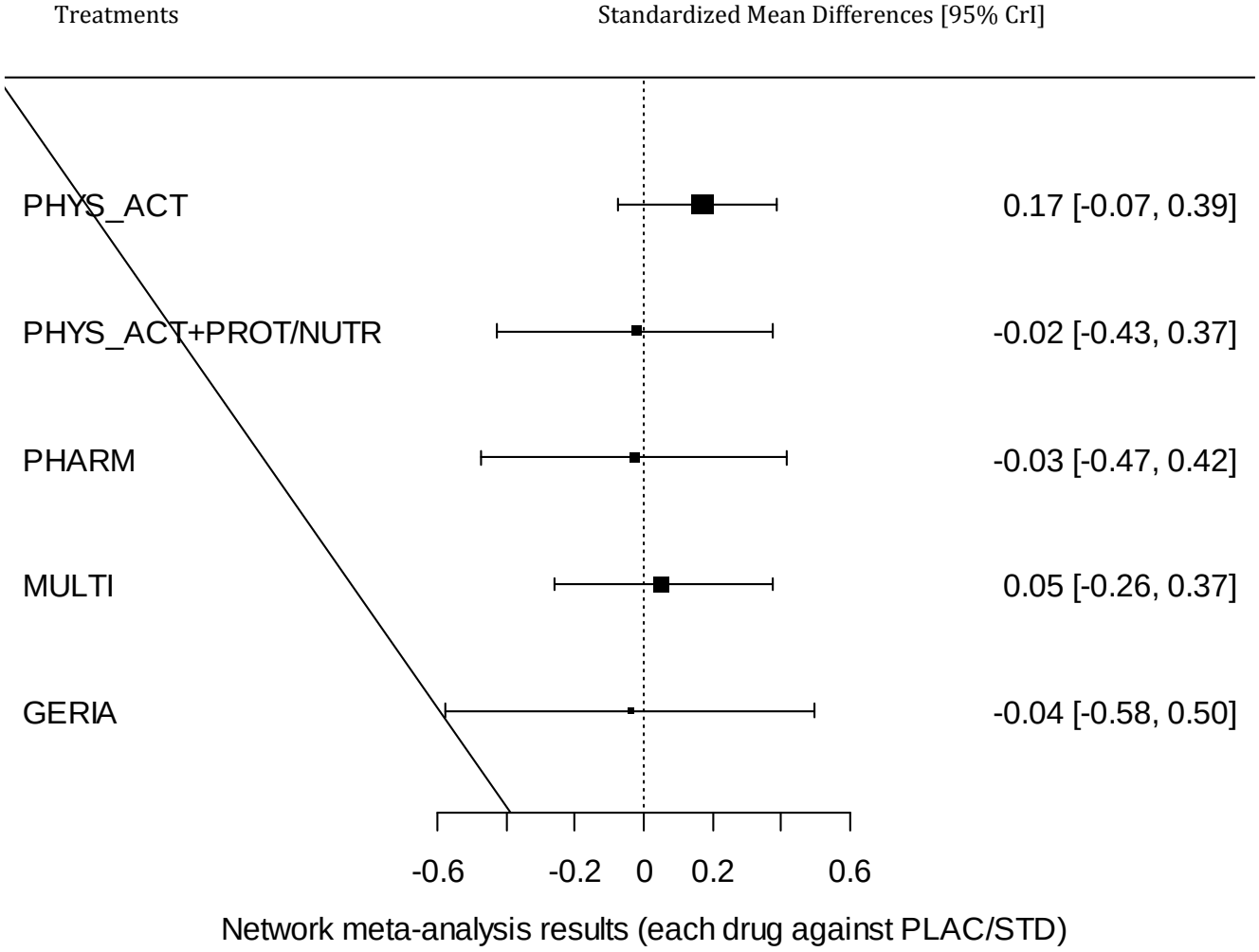
eFigure 2: Pairwise comparison of included interventions versus placebo/standard care

A- Short physical performance Battery



PHYS_ACT = Physical activity, PHYS_ACT+PROT/NUTR = Physical activity and protein or nutrition supplementation, PSYCH = Psychosocial or cognitive training, MED_MAN = Medication management, PHARM = Pharmacotherapy, MULTI = Multifaceted, GERIA = Geriatric Comprehensive Assessments, NUTR = Nutrition Only, PLAC/STD = Placebo/standard care, VIBRA = Vibration wave or sound waves.

B- Quality of life



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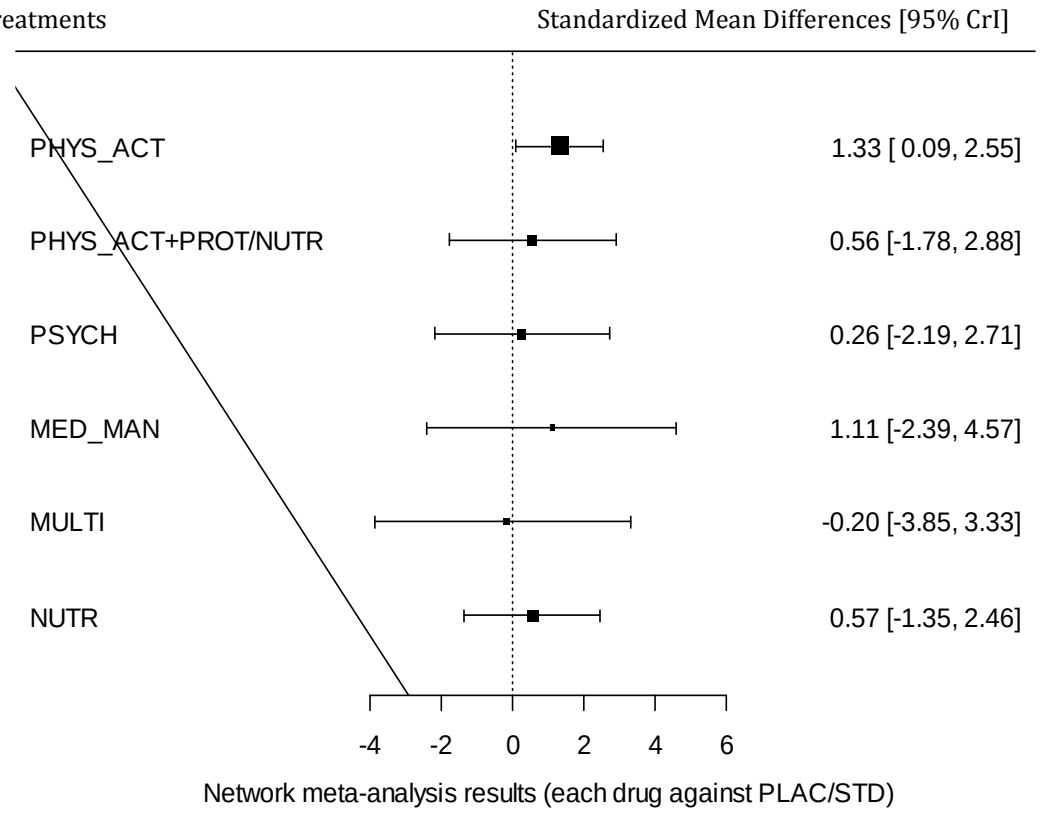
C- Quality of life- physical domain



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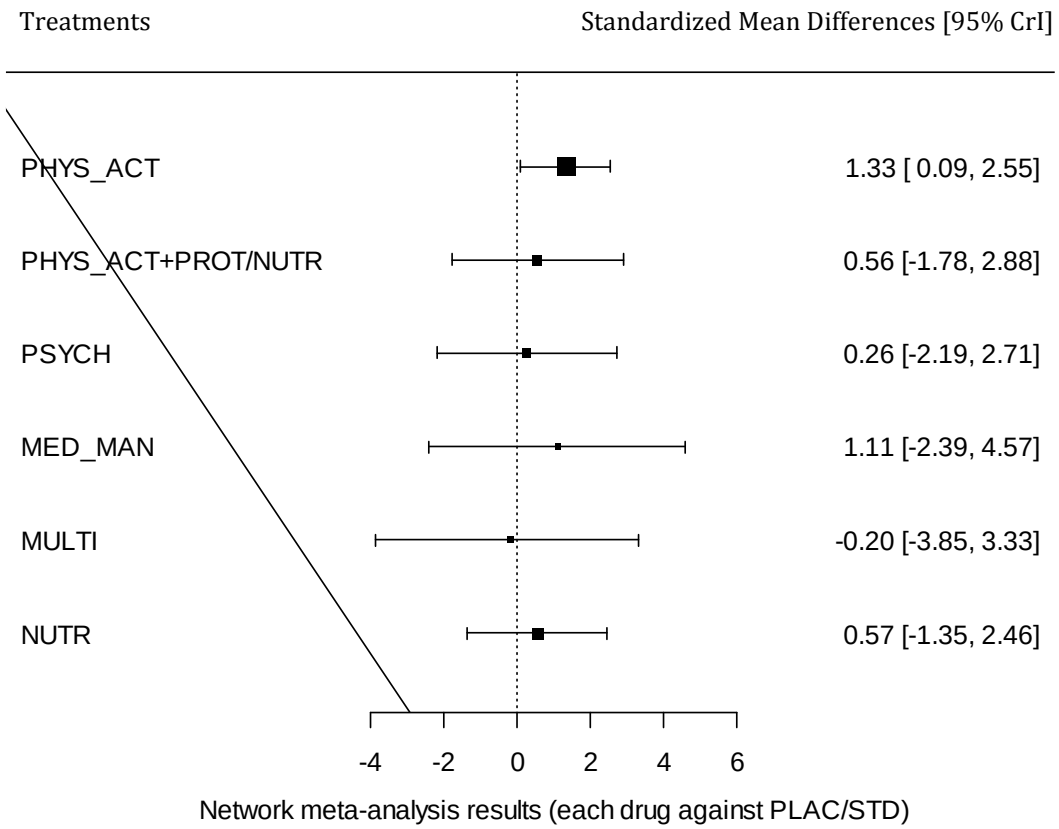
D- Quality of life- mental domain



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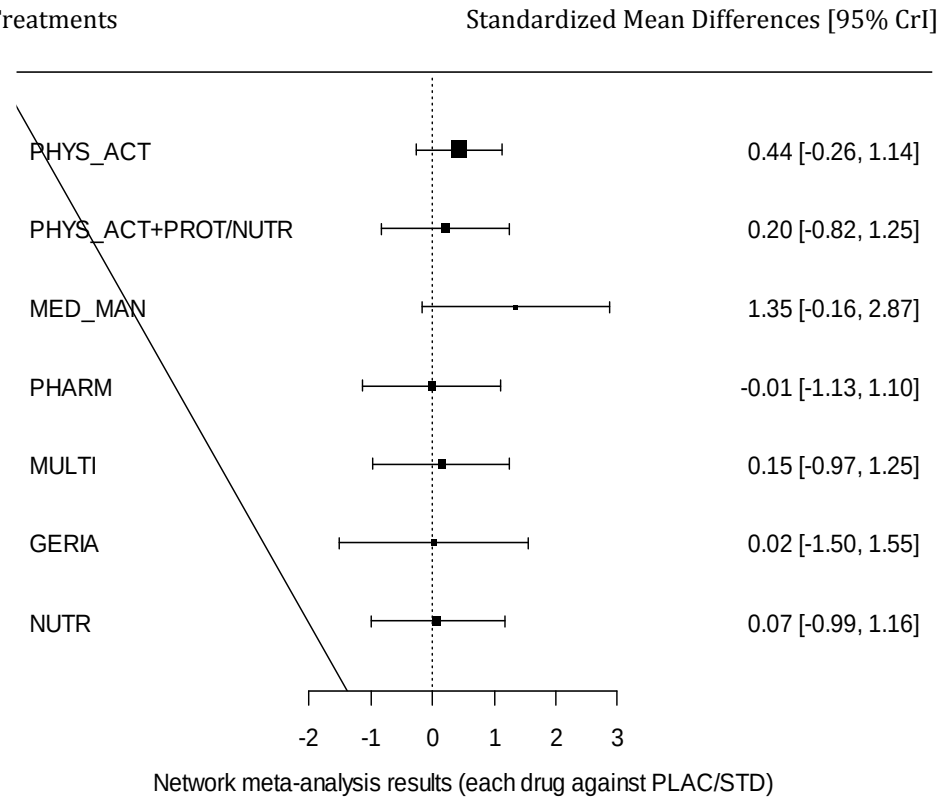
E- Cognition



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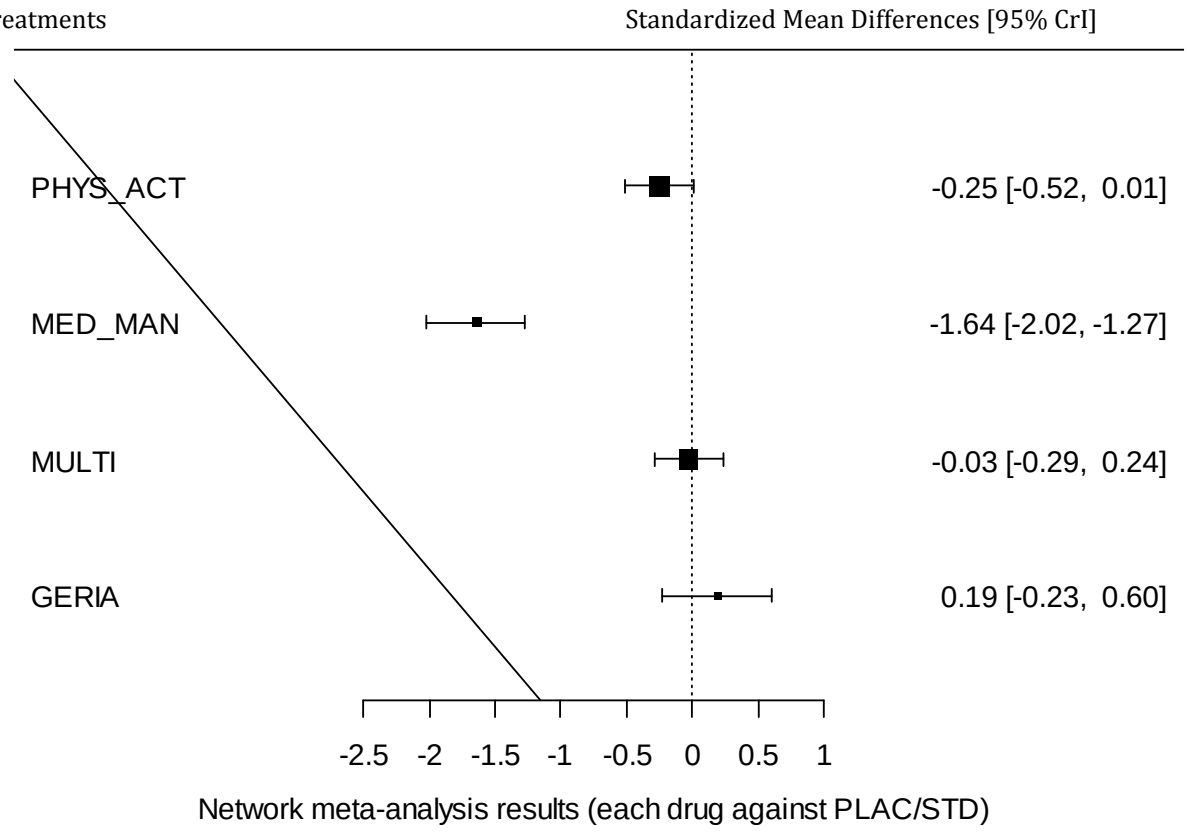
F- Depression



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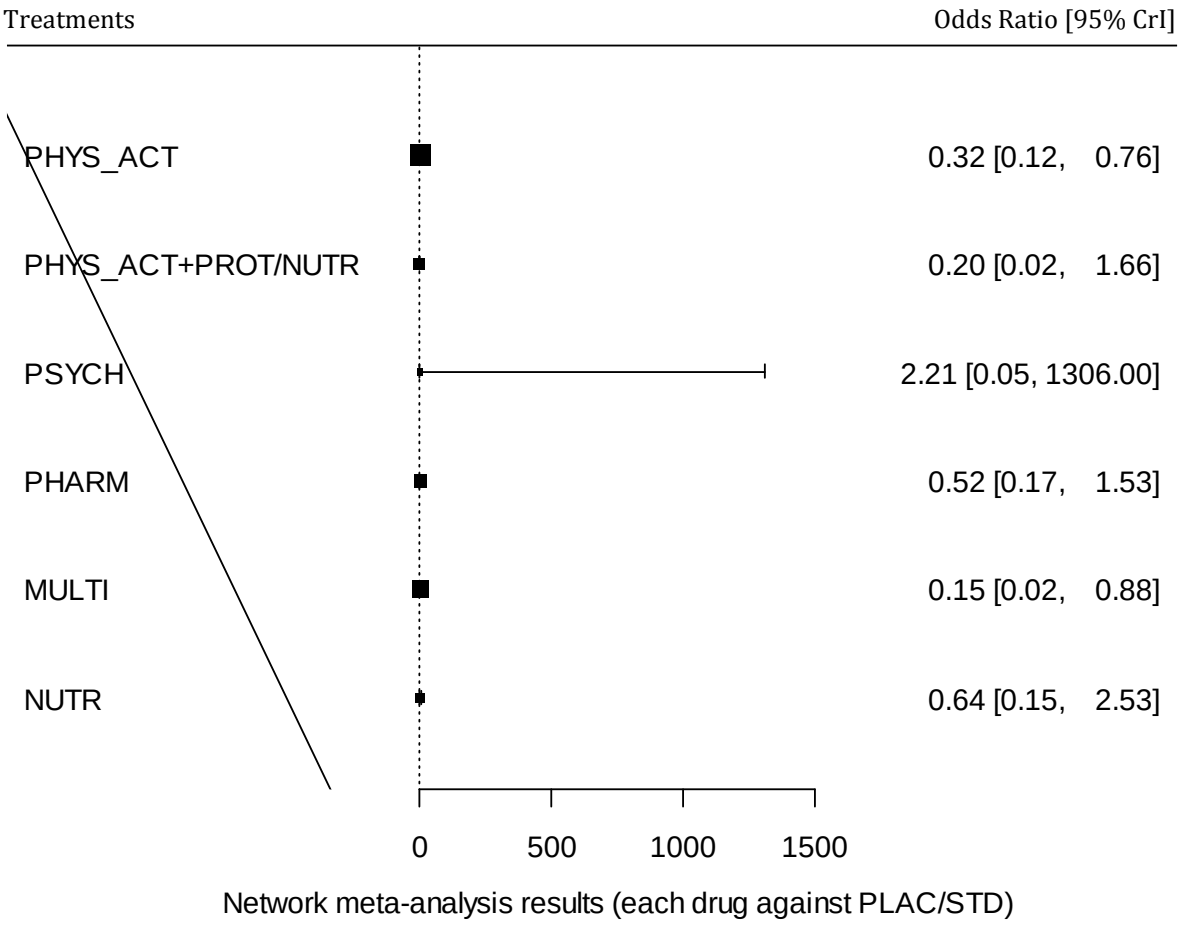
G- Adverse events



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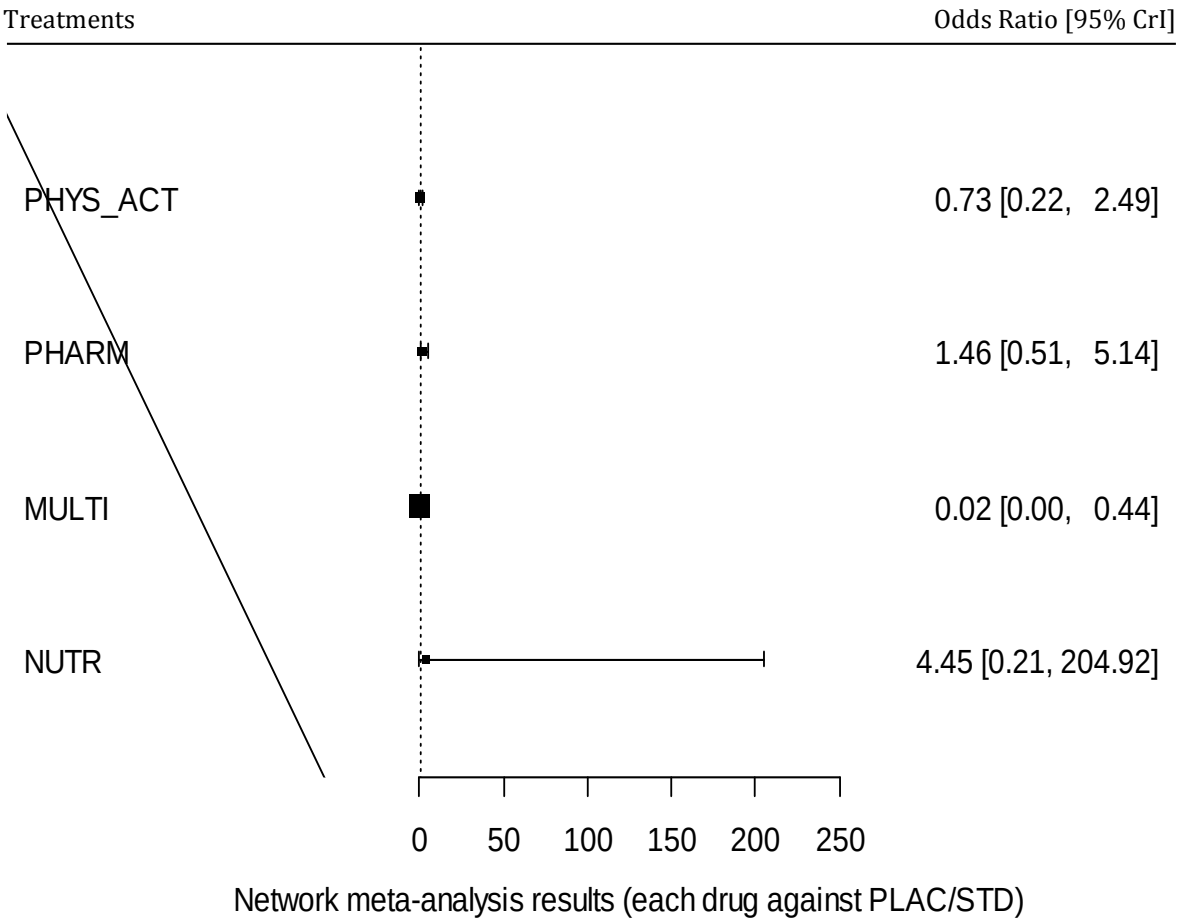
H- Serious adverse events



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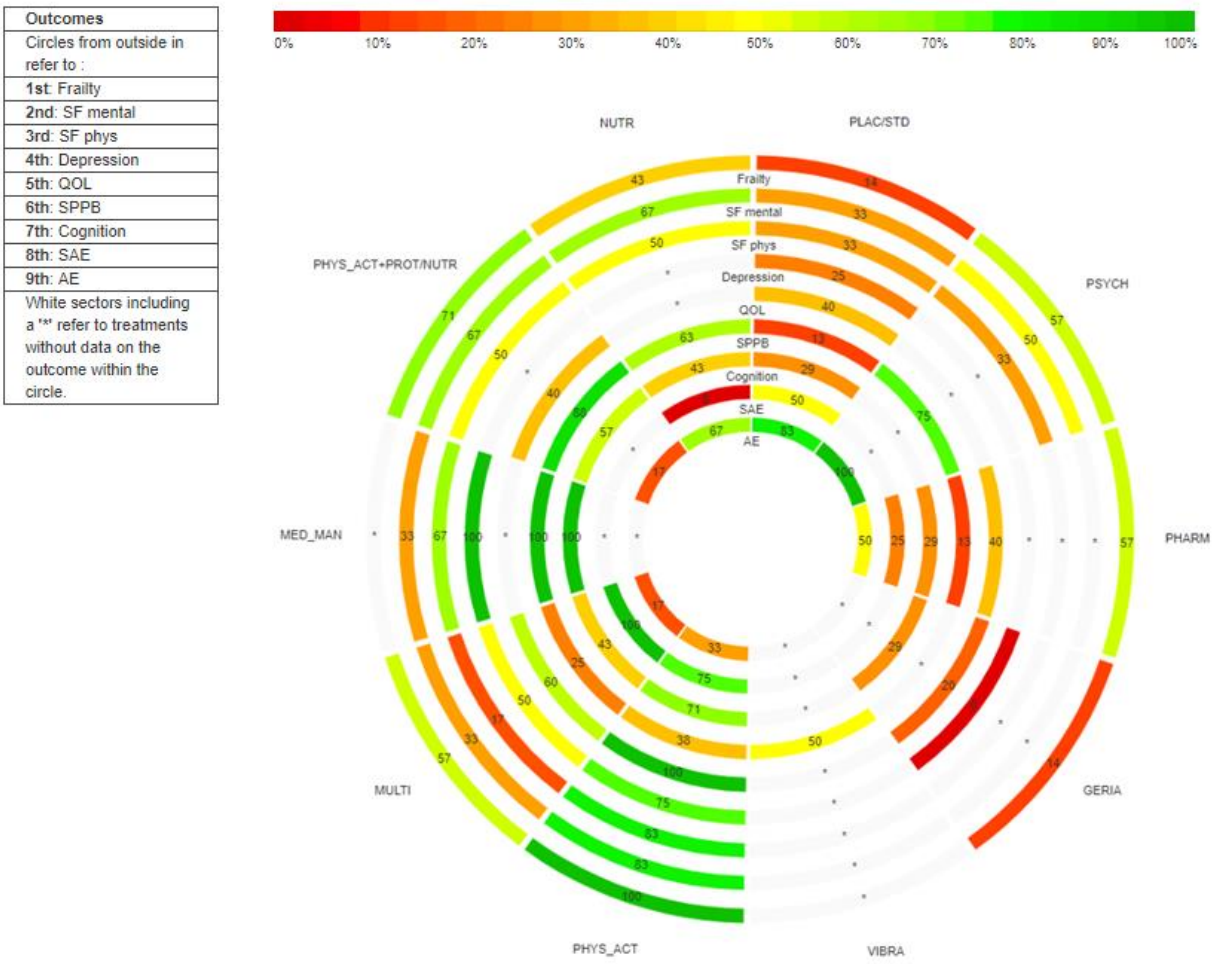
eFigure 3: Rank-heat plot All (consistent) outcomes



Each concentric circle represents a different outcome (as labeled), with the outermost circle representing the frailty, and the innermost circle representing adverse events. The scale bar represents the ranking statistic for each intervention using the P-scores, where 0% (red) indicates the lowest possible rank (worst treatment), and 100% (green) represents the highest possible rank (best treatment). Each rectangle represents an intervention and is coded using a letter outside the outmost circle (see treatment legend). The number within each rectangle represents the ranking statistic of the intervention for the particular outcome circle. See eTable 1 for the coding guide of the treatments.

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CHAPTER 4

Getting Fit for Hip and Knee Replacement: A Protocol for the Fit-Joints Pilot Randomized Controlled Trial of A Multi-modal Intervention in Frail Patients with Osteoarthritis

PREFACE TO CHAPTER 4

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4.1 Abstract

Background: Joint replacement provides significant improvements in pain, physical function and quality of life in patients with osteoarthritis. With a growing body of evidence indicating that frailty can be treated, it is important to determine whether targeting frailty reduction in hip and knee replacement patients improves post-operative outcomes.

Objectives: The primary objective is to examine the feasibility of a parallel group RCT comparing a preoperative multi-modal frailty intervention to usual care in pre-frail/frail older adults undergoing elective unilateral hip or knee replacements. The secondary objectives are:

1. To explore potential efficacy of the multi-modal frailty intervention in improving frailty and mobility between baseline and 6-weeks post-surgery using Fried Frailty Phenotype and Short Performance Physical Battery (SPPB) respectively.
2. To explore potential efficacy of the multi-modal frailty intervention on post-operative healthcare services use.

Methods: In a parallel group pilot RCT, participants will be recruited from the Regional Joint Assessment Program in Hamilton, Canada. Participants who are: 1) ≥ 60 years old; 2) Pre-frail (score of 1 or 2) or frail (score of 3-5; Fried Frailty Phenotype; 3) having elective unilateral hip or knee replacement; and 4) having surgery wait times between 3 to 10 months will be recruited and randomized to either the intervention or usual care group. The multi-modal frailty intervention components will include: 1) tailored exercise program (center-based and/or home-based) with education and cognitive behavioural change strategies; 2) protein supplementation; 3) vitamin D supplementation; and 4) medication review. The main comparative analysis will

take place at 6-week post-operative. The outcome assessors, data entry personnel, data analysts are blinded to treatment allocation. Assessments: feasibility will be assessed by recruitment rate, refusal rate, retention rate and data collection completion. Frailty and healthcare use and other clinical outcomes will be assessed. The study outcomes will be collected at the baseline, 1-week pre-operative, and 6-week and 6-month post-operative.

Discussion: This is the first study to examine the feasibility of multi-modal frailty intervention in pre-frail/frail older adults undergoing hip or knee replacement. This study will inform the planning and designing of multi-modal frailty interventional studies in hip and knee replacement patients.

Trial registration: ClinicalTrials.gov NCT02885337

Keywords: feasibility, frailty, phenotype, Fried, short performance physical battery (SPPB), hip replacement, knee replacement, rehabilitation, exercise, geriatrics.

4.2 Background

Osteoarthritis (OA) is one of the most common chronic condition worldwide and a major cause of morbidity, physical limitation, disability, and health care utilization (1, 2). In 2010, the aggregate cost of managing OA in Canada was $10.2 billion (3). It has been demonstrated that joint replacement provides significant improvements in pain, physical function and quality of life in patients with OA (4). In Canada, during 2015-16, there were approximately 53,000 hip replacements and 64,000 knee replacements representing a 5 year increase of 18.1% and 15.7 5%, respectively (6). It is expected that the number of older adults seeking total joint replacement will continue to rise (7).

Frailty is common in patients undergoing joint replacement (8) and refers to a medical syndrome characterized by "diminished strength, endurance, and reduced physiologic function" and with multiple causes and contributors (9). Pre-frailty is an intermediate stage between non-frail and frail. Adverse outcomes associated with frailty include increased risk for functional disability, hospitalization, fractures (10), admission to long-term care, and increased mortality (11-14). Frail older adults undergoing surgery are also more vulnerable to peri-operative stressors, and are at increased risk of post-operative complications, increased length of stay, and discharge to assisted living (15, 16). Recently, the Society for Perioperative Assessment and Quality Improvement recommended pre-operative frailty screening evaluation and management (17). With a growing body of evidence indicating that frailty can be treated (9) and improved (18), there is a need to examine whether targeting frailty reduction can improve the outcomes of pre-frail or frail adults who are undergoing joint replacement surgery.

Preparing patients for hip or knee replacement surgery through a prehabilitation model should be an integral part of the surgical care (19). A recent systematic review and meta-analysis (20) examined the impact of pre-operative physiotherapy on recovery after hip or knee joint replacement. Wang et al. pooled data from 22 RCTs (N=1492 patients, mean age ranged from 51-76 years) and found that exercise/education slightly reduced pain scores within 4 weeks post-operatively and improved scores on the Western Ontario and McMaster Universities Arthritis Index at 6–8 and 12 weeks. There was no difference in SF-36 scores, length of stay and total cost (20). Another systematic review and meta-analysis (21) aimed to determine the effect of pre-operative interventions (exercise with or without education program) in patient waiting for hip and knee replacement. Wallis et al. included 23 RCTs (N=1461 patients, mean age is 67.2 years) and concluded that exercise reduced pain for patients waiting for hip or knee replacement, and exercise with education programs improved activity after hip replacement (21).

Potential limitations of all the previous RCTs that examined pre-hip or knee replacement interventions include: 1) none of these studies identified prefrail or frail population, 2) none used multi-modal interventions, 3) the duration of the interventions ranged between 2-8 weeks in length (a longer intervention period may improve post-operative and long-term outcomes), 4) most participants were waiting for only knee (not hip) replacement, 5) most studies were at high risk of bias. For example Wang et al included 18 out of 22 studies with high risk of bias (20), thus, high quality RCTs are needed, and 6) most of the studies did not report critical outcomes such as frailty and treatment adherence (20).

Since, frail individuals are at greater risk of post-operative complications (15, 16), it is important to implement strategies to improve the "fitness" of frail patients pre-operatively. While previous studies with single interventions have demonstrated some effectiveness (15), multi-modal approaches have not been examined in individuals undergoing joint replacement surgery. International consensus guidelines (9) recommended an evidence-based multi-modal approach (including exercise, protein-calorie supplementation, vitamin D, and reduction of poly-pharmacy) to target frailty pre-operatively. The proposed study is a pilot RCT comparing a pre-operative multi-modal frailty intervention to usual care among pre-frail/frail patients undergoing unilateral elective total hip or knee replacement surgery. The current report outlines the research design and protocol for evaluating this pilot RCT.

4.3 Theory and development framework

The cycle of frailty model proposed by Fried et al 2001 (Figure 1), identified key elements of frailty (11). The core elements of the Fried Frailty Cycle incorporated the main frailty markers, including age-associated declines in lean body mass, strength, endurance, balance, walking performance, and low activity. The proposed intervention components aim to improve all the frailty markers of the Fried Frailty Cycle (11). As this is the first study to implement preoperative multi-modal intervention, a pilot study is required to assess the fidelity of intervention delivery and the feasibility of: 1) study process (recruitment and retention rate), 2) study resources (required time and budget), 3) management (study personal and data management), and 4) scientific (treatment safety, and estimation of potential treatment effect and its variance) (33).

4.4 Objectives

The primary objective is to examine the feasibility of a parallel group RCT comparing a preoperative multi-modal frailty intervention to usual care in pre-frail/frail older adults undergoing elective unilateral hip or knee replacement. The secondary objectives are:

1. To explore potential efficacy of the multi-modal frailty intervention in improving frailty and mobility between baseline and 6-weeks post-surgery using Fried Frailty Phenotype and Short Performance Physical Battery (SPPB) respectively.
2. To explore potential efficacy of the multi-modal frailty intervention on post-operative healthcare services use including hospital length of stay, rate of complication after hip or knee replacement, readmission to the hospital and number of emergency room (ER) visits.

4.5 Methods

Study Design

Fit Joints study is a pilot parallel group RCT comparing a 3-10 months, pre-operative multi-modal frailty intervention and usual care among pre-frail/frail patients undergoing total hip or knee replacement surgery.

The main group comparisons will occur at 6-weeks post-operative. Both groups will also be assessed at 6-months post-operative. The trial has been registered with Clinical

Trials.gov NCT02885337. We used the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines to guide the reporting of our trial protocol (22). A SPIRIT Checklist is provided as Additional file 1, and a flow diagram is included as Figure 2.

Study Setting

We are recruiting participants from the Regional Joint Assessment Program (23) (RJAP) at a tertiary care academic hospital (Juravinski Hospital) of Hamilton Health Science- Hamilton, Ontario, Canada. RJAP program serves patients with arthritis referred from primary care physicians to be assessed for hip or knee joint replacement by advanced practice physiotherapists (APPs) (physiotherapist with a special orthopaedic training) and orthopaedic surgeons (23). After recruitment, the intervention will take place in a community setting, including the participant's home and community centers.

Eligibility Criteria

Participants will be included if they are: 1) ≥ 60 years old; 2) pre-frail (score of 1 or 2) or frail (score of 3-5; Fried Frailty Phenotype (11)); 3) receiving elective unilateral hip or knee replacement; and 4) waiting time to surgery is estimated to be between 3 to 10 months. Participants will be excluded if reported having: 1) renal insufficiency (due to potential contraindication of additional protein); 2) neuromuscular disorder; 3) active cancer; or 4) any inflammatory arthritis.

Recruitment Strategy

After the APPs and orthopaedic surgeons assess patients referred for hip or knee problems, APPs will explain the study, invite potential participants and screen them for eligibility. A research assistant will help the APPs in administering the Fried Frailty Phenotype. If eligible participants are considering the study and need time to decide, they receive the study information sheet and will be contacted by a research assistant to confirm their participation. The clinic administrators (who are blinded to the patient participation in the study) place the patients in the surgery wait list and assign them a surgery date later.

Randomization and Consent

Once the study research assistant confirms the patient's eligibility, and obtains informed written consent, the research assistant will submit the eligibility form, consent form and participant contact form to a team member (who is not part of the study) who will randomize the participant to the intervention or usual care group based on stratified block randomization list (blocks of 2). To ensure an equal number of participants in the study groups, the allocation ratio will be 1:1. Participants will be stratified based on their age (≥ 80 or ≤79 years) and approximate waiting time (≥ 6 or <6 months). The allocation sequence will be computer generated using SAS 9.3 software (24). To conceal the sequence, only a researcher who is not involved in the study will have the computer-generated allocation list.

After randomization, a blinded outcome assessor will contact the participants to set up an appointment for the baseline assessment. After the baseline assessment, the study research coordinator will inform the participants of their study group. The intervention group participants will be contacted by the study intervention kinesiologist to arrange the first intervention visit.

Those blinded to the intervention will include: the outcome assessors who conduct assessments at the RJAP and in participant homes, the clinic administration, data entry personnel, data analyst who performs the final data analysis, the investigative team and members of the steering committee. The patient will also be blinded at the baseline assessment. The study co-ordinator, study intervention kinesiologist and participants will not be blinded.

Development and piloting the Fit Joint intervention

Due to the complexity of the frailty syndrome, we are developing the proposed multi-modal frailty intervention using the revised Medical Research Council framework for design and evaluation of complex interventions (25, 26). The FIT trial in Australia, demonstrated successful frailty reduction after implementing a 1-year frailty intervention, tailored to each participant based on comprehensive geriatric assessment. The target cohort was frail patients (3 or more Fried criteria) seen in an aged care service (18).

Multi-Modal Fit Joint Intervention Components

The intervention and outcome assessment visits are summarized in figure 3.
Participants in the intervention group will receive, for up to 10 months, a multimodal program intended to target frailty reduction (As described in **table 1**) between randomization and their surgery. The study intervention kinesiologist will manage the coordination of the exercise components of the intervention, and deliver vitamin D and protein supplementation. The study geriatrician will provide the medication review component and two of the study investigators who are expert in nutrition will review the vitamin D and protein supplementation.

Kinesiologist Visit Schedule & Delivery of Coaching/Supplements

After randomization, the study intervention kinesiologist will telephone the participant to book a home visit where goal setting will be done. During months 2-10, the study intervention kinesiologist will have bi-weekly contact (one monthly visit and one phone-call in the interim) (27) to check on progress. At the visits, the kinesiologist will adjust programs as needed, provide ongoing coaching/education, and deliver vitamin D/protein supplements. We will use exercise-reporting guidelines (CERT) to guide reporting of the exercise component of the intervention (28). Participants will be encouraged to use the Borg Rating of Perceived Exertion 10-point Scale to monitor their perceived effort levels and exhaustion for each exercise component (1 means rest/no effort and10 means maximal effort) (29). Participants will be asked to work in a 5-7/10 workload (i.e., 50-60% of their maximal heart rate). The Borg Scale will help participants to work based on how they are feeling, which is safer for the geriatric population. In the first intervention visit, the study kinesiologist will ask the participants if they would prefer to do center-based or home-based exercise, or both.

Center-based exercise

If a participant decides to do center-based exercise, they will be provided with a free membership of the YMCA community center to participate in the "InMotion program". This community-based program is designed for people with chronic bone and joint health problems such as osteoporosis and arthritis. It is also appropriate for those wanting to improve their health before and after having hip or knee replacement surgery. Fitness trainers lead the InMotion program and if needed, an experienced physiotherapist is available for consultation. The program includes hydrotherapy, aerobic exercise and 12 education sessions. Participants will be

encouraged to attend the InMotion program components at least 3 times per week. Additional file 2 shows further description of the Fit Joints exercise.

Cognitive Behavioural Change Strategies (CBCS)

The participant's readiness to exercise and their exercise barriers/facilitators will be determined using a self-reported questionnaire guided by the trans-theoretical model of behaviour change (TTMBC) (30, 31). Based on the participant's readiness to exercise, CBCS may be an effective way to promote exercise in older adults (32). In the current study, the administration of the modules will be dependent on the challenges that the participants express using the exercise barrier/facilitators questionnaire (i.e., lack of time, motivation, social support, etc.). These strategies are based on the TTMBC (30, 31). The seven CBCS topics that will be incorporated over the intervention period will include: 1) goal setting: to assist with the development of their tailored exercise program, 2) self-monitoring: to track their exercise progress/goals/behaviour, 3) time management strategies: to find more time to exercise, 4) overcoming barriers: to overcome adversity in exercise routines, 5) environmental scan: to help participants identify local/available resources and support, 6) social support: to find participants' support system to achieve physical activity, and 7) stimulus control: to create participants' planned reminders for increasing physical activity.

Control group

Patients in the control group will receive usual care, which may include recommendations from their orthopedic surgeon to attend exercise programs, fitness and educational classes, physiotherapy referral, pool therapy, or weight loss program before surgery.

However, these patients will not receive any support from the study intervention kinesiologist. Participants in the control and intervention groups will be instructed to complete a dietary intake log (including days of the week and weekend days) that indicates the type of food and amount ingested over a four-day period in order to calculate energy and micronutrient consumption.

Study outcomes

Primary outcome: Feasibility

Feasibility will be assessed by 1) recruitment rate, 2) refusal rate, 3) retention rate and 4) data collection completion (33). Figure 2 summaries the primary and secondary outcomes and measurement time. The Fit Joint Intervention fidelity (the degree to which the Fit Joint intervention is delivered) will be assessed by measuring the length of the intervention and number of intervention components delivered by the study kinesiologist. We will measure participants' adherence to each component of the intervention (centre-based or home exercise, protein and vitamin D supplement, and medication review). Adherence will be measured by a monthly self-reported form developed specifically for the Fit Joint Trial.

Secondary outcomes:

Frailty will be assessed using: 1) Fried Frailty Phenotype which is composed of 5 items, 3 self-reported (unintentional weight loss, exhaustion and physical activity) and 2 performance-based items (strength (assessment based on the handgrip strength measurement) and gait speed). It is a widely used and validated frailty measure (11, 34). Each item is scored 0 or 1 with a final score out of 5; higher scores indicate greater frailty; and 2) Short Performance Physical Battery (SPPB) (made up of 3 assessments (35): a) the 4-meter walk test (walking speed); b) chair rise:

balance and coordination (the ability to rise from a chair without arms); and c) the standing balance test). The participant is evaluated on each assessment using a score between 0 and 4. A final summary performance score out of 12 is calculated, with higher scores indicating superior lower extremity function (35). The SPPB has also been validated and has demonstrated good internal consistency and responsiveness (36, 37). Healthcare service use (including patients' medications/supplements (dose, frequency, and duration), discharge destination, length of hospital stay, rehospitalisation rate, number of visits to general practitioner, emergency room, specialists, and physiotherapist, and number of home exercise sessions) will be collected using a form specifically developed for this study. Other outcomes listed in Figure 2 will be collected. The study outcomes will be collected at the baseline, 1-week pre-operative, and 6-week and 6-month post-operative.

Adverse events

Adverse events or harm from any source will be reported to the research team and recorded on a structured form. Any serious adverse events will be reported to the Research Ethics Board within 24 hours. Participants will be instructed to contact the study coordinator if they experience any unfavourable/unintended signs or symptoms. An independent Data Safety and Monitoring Committee will review safety data from the trial and advise the investigators and the Steering Committee on the future management of the trial.

Data collection and management

Figure 2 provides an overview of the data collection time-line. The baseline and 1-week preoperative assessments will be conducted in the participant's home and the 6-week and 6-

month assessments will be conducted in the orthopedic clinic. All four assessments will be conducted by blinded assessors. The study assessors will receive an individualized three-day training on how to collect the study outcome measures from frail older adults. Study data will be managed using REDCap electronic data capture tools (38). The study database will be password protected and kept on a secure network system.

Trial management

The coordinating centre for the study is at the Geriatric Education and Research in Aging Sciences (GERAS) Center, Hamilton Health Sciences. The study coordinator and research assistants will be responsible for submitting and maintaining REB documents, scheduling of home visits, receiving and storing consent forms. The study Steering Committee will meet every 6 months to provide overall supervision of the trial. The research coordinator will call more frequent Steering Committee meetings if required. It is anticipated the final results of this study will be completed in 2018.

Data Analysis

Data from the trial will be analyzed and reported in accordance with the CONSORT criteria (33, 39). The baseline characteristics will be reported as mean (standard deviation) or median (inter-quartile range) values for continuous variables and as counts (percent) for categorical variables. Data will be summarized in tabular or graphical form. The main between-group comparison will take place at 6-weeks post-operative. The primary feasibility outcomes will be analyzed using descriptive statistics expressed as percent and corresponding 95% confidence intervals (CI). For clinical outcome, analyses will be performed using the intention-

to-treat principle. We will use linear regression for continuous variables and logistical regression for categorical variables to explore the difference between groups pre- and post-operative. Exploratory subgroup analyses will be conducted to explore the differential effect of home-based versus centre-based exercise and the effect on people undergoing hip versus knee replacement. Sensitivity analysis will be conducted using the per-protocol concept (including adherent participants, who completed 70% of the intervention components (i.e. completed 70% of exercise sessions, took 70% of the vitamin D, protein supplements and the medication review was done)) (40). All *p* values will be reported to three decimal places with those less than 0.001 reported as $p < 0.001$. The criterion for statistical significance will be set *a priori at* alpha = 0.05. Analyses will be performed using STATA V13 (41).

Sample size

The sample size calculation was conducted using PASS software (Kaysville, Utah) and was based on the feasibility outcomes of 80% for screening, retention, and data completion (33). We will need a sample size of 62 participants to produce a two-sided 95% confidence interval with a width equal to ± 10% and an 80% criterion for success.

Ethical considerations

The study was approved by the Hamilton Integrated Research Ethics Board (File #: 2017-1565). Participants will undergo an informed consent process and sign a consent form prior to randomization.

4.6 Discussion

This is the first study to examine the effect of multi-modal frailty intervention in frail and/or pre-frail older adults undergoing hip or knee replacement. We conducted a literature search in Medline database using frailty, hip or knee replacement and randomized controlled trial as key words and we did not find any multi-modal frailty intervention trials. Given this is a pilot study, we will learn about the feasibility of applying this multi-modal frailty intervention in people waiting for hip or knee replacement surgery.

The study intervention will increase the engagement of community resources (such as YMCA centre-based exercise) by older adults, which will contribute to the older adults' community participation and sustainability of the Fit Joints intervention. We hypothesize that a multi-modal intervention targeting exercise, vitamin D and protein supplementation, and a reduction of poly-pharmacy will synergistically improve pre and post-operative frailty status and physical function in pre-frail/frail patients undergoing hip or knee replacement surgery. The results of this pilot trial will inform the design and implementation of a subsequent multi-center trial.

The duration of the Fit Joints intervention will vary according to the surgery waiting time, which addresses practical questions about the risks, benefits, and costs of an intervention as they would occur in routine clinical practice (42), rather than in an ideal setting. The Fit Joints study design emphasizes the contextual factors and real-world applicability of the study (43). Also, Fit Joints intervention and outcomes are relevant to clinicians, patients, and decision makers. Frailty is associated with higher complication rate; readmissions and longer hospital stay

after hip or knee replacement surgery (8). Carrying out the Fit Joints pilot trial is critical to see if a definitive multi-centre trial can determine the effect of the Fit Joint intervention on pre-operative frailty, post-operative outcomes and complication and health services use after hip or knee replacement surgery.

Medical Research Council criteria define a "complex intervention" as interventions that are built up from a number of components, which may act both independently and inter-dependently (44). These components include behaviours, behaviour parameters and methods of organizing those behaviours, and they may have an effect at the individual patient level, organizational or service level or population level (or all of these in some cases). As any complex intervention, the Fit Joints intervention has several articulating components (including, centre and/or home-based tailored exercise program, cognitive behavioural coaching, protein and vitamin D supplements and medication review). It is a challenge to 1) standardize all these intervention components and 2) determine the contribution of each intervention component and any interaction between these components (25). Phase 0 (Choosing an intervention theoretical model) and phase 1(identify the intervention components and the supporting evidence) of the Medical Research Council framework have been completed. The proposed study represents phase 2 of the Medical Research Council framework (which is examining the feasibility of the intervention). After completing this pilot study, we will complete phase 3 (definitive study) and phase 4 (dissemination and implementation).

The proposed study has some limitations. Participant recruitment will take place within one hospital site, which may limit its generalizability to other hospital care settings. Fit Joints

investigators have considered the challenge of applicability to other settings during the study protocol development. Participants will be offered to do center-based or home exercise; however, some participants may not have access to the center-based exercise due to various reasons such as lack of time or transportation. Also, the pre-operative assessments will occur in different time points for different participants due to the variable intervention duration and that might lead to heterogeneity of the intervention effect across participants.

Strengths of our proposed study include: 1) valid and reliable patient reported measures were used; and 2) Fit Joints study engaged all key stakeholders in the process of implementation, including patients, interdisciplinary healthcare teams, community organizations and researchers. Having each perspective will enhance the participants experience throughout the study course.

The lessons learned from this pilot RCT will be helpful when planning and designing future frailty studies and will provide a better understanding of pre-operative frailty and surgical outcome. This includes insights on the study implementation process (e.g., participants' recruitment and retention), resources (time and budget issues), management (personnel and data management issues), and scientific evidence (effect sizes) (33).

Trial status

Participants are currently being recruited. Recruitment will be completed approximately on April 2018.

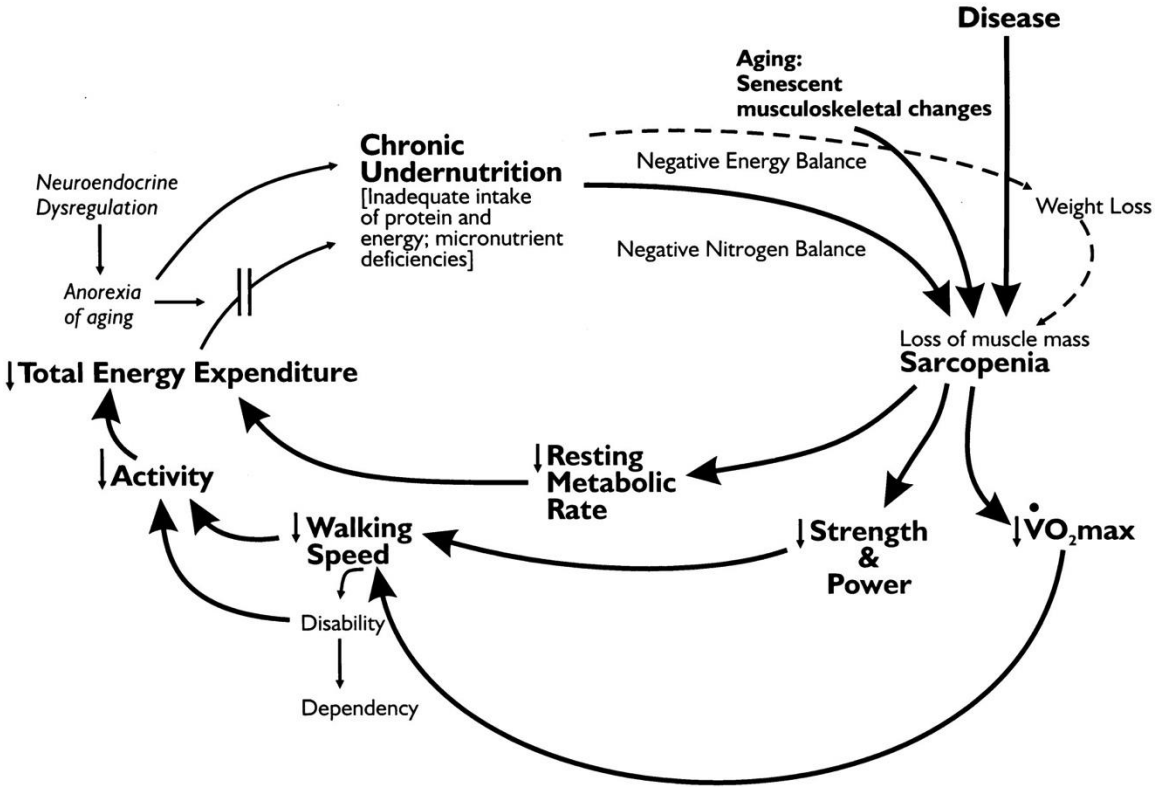
Table 4-1: Components of the Multimodal Intervention

Component	*Dose/Material Provided*	*Description*
Exercise & Coaching	Based on Canada's Physical Activity Guidelines[1] Minimum: 3x week for 45-60 minutes at home and/or YMCA (27, 44)	• Kinesiologist Assessment: Goal setting, Cognitive Behaviour change strategies[2] • *HOME:* Tailored exercise program based on individual ability and exercise preference (i.e., chair versus standing exercises). Functional movements to mimic ADL's (i.e., getting up from a chair). Exercise bands will be provided. • All participants will progress based on their current physical activity levels while focusing on personal fitness and health goals set at the beginning of the program. • *YMCA: InMotion program* • GOAL: endurance, resistance, and balance training 3x week for 45-60 minutes at home and/or YMCA • Monthly Kinesiologist Visit/Bi-weekly phone-calls (27). • Participants will track their exercise in a study-tracking logbook.
Protein	1-2 Ensure Enlive™ protein daily	• Each serving (vanilla or chocolate flavor) contains 350 kcal, 20-gram protein, 1.5 g β-Hydroxy β-Methylbutyrate (HMB) • Advised to take the protein supplement with a meal or within 3 hours of exercise on activity days (31, 32). • Pre-albumin serum level tested at the screening and 6-week postoperative visits (carried out by the clinic nurse during these visits).
Vitamin D	1x1000 IU/day, unless prescribed otherwise by Family Physician.	• proVitamin D3 (1000 IU tablets) • Serum 25 (OH). Vitamin D serum level tested at the screening and 6-week postoperative visits.
Medication Review		• A pharmacist trained geriatrician (Dr. Lee) will review the medications of participants in the intervention arm using subsets of Beers (45) and STOPP/START criteria (46) to check for any inappropriate medications.

		• Any recommendations will be mailed/faxed to the participants' family physicians for their consideration by the central site coordinator.

[1] *Based on Canadian Physical Activity Guidelines for those aged 65 years or older which recommend cardiorespiratory, strength, balance, and flexibility exercise components (24).*
[2]*Topics to support patients in achieving their health goals could include 1. Goal Setting, 2. Self-Monitoring, 3. Time Management, 4. Overcoming Barriers, 5. Environmental Scan, 6. Social Support, and 7. Stimulus Control.*

Figure 4-1: Cycle of frailty



Reproduced with permission from (18).

Figure 4-2: Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) Schedule of enrolment, interventions and assessments

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
TIMEPOINT	Screening		Baseline Assessment	1-week Pre-operative Assessment	6-week Post-operative Assessment	6-month Post-operative Assessment
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Study Intervention			←	—	→	
Standard Care			←	—	→	
ASSESSMENTS:						
Primary Outcome: Feasibility						
Proportion of recruited patients*			X			
Recruitment Rate**			X			
Refusal Rate*			X			
Retention*			X			

Data Collection completion*			X			
Secondary Outcomes						
Fried Frailty Phenotype		X	X	X	X	X
GERAS Fit Frailty Index		X	X	X	X	X
Shot Physical Performance Battery			X	X	X	X
Length of stay after surgery					X	X
Length of stay - rehabilitation					X	X
Surgical Complications					X	X
Readmission to hospital					X	X
Number of ER visits			X	X	X	X
Other variables						
Oxford Hip or Knee Score	X		X	X	X	X
Sarc-F			X	X	X	X
EQ-5D			X	X	X	X
Mini-cog			X	X	X	X

Self-reported Falls			X	X	X	X
Height			X	X	X	X
Weight			X	X	X	X
Medications and supplements			X	X	X	X
Discharge destination					X	X
Number of GP visits / walking clinic			X	X	X	X
Number of specialist visits			X	X	X	X
Number of physiotherapy sessions after surgery					X	X
Number of home exercise sessions after surgery					X	X

* = Hypothesis/Criterion is ≥80%; ** = Hypothesis/Criterion is 4 patient/month.

Figure 4-3: Study Intervention and outcome assessments

	Intervention	Control
Screening		
Usual care in the RJAP Clinic	□	□
Randomization		
Baseline Assessment (t_0)	□	□
Week 0 (Intervention Visit 1)	□	
Week 1 (Intervention Visit 2)	□	
Week 2 (Phone call 1)	○	
Week 4 (Intervention Visit 3)	□	
Week 5 (Phone call 2)	○	
Monthly visit till surgery	□	
Bi-weekly phone call till surgery	○	
Pre-operative assessment (t_1)	□	□
Surgery		
6 week post-operative assessment (t_2)	□	□
6 month post-operative assessment (t_3)	□	□

RJAP: Regional Joint Assessment Program

☐	Potentially referred to • InMotion • Physiotherapy • Home exercise • Weight loss program • Knee braces • Family doctor
☐	• Baseline assessments (t_0)
☐	• Introduction to the study education modules and resources • Introduction to center-based physical activity: YMCA Inmotion Program • Applying exercise barriers questionnaire to tailor the cognitive behavioural change strategies • Exercise goals setting • Protein/vitamin D distribution with tracking sheet
☐	• Review of exercise Importance • Home exercise prescription
◯	• Bi-weekly adherence check in
☐	• Cognitive behavioural change strategies • Review and modify exercise • Complete monthly protein/vitamin D /exercise adherence questionnaire • Protein/vitamin D distribution with tracking sheet
☐	• Pre-operative assessment (t_1)
☐	• 6 week post-operative assessment (t_2)
☐	• 6 month post-operative assessment (t_3)

4.7 References

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4.8 Additional file 1: SPIRIT Checklist.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____4_____
	2b	All items from the World Health Organization Trial Registration Data Set	____1,4-8, 10, _
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	___10_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1_____
	5b	Name and contact information for the trial sponsor	_____1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____10_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____7_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-6

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7-8
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7-8
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7-8

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____5_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____10_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

4.9 Additional file 2: Detailed description to the Fit Joints exercise.

Participants will be encouraged to progress on all components of exercise: cardiovascular, muscular strength, balance and flexibility. All exercises are prescribed based on the recommendations from the Canadian Physical Activity Guidelines for older adults 65+ (Tremblay, et al., 2011). Participants will be encouraged to use a rating of perceived exertion to monitor their perceived effort levels and exhaustion for each exercise component (Borg, 1982). All participants will progress based on their current physical activity levels while focusing on personal fitness and health goals set at the beginning of the program.

Cardiovascular – participants are encouraged to obtain 150 minutes of moderate to vigorous physical activity per week in bouts of ten minutes or more. Participants will progress in 3 ways: i. increase the number of minutes per week or session, ii. Increase the intensity (30%-70%), or iii. Increase the number of days performing the exercise per week.

Muscular strength – participants should complete a minimum of 2 days of strength training per week with at least one exercise per major muscle group (i.e. chest, back, etc.). To progress, participants will increase the number of repetitions and/or sets as well as increase the level of the resistance band (i.e., light, medium, heavy). Participants can also progress by increasing the number of days per week they complete the exercises.

Balance – participants will be encouraged to complete regular balance training, these types of exercises can be performed daily to prevent falls or loss of balance. Participants will progress by increasing the level of difficulty for each exercise. Participants may progress from a stationary exercise (i.e., standing in one spot) to a dynamic exercise (i.e., tandem walking). Further, participants can be challenged by closing their eyes, if they feel safe doing so.

Flexibility – participants will be encouraged to complete daily flexibility exercises to preserve range of motion. Participants will progress by increasing the number of days they partake in this component as well as how long they hold each stretch for. Lastly, participants can progress by increasing the number of stretches or major muscle groups involved.

References

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Med sci sports exerc*, *14*(5), 377-381.

Tremblay, M. S., Warburton, D. E., Janssen, I., Paterson, D. H., Latimer, A. E., Rhodes, R. E., ... & Murumets, K. (2011). New Canadian physical activity guidelines. *Applied Physiology, Nutrition, and Metabolism*, *36*(1), 36-46

	F	I	T	T
Exercise Type*	**F**requency: Times/week	**I**ntensity: Rating of perceived exertion	**T**ype: Equipment	**T**ime: Duration/Sets
Cardio	**Beginner** 2-3x/week **Moderate** 4-5x/week **Challenging** 6+x/week	**Beginner** 3-4 RPE **Moderate** 5-6 RPE **Challenging** 7-8 RPE	**Beginner** Walking, leisure Swimming, Cycling **Moderate** Brisk walking, pole walking, Aqua-Fit **Challenging** Jogging, Racquet sports, golf	**Beginner** 5 -10 mins **Moderate** 10-30 mins **Challenging** 30+ mins
Strength	**Beginner** 2x/week **Moderate**	**Beginner** Yellow **Moderate**	**Beginner** Seated exercises **Moderate**	**Beginner** 1 set of 15 reps **Moderate**

	3x/week **Challenging** 4-7x/week	Green **Challenging** Red, Purple	Standing exercise/functional exercises **Challenging** Dynamic standing exercises	1-2 sets of 8-15 **Challenging** 1-2 sets of 10-15
Balance	**Beginner** 2-3x/week **Moderate** 3-4x/week **Challenging** 5-7x/week	**Beginner** Level 1 – stationary **Moderate** Level 2 – eyes closed stationary **Challenging** Level 3 - dynamic	**Beginner** Holding on to a chair/counter **Moderate** Without holding on to supports **Challenging** Without holding supports and	**Beginner** 5-10 secs **Moderate** 10-20 secs **Challenging** 30+ secs
Flexibility	**Beginner** 2-3x/week **Moderate** 3-4x/week **Challenging**	**Beginner** 5 secs/stretch **Moderate** 6-15 secs/stretch **Challenging**	**Beginner** 1 stretch per major muscle groups **Moderate** 1-2 stretches	**Beginner** 5-10 mins **Moderate** 10-30 mins **Challenging**

	5-7x/week	16-20 secs/stretch	**Challenging** 3 stretches	30+ mins

Exercise Type* see Additional file 2 for descriptions.

Participant Exercise Options

	YMCA	***Home***
Supervision & Qualifications	Certified Fitness Instructors, Registered Physiotherapist (Who instructs the Education Series).	Registered Kinesiologist with 5+ years' experience with special populations and exercise prescription.
Setting	Community, group exercise, class setting (~20-30 people/class)	Home setting (1-2 people if partner or family support)
Consultation Points	Available to address questions/concerns at each exercise session	The Kinesiologist checks in once per month to review, progress, and/or change exercises.
Specific/Tailored	Group environment, exercises are presented with exercise options (beginner or advanced) – participants are encouraged to complete the exercise intensity or challenge that is most appropriate for them.	Exercising on their own at home. Participants are encouraged to complete an exercise intensity that is appropriate for them, using pain as their guide (monitoring how the participant feels during and after exercise).
Warm-up & Cool-down activities	5-10 minutes to elevate heart rate. The goal is to increase overall ROM. Cool-downs will consist of a goal to bring heart rate back to normal (pre-exercise HR), in addition to static stretches of the major muscle groups.	

Participant Exercise Familiarization/ Experience	If participants are new to the exercises they are supervised closely to ensure proper technique and safety. If exercises are too challenging or painful to complete, a modified movement to engage similar muscle groups will be demonstrated to the participant.	
Exercise Order	Warm-up, main exercises, cool-down	
Rest periods	30 seconds to 1 minute will be encouraged between exercises. Depending on participant's current fitness levels, rest times will be longer for beginners until cardiovascular capacity has increased. As participants progress, rest periods will be shorter in duration.	
Baseline fitness levels	All participants are encouraged to slowly and cautiously progress with the amount of exercises they complete and to take breaks as needed.	
Motivation & support	Encouraged and supported throughout the exercise sessions by fitness instructors. Instructors are always available for questions as needed by the participants.	Participants are positively encouraged throughout the intervention with a monthly visit to review goals, and bi-weekly check-ins to address questions or concerns.
Adverse Event documentation and reporting	If an event occurs that is serious in nature, the YMCA records and follows YMCA safety and first aid protocols.	Participants report all AE's and fall to research assistants at monthly checkpoints.

CHAPTER 5

IMPACT OF THE HEALTH TAPESTRY APPROACH IN PRIMARY CARE ON CAREGIVERS AND NON-CAREGIVERS- SUBGROUP ANALYSIS OF RANDOMIZED CONTROLLED TRIAL

PREFACE TO CHAPTER 5

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5.1 Abstract

Background

Caregiving may lead to unfavorable health-related outcomes. Studies examining a primary care approach to identify and support caregivers are lacking. Our primary objective of this study was to determine if caregiver status (caregiver vs. non-caregiver) modified the effect of a complex intervention to promote optimal aging through the support of technology, community volunteers, an inter-professional healthcare team, and system navigation and better links between primary care and community organizations on quality of life, social support, hospitalizations and ED visits.

Methods

This is a subgroup analysis of a delayed pragmatic randomized controlled trial. Participants included rostered patients of McMaster Family Health Team who were ≥70 years and living in the community. The baseline characteristics of participants were collected. Self-report measures of quality of life, social support, hospitalizations and ED visits were assessed at baseline and at 6 months.

Results

There were no differences between caregivers and non-caregivers in quality of life, social support, hospitalization, and ED visits at 6-month follow-up.

Conclusion

A primary care team was able to identify older adults with caregiver roles, however, there

was no evidence that the Health TAPESTRY approach resulted in decreased caregivers' ED visits or hospitalizations or improved quality of life, social support satisfaction and interaction during the study follow-up period. Also, the effect of the Health TAPESTRY approach was not statistically different between caregivers and non-caregivers. Further exploration of models to identify and support caregivers in primary care settings is needed.

Keywords: Informal caregivers, frailty, caregiver, primary care, quality of life, hospitalization.

Trial registration: ClinicalTrials.gov NCT02283723. Registered 5 November 2014

5.2 Introduction

In 2017, there were 962 million people ≥ 60 years worldwide (1). In 2030, older adults are expected to outnumber children under the age of 10 (1.41 billion versus 1.35 billion, respectively) (1). It has been estimated that 25% of Canadians will be ≥ 65 years by 2036 (2). As people age, they are more likely to develop a physical and/or cognitive impairment which impacts their ability to function independently (3, 4). By the age of 85 years, 58.5% of American older adults receive a family caregiver's help because of health problems or functional limitations and only 24% of individuals over 90 years no longer need some help from caregivers (5). In 2012, 28% of Canadians (about 8 million people) provided care to a relative or friend with a chronic health problem (6).

Family and friend caregivers are individuals who provide unpaid care to a family member or friend with a long-term health condition, a physical or mental disability (7). Canadian caregivers spend about 21 hours/week caring for individuals at home (8, 9). Typically, caregivers provide help with instrumental activities of daily living, such as meal preparation, housework, medication management, shopping and transportation, as well as activities of daily living, such as personal hygiene, toileting, locomotion and eating. These caregivers also provide emotional support (10). In addition to reducing the costs associated with health services and institutionalization, caregiving also benefits the care-recipients, allowing them to remain at home and maintain a better quality of life (6).

Caregivers are often older adults themselves (12% of all caregivers in Canada (11)) and may have their own health problems. One third of Canadian caregivers reported having at least one chronic condition and about one-quarter reported having two or more (9). Although caregiving can be rewarding (12), it can be associated with negative

outcomes such as poor mental and physical health (13). A review of the caregiver literature suggests that older caregivers who experience chronic stress are at a greater risk for injury or aggravating pre-existing health issues, and their activities are limited as a result of their caregiving responsibilities and lack of access to resources and services (14). Given the potential negative impact of caregiving, caregivers may require support to ensure their own well-being.

Several studies have compared health and well-being outcomes between caregivers and non-caregivers. Caregivers have higher levels of stress, depression and mortality and lower levels of subjective well-being, physical and mental health, self-efficacy and quality of life compared with non-caregivers (27-33). One study used responses from the 2011-12 English General Practice Patient Survey to compare the health-related quality of life and experiences of primary care between caregivers and non-caregivers (34). This study found that informal caregivers experience a double disadvantage of poorer health-related quality of life and poorer patient experience than non-caregivers in primary care (34). It is critical to compare the effect of primary care interventions on caregivers and non-caregivers to determine if the potential detrimental health effects of being a caregiver modify the effectiveness of primary care interventions (33).

Many caregiver interventions have been examined for their effectiveness on a number of caregiver outcomes. A systematic review of online psycho-educational interventions for caregivers of people with dementia included seven studies and concluded that the psycho-educational intervention showed improvement in caregivers' self-efficacy, anxiety and depression (15). Another systematic review of 21 studies

examined the effect of different psychosocial interventions (including cognitive behavioral therapy, emotion-focused therapy, telephone interpersonal counseling, problem-solving intervention) on quality of life, depression and anxiety of cancer caregivers (16). This review showed mixed results with both statistically significant and non-significant findings on various caregiver outcomes (16). For example, 10 out of 14 studies showed a statistically significant improvement in quality of life and 7 out of nine studies showed a statistically significant improvement in anxiety outcome (16). Most of the caregiver intervention studies examined the effect of psychological, psychosocial, educational and support group interventions. However, the inherent stress of caregiving can worsen the caregiver's own health condition, limit their ability to maintain a healthy lifestyle, and may result in increased risk of premature death (17-19). Additionally, the fragmented health care systems increase caregiver burden as they try to access multiple health services from multiple providers in health and social care sectors for their care-recipients and for themselves (20).

Studies examining interventions that aim to optimize caregivers' health are lacking. A study investigating the attitude of caregivers toward respite care showed that caregivers need, and would benefit from, more psychological counseling and information from health care providers and the interdisciplinary team (21-23). Primary care teams are well placed to recognize and support caregivers because of their frequent interaction with the care recipient or simply through normal consultations (23, 24). Promoting and protecting the health and well-being of caregivers is an important public health priority for both pragmatic and ethical reasons (25), and providing high quality primary care services for them is central to such efforts (26).

This study describes subgroup analyses from a large pragmatic randomized controlled trial (RCT) to evaluate the effectiveness of Health Teams Advancing Patient Experience: Strengthening Quality (Health TAPESTRY) (35) on the health outcomes of caregivers and non-caregivers. Health TAPESTRY aims to promote optimal aging through the support of technology, community volunteers, an inter-professional health care team, and system navigation and better links between primary care and community organizations (35). The protocol for the main trial with a detailed description of the intervention is reported elsewhere (35).

5.3 Objective and hypotheses

The primary objective of this study was to determine if caregiver status (caregiver vs. non-caregiver) modified the effect of our intervention (the Health TAPESTRY approach vs. control) on quality of life, social support, hospitalizations and emergency department (ED) visits. Our hypothesis was that the intervention has a greater positive effect on non-caregivers' quality of life, social support, hospitalizations and ED visits as compared with caregivers due to the potential detrimental health effects of being a caregiver (33).

5.4 Methods/Design

This was a subgroup exploratory analysis of the Health TAPESTRY RCT. In brief, rostered participants with the McMaster Family Health Team (Hamilton, Ontario) were ≥ 70 years and living in the community in the Hamilton (Ontario) area. Participants were excluded if they resided in long-term care, would be out of the country for more than

50% of the trial duration, were palliative or receiving end-of-life care, did not speak English nor had a family member who spoke English. Participants were randomized into the intervention (Health TAPESTRY) or control group using an automated central (allocation concealed) computerized randomization sequence. The study was approved by the Hamilton Integrated Research Ethics Board (File #14-726) and all participants provided written informed consent.

Intervention

The participants received an in-home visit from a dyad of trained volunteers. The volunteers worked together to collect information electronically using a tablet computer via the web-based Health TAPESTRY Application (TAP-App). The TAP-App contained standardized surveys and text field areas the volunteers used to record further information they wanted to transmit to the health care team. Information related to life and health goals, daily life activities, health risks and alerts was collected. At baseline, participants were asked whether or not they were caregivers, defined for participants as someone who provides unpaid care to a family member or friend with a long-term health condition, a physical or mental disability. Data were summarized into a report (TAP-Report) and sent securely electronically to the inter-professional health care team (the TAP-huddle) at the clinic. The TAP-huddle included any combination of health care professionals, including physical and occupational therapists, social workers, pharmacists, among other allied health care professionals. The TAP-huddle reviewed the reports and then developed a plan of care to address the client's goals and health risks. The plan of care involved services and supports both within (clinic appointments, medication review, referral to

clinical program) and outside (i.e., community services) the clinic. The intervention period was 6 months.

Control

The control group received usual care and these individuals did not have volunteer visits. There was no restriction on receiving care as usual from the same inter-professional primary care team members as the intervention group; however, control group patients were not discussed at the TAP-huddle team meetings. At the conclusion of the 6-month trial, the control group had the option of receiving the intervention.

Measurements

Baseline characteristics of participants were collected (i.e., age, gender, education, marital status, number of medications and falls, caregiver's relationship and co-morbidities). Caregiver status was determined by a yes/no question. All participants were followed up at 6 months. Both groups had baseline and follow-up (6 month) data collection by research staff working independently from clinic program operations. Frailty was assessed using the Edmonton Frail Scale (EFS). The EFS assesses nine domains of frailty (cognition, general health status, functional independence, social support, medication usage, nutrition, mood, continence, functional performance) (36) and scores range from 0 to 17, with higher scores representing a higher degree of frailty. Participants were classified into three categories: Not frail (≤5 points), vulnerable (6 to 11 points) or frail (12 to 17 points) (36).

Study Outcomes

Quality of life was measured by the EuroQol-5 dimensions (EQ5D-5L) questionnaire (37). The EQ5D-5L has five components asking about mobility, self-care,

usual activities, pain/discomfort, and anxiety/depression. Total scores range from 0 to 1, with higher scores on the EQ5D-5L representing higher quality of life (37). Respondents also use a Visual Analog Scale (VAS) to report their perceived health status, 0 (the worst possible health status) to 100 (the best possible health status).

Social support was measured by the Duke Social Support Index (DSSI) (38). The DSSI contains two subscales, social interaction (4 items) and social satisfaction (7 items). The total score for the DSSI ranges from 11-33 with increased values indicating higher levels of support (38).

Hospitalization and emergency department (ED) visits were recorded separately via electronic medical record abstraction.

Statistical Analysis

Descriptive analyses of demographic characteristics were expressed as mean ± standard deviation (*SD*) for continuous variables and number (%) for categorical variables. Multiple regression was used to adjust the analyses for age, gender, and frailty. Linear regression was used to compare the effect of the Health TAPESTRY approach on quality of life, social support satisfaction and interaction, while logistic regression was used to compare hospitalizations and ED visits in caregivers versus non-caregivers. A group (intervention, control) by caregiver status (caregiver, non-caregiver) interaction term was used to examine the differential effect of Health TAPESTRY approach on quality of life, social support, hospitalization and ED visits. The analyses were done using STATA 13. The level of significance was set at alpha = 0.05.

5.5 Results

The baseline characteristics of participants who self-identified as caregivers or non-caregivers are shown in Table 1. Of the 335 Health TAPESTRY participants, 104 (31%) were caregivers (47 were in the intervention and 57 in the control group). The baseline characteristics of caregivers and non-caregivers were similar across the study groups. The study outcomes at baseline and 6-month follow-up were summarized in Table 1.

Study outcomes

Among caregivers, there was no significant difference at 6 months between the intervention compared to the control group on EQ5D-5L (mean difference = -0.02 (-0.06, 0.03)), DSSS (mean difference = -0.08 (-0.93, 0.7)), and DSSI (mean difference = -0.02 (-0.06, 0.06)). Also, there was no between-group differences in hospitalizations (OR= 5.7 (0.60, 56)) and ED visits (OR= 1.1 (0.30, 3.7)). Overall, there was no significant differential effect of the Health TAPESTRY approach between caregivers and non-caregivers (Figure 1) on any of the study outcomes.

5.6 Discussion

Given the established high prevalence and socio-economic burden of caregiving in the aging population (14, 17), there is a critical need to identify caregivers and then tailor an integrated health and social support system for them. This was the first study to identify caregivers and examine the differential effect of a program anchored in primary care to promote optimal aging on caregivers (35). Health TAPESTRY approach identified 31% of the included participants as caregivers which is similar to the percent of

caregivers a previous report in the literature (28%) (6). These results suggest that Health TAPESTRY approach was successful in identifying caregivers in a primary care setting. The Health TAPESTRY approach was not associated with improvements in caregiver's quality of life, social support, hospitalization and ED visits at 6 months compared to the control group. There were several possible reasons for no associations found including; 1) the intervention period (6 months) might not have been long enough to improve quality of life, social support, hospitalizations or ED visits and longer interventions need to be examined, 2) lack of statistical power (small sample size), as Health TAPESTRY RCT was not powered for this secondary analyses (35), and 3) the Health TAPESTRY intervention is a broad approach designed to address health goals *and* health risks, not solely centred on caregivers' needs. Caregivers in the study had multiple health risks and alerts identified, and so; the plan of care developed in the TAP-huddle would have reflected the nature and number of health risks and alerts. Commonly reported alerts included suboptimal physical activity and nutritional risk and the average number of alerts per participant was 3.46.

As we explore the longitudinal effect of being a caregiver, our results showed that there was no difference between caregivers and non-caregivers in quality of life, social support, hospitalizations and ED visits at 6-months follow-up. These results are inconsistent with previous studies that showed detrimental effects of being a caregiver on quality of life and well-being (27-33). However, it is consistent with studies suggesting that the caregiving role may benefit the health and well-being of caregivers including perceived general health, tiredness, and depression (39, 40).

The primary care team is well positioned to identify and support caregivers and a

review found a number of successful initiatives in primary care to identify and support caregivers in the UK (41). An example of these initiatives includes: Royal College of General Practitioners (GP) Supporting Caregivers in General Practice Programme. This programme aims to increase the identification of caregivers and support for caregivers in GP practices, since caregivers are more likely to have an interaction with a health care provider than with a social care provider. Numerous resources were developed to help GPs and primary care staff support caregivers (e.g., Supporting Caregivers Action Guide, eLearning Programme, training DVD, educational framework and learning resource for GPs and primary care teams). A key component of this initiative was the GP Champions for Caregivers, which consisted of a team of GP caregiver champions who worked in their local areas to raise awareness about caregivers. Another example of the primary care initiatives is Surrey NHS Caregivers Prescription. This is one of the most successful initiatives within a primary care setting and is a wide ranging, well researched and rapidly growing program. The initiative emerged from survey results, which highlighted the need for caregiver breaks. The Surrey Caregiver Prescription initiative expanded from GP offices to include a presence in hospitals and community pharmacy. The Caregiver Prescription can be used by a GP to prescribe a break for caregivers, or prescribe a referral to a range of support services (e.g., carers assessment with social care services, Surrey Young Carers). The program process of giving a prescription can now be done electronically and has been extended to other health care providers who can refer caregivers to available supports. Key informants advised that “getting GPs on board to engage with caregivers was not a barrier as they were keen to support caregivers; they just needed information, resources and mechanisms in place to ensure an easy to use

referral process" (41). Unlike the Health TAPESTRY approach, these two initiatives were tailored to caregiver needs.

This study has several limitations. First, the study did not capture the duration or tasks of caregiving. Also, the comorbidities and health status of care-recipients were not collected which are important variables that might influence the intervention effect on caregivers. Finally, the study was conducted in a 2-site academic primary care setting and may not be generalizable to other settings.

Future research to address caregivers' needs in the primary care setting is needed. Some of the proposed next steps are implementing primary care staff training and an education program to identify and support patients who are caregivers and refer them to available community resources. A survey for the caregivers attending primary care clinics is needed to learn about their needs and expectations. Piloting a tailored caregiver intervention based on their needs would be critical to optimizing caregivers' health outcomes.

5.7 Conclusion

A primary care team was able to identify older adults with caregivers' role, however, the generalized patient-centred primary care Health TAPESTRY approach was not associated with a decrease in caregivers' ED visits or hospitalizations or improved quality of life, social support satisfaction and interaction during the 6-month study follow-up period. Also, the effect of the Health TAPESTRY approach was not statistically different between caregivers and non-caregivers. Bolstering Health

TAPESTRY and other primary care interventions to support caregiver needs is essential to meet the demands of caring for an ever growing an aging population at home.

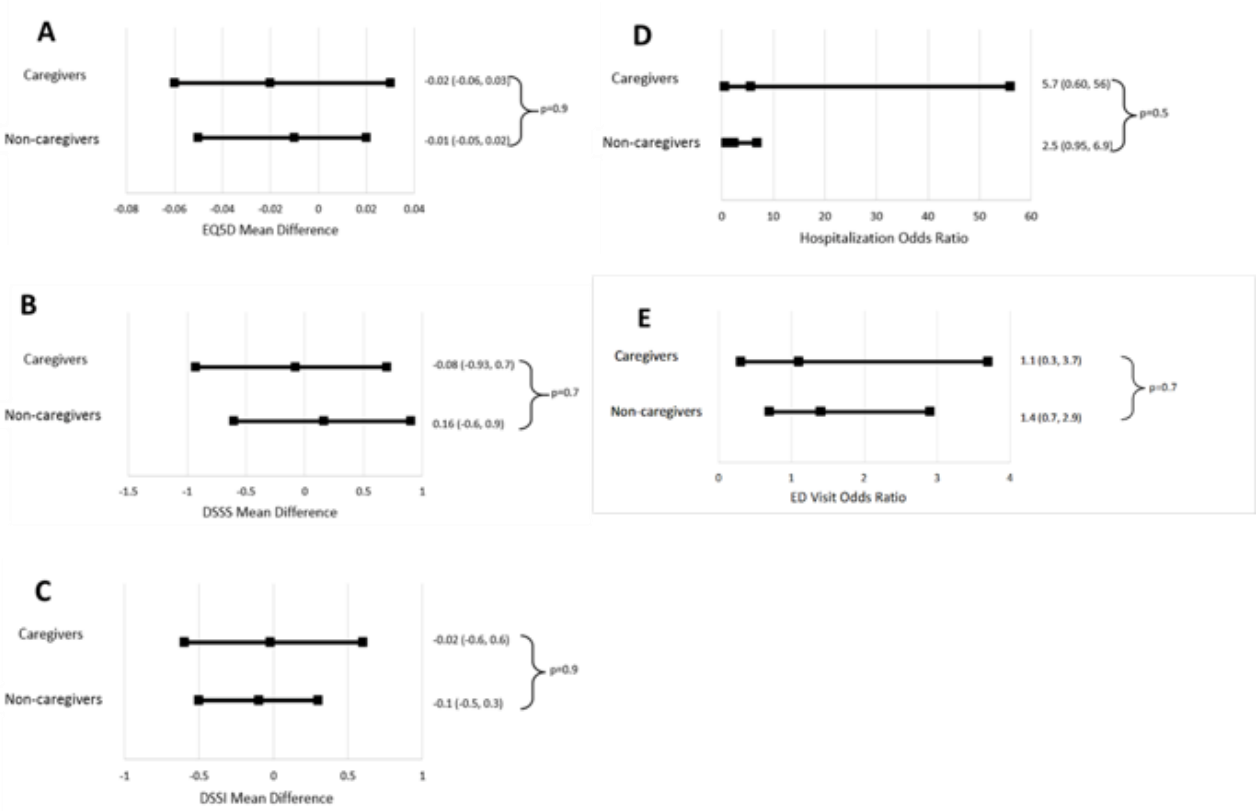
Table 5-1 Baseline characteristics and outcome measures

Characteristic	**Caregivers (n = 104)**		**Non-caregivers (n = 231)**	
	Intervention (n = 47)	Control (n = 57)	Intervention (n = 136)	Control (n = 120)
Age (years): mean (SD)	77.3 (6.2)	78.3 (5.7)	78.3 (6.2)	79.5 (6.9)
Gender, Female: n (%)	26 (55.3)	36 (63.2)	85 (62.5)	71 (59.2)
Marital status n (%) Married Divorced/separated Widower Other	 28 (59.6) 4 (8.5) 9 (19.1) 6 (12.8)	 29 (50.9) 5 (8.8) 10 (17.5) 13 (22.8)	 59 (50.9) 13 (11.2) 36 (31.0) 8 (6.9)	 55 (53.4) 8 (7.8) 33 (32.0) 7 (6.8)
Highest education level: n (%) Secondary College University	 13 (27.7) 13 (27.7) 21 (44.7)	 26 (33.9) 6 (10.7) 24 (55.4)	 55 (42.3) 24 (18.5) 51 (39.2)	 53 (48.2) 14 (12.7) 43 (39.1)
Prescription medications: Mean (SD)	4.6 (2.9)	3.4 (2.6)	3.7 (3.1)	5.1 (4.1)
Number of falls within the past year: n (%) No falls At least one fall	 28 (63.6) 16 (36.4)	 34 (65.4) 18 (34.6)	 90 (78.3) 25 (21.7)	 70 (70.7) 29 (29.3)
Co-morbidities: n (%) Diabetes Stroke Hypertension Cancer COPD Osteoarthritis Heart Disease Others	 10 (21.3) 8 (17.0) 29 (61.7) 14 (29.8) 4 (8.5) 19 (40.4) 16 (34.0) 10 (21.3)	 4 (7.0) 1 (1.8) 20 (35.1) 14 (24.6) 5 (8.8) 23 (40.4) 10 (17.5) 15	 24 (17.6) 6 (4.4 49 (36.0) 24 (17.6) 13 (9.6) 47 (34.6) 37 (27.2) 21 (15.4)	 24 (20.0) 6 (5.0) 52 (43.3) 31 (25.8) 12 (10.0) 40 (33.3) 36 (30.0) 37 (30.8)

		(26.3)		
Caregivers Relationship Spouse Others	 22 (35.48) 40 (65.52)	 34 (49.28) 35 (50.72)		
Hospital admissions: n (%) Baseline (in the past year) No visit At least one visit Post-intervention (6-month) No visit At least one visit	 37 (82.2) 8 (17.8) 44 (97.8) 1 (2.2)	 47 (90.3) 5 (9.7) 47 (90.4) 5 (9.6)	 99 (85.3) 17 (14.7) 110 (94.0) 7 (6.0)	 82 (82) 18 (18) 90 (84.9) 16 (15.1)
ED visits: n (%) Baseline (in the past year) No visit At least one visit Post-intervention (6-month) No visit At least one visit	 26 (74.3) 9 (25.7) 40 (86.9) 6 (13.1)	 36 (75.0) 12 (25.1) 46 (86.8) 7 (13.3)	 69 (71.1) 28 (28.9) 100 (86.2) 16 (13.8)	 64 (76.2) 20 (23.8) 85 (81) 20 (19.1)
Duke Social Support Satisfaction: Mean (SD) Baseline Post-intervention (6-month)	 19.3 (2.2) 19.5 (2.3)	 19.4 (2.1) 19.4 (2.0)	 18.9 (2.4) 18.9 (2.9)	 19.0 (2.4) 18.9 (2.9)
Duke Social Support Interaction: Mean (SD) Baseline Post-intervention (6-month)	 8.9 (1.6) 8.9 (1.4)	 8.9 (1.5) 9 (1.3)	 8.9 (1.5) 8.7 (1.6)	 8.6 (1.7) 8.5 (1.6)
EQ5D-5L: Mean (SD) Baseline Post-intervention (6-month)	 0.8 (0.1) 0.9 (0.1)	 0.8 (0.1) 0.8 (0.1)	 0.8 (0.1) 0.8 (0.1)	 0.8 (0.1) 0.8 (0.1)

COPD = Chronic Obstructive Pulmonary Disease; SD = standard deviation; ED = Emergency Department, EQ5D-5L = EuroQol-5 dimensions, DSSS = Duke Social Support Satisfaction, DSSI = Duke Social Support Interaction.

Figure 5-1: Study outcomes scores in caregivers and non-caregivers



EQ5D-5L = EuroQol-5 dimensions, DSSS = Duke Social Support Satisfaction, DSSI = Duke Social Support Interaction.

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CHAPTER 6

VALIDATION OF A ONE YEAR FRACTURE PREDICTION TOOL FOR ABSOLUTE HIP FRACTURE RISK IN LONG TERM CARE RESIDENTS

PREFACE TO CHAPTER 6

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6.1 Abstract

Background

Frail older adults living in long term care (LTC) homes have a high fracture risk, which can result in reduced quality of life, loss of mobility, pain and death. The Fracture Risk Scale (FRS) was designed for fracture risk assessment in LTC, to optimize targeting of services in those at highest risk. This study aims to examine the construct validity and discriminative properties of the FRS in three Canadian provinces.

Methods

LTC residents were included if they were: 1) Adults admitted to LTC homes in Ontario (ON), British Columbia (BC) and Manitoba (MB) Canada; and 2) Received a Resident Assessment Instrument Minimum Data Set Version 2.0. After admission to LTC, one-year hip fracture risk was evaluated for all the included residents using the FRS (an eight-level risk scale, level 8 represents the highest fracture risk). Multiple logistic regressions were used to determine the differences in incident hip or all clinical fractures across the provinces and FRS risk levels. We examined the differences in incident hip or all clinical fracture for each FRS level across the three provinces (adjusted for age, BMI, gender, fallers and previous fractures). We used the C-statistic to assess the discriminative properties of the FRS for each province.

Results

Descriptive statistics on the LTC populations in ON (n=29,848), BC (n=3,129), and MB (n=2,293) are: mean (SD) age 82 (10), 83 (10), and 84 (9), gender (female %) 66%, 64%,

and 70% respectively. The incident hip fractures and all clinical fractures for FRS risk level were similar among the three provinces and ranged from 0.6 to 19.2 % and 0.9 to 19.2% respectively. The overall discriminative properties of the FRS were similar between ON (C-statistic= 0.673), BC (C-statistic= 0.644) and MB (C-statistic= 0.649) samples.

Conclusion

FRS is a valid tool for identifying LTC residents at different risk levels for hip or all clinical fractures in three provinces. Having a fracture risk assessment tool that is tailored to the LTC context and embedded within the routine clinical assessment may have significant implications for policy, service delivery and care planning, and may improve care for LTC residents across Canada.

Keywords: Nursing home, Long Term Care, Hip fracture, Mortality, InterRAI Prediction

6.2 Background

It has been estimated that 1 in 4 Canadians will be 65 years or older by 2036 (1). As the population ages, a greater number of older adults will need residential support such as long-term care (LTC). LTC Residents are often frail, since their multiple physical and cognitive deficits place them at high risk of falls, disability, and death (2, 3). Hip fractures are the most common type of fracture in LTC (49% of all fractures) (4). They are more common in older adults living in LTC (49%) than in the community (29%) (4, 5), and lead to more hospitalizations (6) and worsening health-related quality of life (7). In Canada, 45% of LTC residents with hip fracture die within 12 months (8) and of the survivors, 48% are no longer ambulatory (8).

Hip fracture prediction and prevention in LTC residents receive little attention due to the multiple comorbidities and medical complexity of LTC residents (9, 10) and the challenges of predicting fracture in this population. It is difficult to identify LTC residents with high fracture risk, as the commonly used fracture risk assessment tools in Canada, including the Canadian Fracture Risk Assessment Tool (FRAX) and the Canadian Association of Radiologists and Osteoporosis Canada tool (CAROC) (11-14), are not valid or generalizable for residents of LTC (15, 16). FRAX and CAROC typically provide a 10-year fracture risk assessment timeframe, which is too long, given the mean 2.4-year life expectancy of LTC residents (17). A recent study showed that FRAX (with bone mineral density) may predict incident hip fracture at one year (18). Bone mineral density is heavily weighted in current fracture risk assessment protocols, but bone

mineral density is not feasible to obtain in LTC. In addition, FRAX is not tailored to frail, institutionalized LTC residents. Thus, fracture prediction outputs of FRAX-Canada and CAROC may not be suitable for decision-making and care planning among frail LTC residents (19, 20).

Recently, our team developed the Fracture Risk Scale (FRS) (21), a standardized outcome scale for identifying LTC residents at risk for fracture within one year. The FRS can be obtained from the Resident Assessment Instrument Minimum Data Set (RAI-MDS 2.0), which is a comprehensive, standardized assessment that is used upon admission and on a quarterly basis thereafter, to gather information on a wide range of socio-demographic and clinical characteristics (22-24). The FRS was developed using Ontario residents' data from the RAI-MDS 2.0, the Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS). However, the FRS was not externally validated (in a population other than the tool development sample), nor was its validity tested in other Canadian provinces. As a predictive model, the FRS' reproducibility (performing sufficiently accurate across new samples from the same target population) and transportability (performing well across samples from different but related source populations) (25) need to be tested prior to widespread adoption. Therefore, we conducted this validity study to examine the FRS performance across a new sample and in different but related population of LTC residents in other provinces (21).

This study aims to: 1) examine the construct validity of the FRS tool by comparing incident hip fractures and all clinical fractures (includes hip, spine, humerus, forearm, pelvis fractures) for each fracture risk level in LTC residents across three Canadian provinces; 2) compare incident hip and all clinical fractures in LTC residents across three Canadian provinces; and 3) compare incident hip and all clinical fractures between the FRS risk levels. To examine the construct validity study of the FRS (26), we hypothesize that incident hip fractures for each fracture risk level in LTC residents in the three Canadian provinces are not statistically different when type 1 error is ≤ 0.05.

6.3 Methods

Study Design and population

This retrospective cohort study uses data from the RAI-MDS 2.0. LTC residents were included if they: 1) were adults admitted to LTC homes in Canada from April 1st, 2006 to March 31st 2010; and 2) were assessed with the RAI-MDS 2.0. LTC residents were excluded if they: 1) had multiple admissions; 2) reported on the RAI-MDS 2.0 to have end stage disease, were comatose, received hospice, or respite care; 3) expected a short stay; 4) had the admission assessment completed more than 14 days after the date of admission; or 5) had no reassessments during the one-year follow-up. The project received ethics approval from the University of Waterloo Office of Research Ethics (ORE no 17045).

Fracture Rating Scale

The FRS is different from existing fracture risk assessment tools in that it does not use bone mineral density, and includes fracture risk factors that are relevant in the LTC population (21). Moreover, to ensure that it was valid for long-term care residents and easily scalable, it was designed and validated using large population-based datasets that include routinely collected data from long-term care residents. The FRS were developed using decision tree analysis and the included items are: walking in corridor, wandering, falling, cognitive performance scale, transfer status, age, body mass index (BMI), and previous fractures (21). The FRS includes eight fracture risk level categories (level 1 represents the lowest and level 8 represents the highest hip fracture risk).

Incident Fractures

Over the course of the one-year follow-up period, residents were classified as to the presence or absence of an incident fracture. To capture incident fracture, we accessed in-patient hospital records and emergency department records (23 24). DAD is received directly from acute care facilities or their respective health/regional authority or ministry/department of health and it contains demographic, administrative and clinical data of all Canadian provinces except Quebec (27). NACRS contains data for all hospital-based and community-based ambulatory care including day surgery, outpatient and community-based clinics and emergency departments (28). NACRS data are received directly from participating facilities or from regional health authorities or ministries of health. Data collection methods may vary by facility. We were able to link DAD and NACRS data to RAI-MDS data for this analysis.

Incident fractures were defined using International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) codes, captured in DAD and NACRS. The codes were selected using the Revised Framework for National Surveillance on Osteoporosis and Osteoporosis-related Fractures of the Public Health Agency of Canada (29). A resident with one of the hip fracture codes (hip (S72.0, S72.1, S72.2) present on either a hospitalization or emergency department visit within one year after the admission assessment was coded as having hip fracture. A resident with at least one of these codes within one year after the admission assessment was coded as having a fracture (hip (S72.0, S72.1, S72.2), spine (S22.0, S22.1, S32.0, S32.7, S32.8), humerus (S42.2), forearm (S52.x, S62.x) and pelvis (S32.1, S32.3, S32.4, S32.5, S32.7, S32.8)).

Statistical analysis

The study population demographics, prior falls and fractures, and fracture incidence estimates are expressed as mean (SD) for continuous data and counts and percentages for categorical data. Percent of incident hip fracture and all clinical fractures (hip, spine, humerus, forearm, pelvis fractures) for each FRS risk level in the three provinces were calculated. Multivariable logistic regression models were used to determine if incident hip fractures are different across the provinces and to calculate the odds ratio of incident hip fractures in each FRS risk level. In this logistic regression, the incident hip fractures were the dependent variable (DV) and provinces (Ontario was used as the reference group) and FRS risk levels (FRS risk level 1 was used as the reference

level) were the independent variables (IV). We tested the significance of the interaction term of FRS and provinces in the logistic regression model to determine if the incident hip fracture in each FRS risk level is different across the provinces. The logistic regression analyses were adjusted for age, BMI, gender, fallers in the last 180 days, previous fracture, and the size of the residential home (small, medium or large). All the analyses were repeated using all incident fractures as DV. To assess the discriminative properties of the FRS for each province, we used the C-statistic. All the statistical analyses were conducted using SAS V.9.4 (SAS Institute).

6.4 Results

The final study sample includes 35,270 participants (ON=29,848, BC=3,129 and MB=2,293) and is displayed in figure 1. Table 1 demonstrates the characteristics of LTC residents in the three provinces. The age, gender distribution and comorbidities are similar across the provinces; with less than 1% of LTC residents having had a hospital admission within 3 months from LTC admission. Falls and incident fractures, BMI were similar across the provinces as well. All of the Manitoba homes in the study were from one urban centre, as the remainder of the province does not use RAI-MDS.

Incident hip fractures and all clinical fractures in all risk levels ranged from 0.6 to 19.2% and 0.9 to 19.2% respectively (Figures 2 and 3, respectively). There was no statistically significant difference in incident hip or all clinical fractures across the three provinces (Table 2). When adjusting for the provinces, the odds of incident hip fractures

and all clinical fractures in all the FRS risk levels were significantly different compared to level 1 with consistently increasing odds of fractures with higher FRS risk levels, as shown in Table 2.

None of the interaction terms of FRS risk levels and provinces were statistically significant. This indicates the similarity of incident hip fractures and all clinical fractures for each FRS risk levels in the three provinces. The overall discriminative properties of the FRS were similar between ON (c-statistic= 0.67), BC (c-statistic= 0.64) and MB (c-statistic= 0.65) samples.

6.5 Discussion

Our study demonstrates the validity of the FRS for predicting hip and all clinical fractures in LTC residents living in several Canadian provinces. As recommended by the Cosmin initiative (26), an international initiative that aims to improve the selection of health measurement instruments; hypothesis-testing construct validity is a critical component of evaluating outcome measures' psychometric properties. This study confirmed our hypothesis and showed that incident hip and all clinical fractures for each FRS risk levels in LTC residents in the three Canadian provinces were similar, confirming that the FRS is reproducible and transportable for LTC residents living in different geographical areas (25). Therefore, our results confirmed that FRS can be used to identify LTC residents with high risk of hip or all fractures across different Canadian provinces.

We have previously shown that the FRS is able to identify LTC residents at highest risk of fracture in the initial FRS development study (21). The FRS is an adequate reflection of the outcome of interest (one-year incident fracture). Our study builds on this work by examining FRS performance. A clinical prediction tool performance is characterised by evaluating a model's calibration and discrimination (30). Calibration is the agreement between prediction from the model and observed outcomes and reflects the predictive accuracy of the model (31). Our results confirm that LTC residents who are at higher FRS risk level (FRS model prediction) have a higher rate of incident hip and all clinical fractures (observed outcome) (Table 2), which shows the agreement between the FRS prediction model and the observed outcome. Discrimination refers to the ability of the prediction model to separate individuals with and without the outcome event; those with the outcome event should have a higher predicted risk compared to those who do not have the outcome event (31). In Table 2, we showed that the odds ratio of hip and all clinical fracture is higher in LTC residents with higher FRS risk levels; therefore, FRS can discriminate between residents at higher and lower risk of incident hip or all clinical fracture.

Unlike commonly used fracture risk assessment tools (FRAX and CAROC), FRS is a unique one-year fracture prediction tool that is composed of risk factors specific to LTC residents. FRS is embedded in the RAI-MDS 2.0, which is completed within 14 days of a resident entering a home and quarterly thereafter. In addition, the FRS can be obtained from the interRAI Long Term Care Facility assessment, which is the successor

to the RAI-MDS 2.0 (24, 32). Thus FRS can be easily and regularly implemented in LTC without burden on the LTC staff (9, 10, 33, 34). As we demonstrated the FRS' validity, we suggest it can be used for LTC resident care planning across Canada and possibly internationally.

Recently, Fracture Risk Assessment in Long-term Care (FRAiL) tool has been developed, which aims to predict two-year hip fracture risk in nursing home residents (16). The FRAiL tool developed using RAI-MDS 2.0 assessment of nursing home residents in the United States. FRAiL tools included fifteen items to predict hip fracture: older age, white race, female, impaired cognition, activities of daily living independence, locomotion independence, urinary continence, previous falls, transfer independence, easily distracted, wandering, absence of osteoarthritis, absence of pressure ulcer, low BMI, and diabetes. There are some common items in FRS and FRAiL tools such as wandering, falling, cognitive performance scale, transfer status, age, BMI, and previous fractures. However, FRAil was not validated in a population other than the tool development sample.

Recommendations for preventing fracture in LTC have been developed to provide non-pharmacologic and pharmacologic strategies for fracture prevention in frail older adults living in LTC (35). However, there is a current gap in osteoporosis treatment and fracture prevention in LTC residents (36-41). One of the barriers to implement fracture prevention guideline is the lack of information about fracture risk assessment (42). The easily implemented and validated FRS tool may overcome this barrier. To help LTC clinicians prescribing the appropriate intervention to residents who are identified as "at

risk", our team will develop and implement an electronic Clinical Assessment Protocol (CAP) in LTCs. The Fracture Risk CAP will automatically produce recommendations for residents based on their FRS fracture risk level and will inform clinical decision-making as part of the person-centered care planning process to fill the gap of fracture prevention in LTC. Other CAPs have been developed to draw the attention of the healthcare provider to a matter (such as Activities of daily living, delirium and cardiorespiratory) that can be improved and should be considered in LTC residents' care plan (43).

Strengths of this study include the use of a large, representative sample of LTC residents with RAI-MDS 2.0 data linked with DAD and NACRS. The value of a prediction model depends on its performance outside of the development sample, and it is, therefore, external validation of the model in samples from related source populations (LTC residents in other provinces) is recommended (25). Quantifying the relatedness between the development and validation samples allowed us to interpret the FRS performance in terms of (clinical) transportability and (statistical) reproducibility (25). We acknowledge that our study has limitations. We excluded LTC residents if they have a life expectancy of less than one-year at the time of the assessment period. Therefore, our findings may not be generalizable to these residents. Our study was limited to the variables collected in the RAI-MDS 2.0 and may not have captured all relevant risk factors for hip or all clinical fractures in LTC residents.

6.6 Conclusion

The FRS is a valid tool for identifying LTC residents at different risk levels for hip or all clinical fractures in three provinces. Having a fracture risk assessment tool that is tailored to the LTC context and embedded within the routine clinical assessment may have significant implications for policy, service delivery and care planning, and may improve care for LTC residents across Canada.

Table 6-1: Baseline Characteristics of the study participants

Variables	ON (N=29,848)	BC (N=3,129)	MB (N= 2,293)
Age, yrs. Mean (SD)	82.1 (9.6)	83.0 (9.6)	83.5 (9.3)
Gender, Female, n (%)	19,706 (66.1)	2,023 (64.7)	2,293 (69.8)
Married, n (%)	8978 (30.1)	818 (26.2)	608 (26.5)
Chronic Disease Number, n (%)			
Osteoporosis	7,247 (24.3)	663 (21.2)	353 (15.4)
Diabetes Mellitus	7,239 (24.3)	610 (19.5)	472 (20.6)
Arthritis	10,486 (35.1)	1,058 (33.8)	811 (35.4)
Alzheimer's Disease	5,513 (18.5)	523 (16.7)	289 (12.6)
Cancer	2,935 (9.8)	280 (9.0)	279 (12.2)
Neuromuscular diseases	47 (0.2)	11 (0.4)	1 (0.04)
Parkinson's Diseases	81 (0.3)	2 (0.1)	6 (0.3)
Liver Disease	69 (0.2)	7 (0.2)	7 (0.3)
Arteriosclerotic Diseases	2,004 (6.7)	199 (6.4)	127 (5.5)
Hospital admissions in past 90 days, n (%)			
No Visit	29,603 (99.2)	3,106 (99.3)	2,281 (99.5)
≥ 1 Visit	245 (0.8)	23 (0.7)	12 (0.5)
Emergency room visits in past 90 days, n (%)			
No Visit	26,590 (89.1)	2,927 (93.5)	2,232 (97.3)
≥ 1 Visit	3,258 (10.9)	202 (6.5)	61 (2.7)
Falls within the last 180 days, n (%)			
No Falls	1,9444 (66.1)	1,969 (66.5)	1,540 (69.8)
≥ 1 Fall	9,957 (33.9)	991 (33.5)	666 (30.2)
Prior hip fracture in last 180 days, n (%)	179,088 (6)	18,774 (6)	6879 (3)
Incident hip fractures, n (%)	95,514 (3.2)	12,516 (4)	9,172 (4)
Incident fracture, n (%)	155,210 (5.2)	15,332 (4.9)	10,089 (4.4)
Number of prescribed medications, Mean (SD)	9.7 (4.63)	8.45 (4.04)	8.02 (4.66)
BMI, Mean (SD)	24.94 (5.96)	24.42 (5.97)	24.94 (5.78)
Changes in Health, End-Stage Disease, Signs, and Symptoms (CHESS Score), n (%)			
0	110,18 (58.69)	1309 (68.64)	664 (72.49)
1	4665 (24.85)	362 (18.98)	188 (20.52)
2	2179 (11.61)	176 (9.23)	51 (5.57)

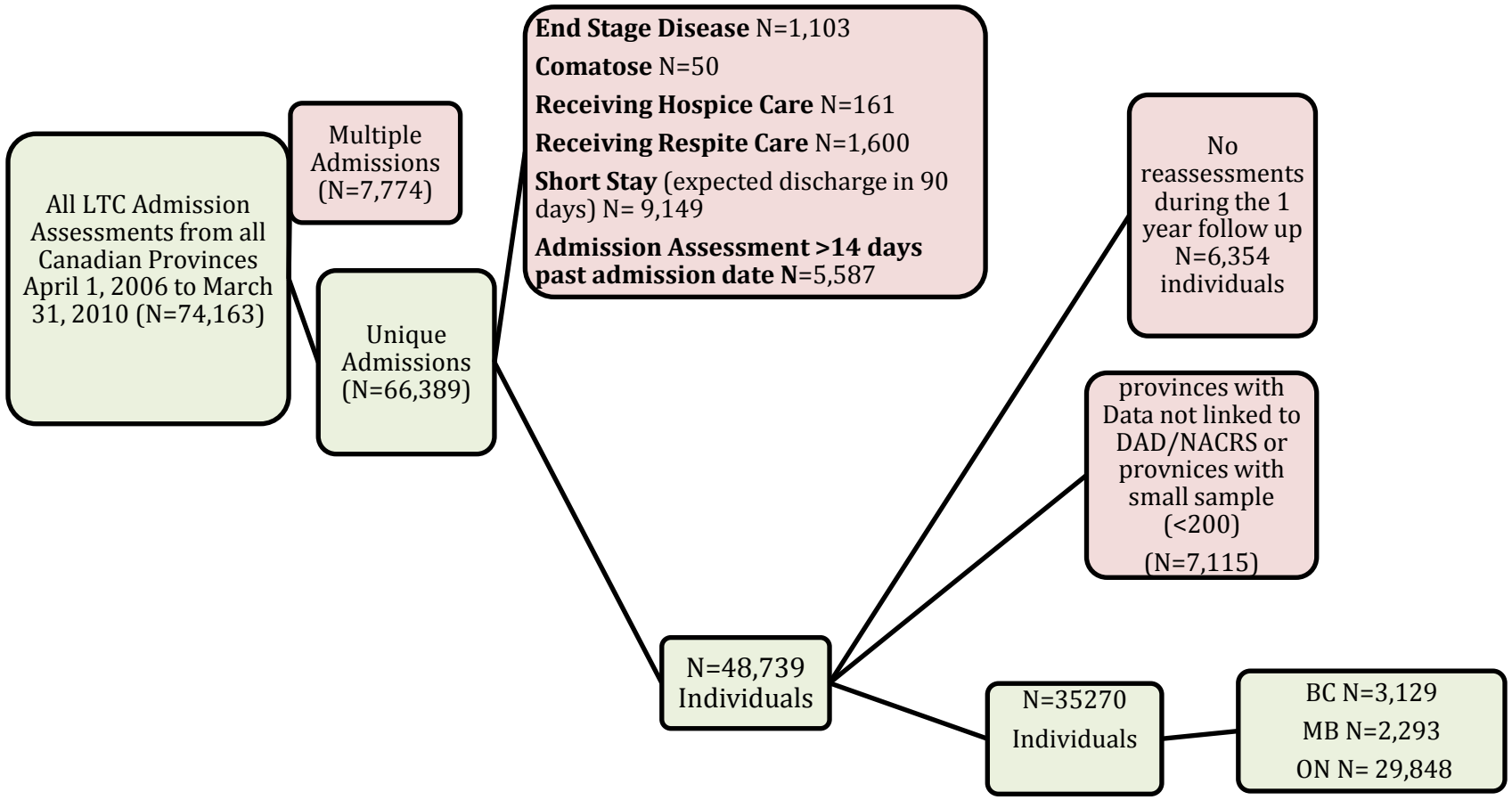
3 **4** **5**	692 (3.69) 219 (1.17) 0	49 (2.57) 11 (0.58) 0	11 (1.20) 2 (0.22) 0
Home size, n (%) **Small (≤50 beds)** **Med (51-99 beds)** **Large (≥ 100 beds**	 583 (1.95) 511,9 (17.15) 24146 (80.90)	 276 (8.82) 103,7 (33.14) 181,6 (58.04)	 0 278 (12.12) 2015 (87.88)
Overall case mix index of the residents at **Baseline, Mean (SD)**	 0.64 (0.18)	 0.57 (0.16)	 0.58 (0.14)
Ownership, n (%) **Public/religious/not for profit** **Private**	 127,41 (42.69) 171,07 (57.31)	 157,3 (50.27) 155,6 (49.73)	 122,3 (53.34) 107,0 (46.66)
Rurality, n (%) **Urban** **Rural**	 255,96 (85.75) 410,5 (13.75)	 272,3 (87.02) 401 (12.82)	 2293 (100) 0

Table 6-2: Differences in Hip Fracture across provinces and Fracture risk scale risk levels

Variables	Hip Fractures	All Fractures
	OR (CI)	OR (CI)
Provinces		
ON	1	1
BC	1.27 (1.04, 1.55)	0.97 (0.81, 1.16)
MB	1.30 (1.04, 1.62)	0.84 (0.68, 1.04)
FRS risk levels		
1	1	1
2	3.08 (1.86, 5.11)	2.64 (1.79, 3.89)
3	5.56 (3.52, 8.80)	5.28 (3.74, 7.45)
4	4.29 (2.68, 6.92)	3.84 (2.68, 5.50)
5	8.02 (5.06, 12.72)	6.93 (4.90, 9.81)
6	12.17 (7.15, 20.73)	8.97 (5.90, 13.65)
7	10.52 (6.60, 16.79)	8.36 (5.86, 11.91)
8	17.00 (10.15, 35.55)	10.90 (6.41, 18.59)

OR: Odds Ratio, CI: 95% Confidence Interval, ON: Ontario, BC: British Colombia, MB: Manitoba, FRS: Fracture Rating Scale. The analyses were adjusted for age, BMI, gender, fallers in the last 180 days, previous fracture, and Home size (small, medium or large).

Figure 6-1: Study sample flow diagram



LTC: Long-term care, DAD: Discharge Abstract Database, NACRS: National Ambulatory Care Reporting System

Figure 6-2: Incident Hip fracture for Fracture Rating Scale risk levels

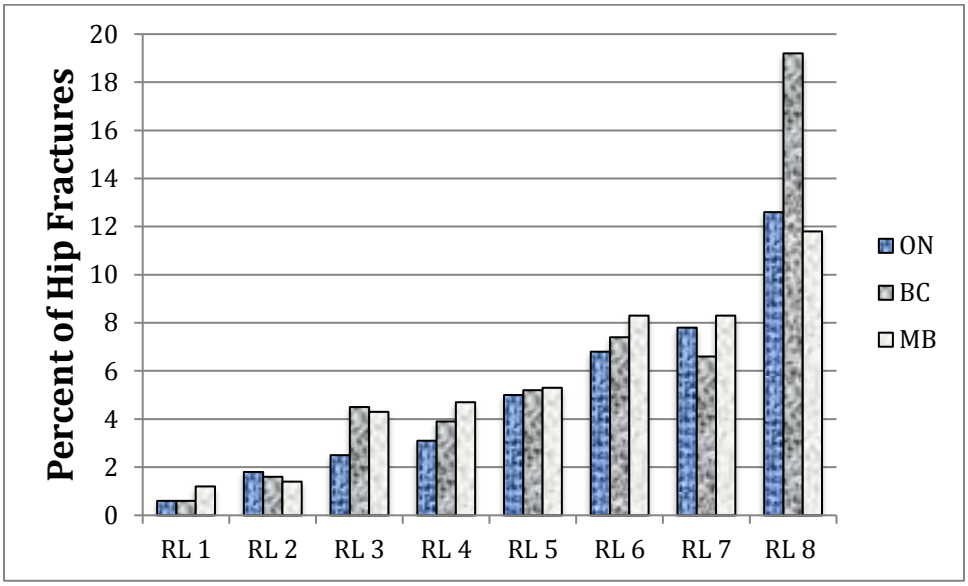
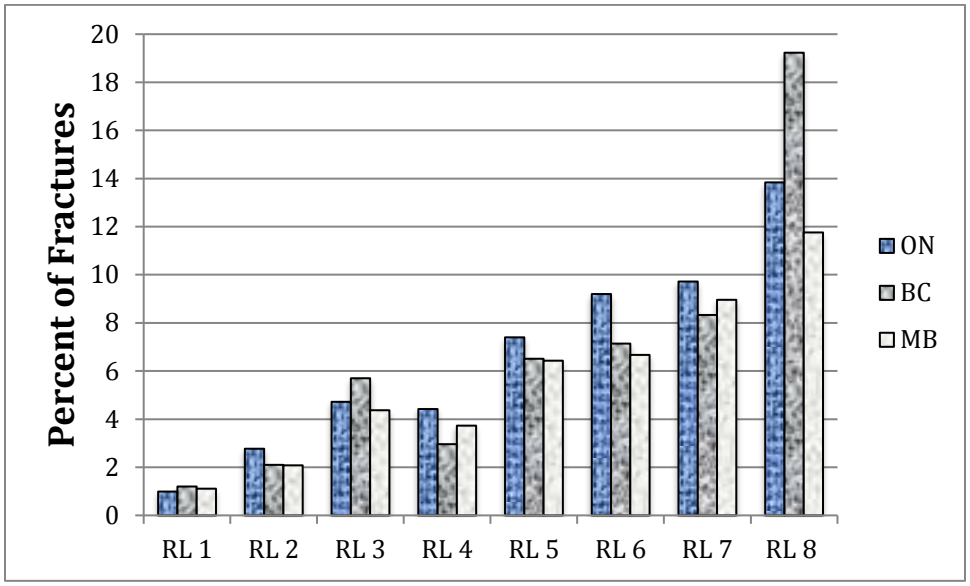


Figure 6-3: All Incident fracture for Fracture Rating Scale risk levels



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CHAPTER 7

7.1 DISCUSSION

The overall thesis objective was to improve management of frail older adults by identifying the most effective frailty intervention using the network meta-analysis methodology, examining the feasibility of implementing preoperative frailty intervention in joint replacement candidates, examining the effect of a complex primary care intervention on older adults' caregivers and assessing the validity of a fracture prediction tool in frail long-term care (LTC) residents. This chapter discusses the implication of the results of the thesis and identifies the key strengths and limitations of the studies. The contributions of the thesis and future directions are also identified for each chapter. This thesis work contributes to the care of older adults and their caregivers in different setting including LTC, community and preoperative settings. As population ages, predictive tools to identify older adults and caregivers at risk are needed as well as interventions and model of care to support them.

Chapter 2 describes the rationale and methodology for the systematic review and network meta-analysis examining the comparative effect of interventions targeting the prevention or treatment of frailty. The network meta-analysis methodology is an emerging methodological and statistical approach that aims to combine direct (i.e., head-to-head trials) and indirect comparisons (which provides the relative treatment effects between two interventions when head-to-head trials are not available (1)) (2).

A recent scoping review aimed to summarise frailty interventions and international policies in community-dwelling older adults (3). This review included 14 studies, 12 RCT and 2 cohort studies. This scoping review included similar frailty interventions to what we included in our network meta-analysis such as physical activity; physical activity combined with nutrition; physical activity plus nutrition plus memory training; home modifications; prehabilitation (physical therapy plus exercise plus home modifications) and comprehensive geriatric assessment (CGA) (3). Another systematic review aimed to summarize the best available evidence regarding the effectiveness of interventions for preventing frailty progression in older adults. Due to the heterogeneity of the included studies, the authors reported only a narrative summary of the included studies (21 studies) (4). This review found mixed results regarding the effectiveness of frailty interventions. It was concluded that further research is required to reinforce current evidence and examine the impact of the initial level of frailty on the benefits of different interventions (4).

In Chapter 3, we describe the results of the frailty systematic review and network meta-analysis. Consistent with our results that show the effectiveness of physical activity interventions, a recent systematic review and meta-analysis examined the effect of exercise on older adults with sarcopenia and included 6 RCTs (5). In this review, exercise interventions significantly improved strength, balance and muscle mass, but the exercise effect was inconsistent due to heterogeneity in exercise interventions' mode, duration and intensity (5). Another systematic review of physical exercise interventions in frail older adults included 9 studies and found that exercise could benefit frail older adults (6).

However, the optimal program remains unclear and more studies are needed to select the most effective exercise program (6).

However, medication management was the most effective intervention in improving cognition, short physical performance battery and depression. Only one study in our network meta-analysis examined the effect of a medication management program (medication-dispensing machine or a medplanner) (7). More studies to examine the effect of mediation management programs are needed to increase the confidence of our results. These results are consistent with another systematic review of interventions for preventing falls in older adults living in the community (8). It was shown that two different medication management interventions (gradual withdrawal of psychotropic medication and a prescribing modification program) reduced the rate of falls and the risk of falling in older adults (8).

Other interventions were not ranked superior to improve most of the outcomes such as nutritional supplementation, psychosocial/cognitive training, and multifaceted intervention. Several reasons could explain the lack of effectiveness of these interventions, such as 1) the variability of interventions within each treatment node. For example, the nutritional supplementation node included different types of supplementations (such as vitamin D, protein or other supplementations), 2) the short intervention duration of most of the studies (most studies were shorter than 6 months), and 3) the differences of population characteristics (age, gender, frailty level) of the studies. More studies to explore the effectiveness of these interventions are needed.

Our results indirectly showed the similarity of the frailty phenotype (9) and cumulative deficient models (10) of frailty measurement. In our analysis, we combined

frailty measured by Fried Frailty phenotype and frailty index and there was no significant heterogeneity across the frailty outcome. The association between the frailty phenotype (9) and cumulative deficient frailty models (10) was previously shown in people with HIV infection (11).

As we combined a group of similar interventions in the treatment nodes of this network meta-analysis, it became a future network meta-analysis to determine the most effective intervention within each of the included node. For example, we combined different types of exercise (strength, endurance, walking program) in the physical activity node, therefore, a future network meta-analysis to identify the most effective exercise program in treating/preventing frailty is needed. Similarly, a future network meta-analysis to compare different types of nutritional supplementation included in this node of the current network meta-analysis is needed.

Finally, more RCTs with rigorous methodology are needed to increase the certainty of our current results, as the quality of evidence of this review was graded low and very low. In most of the comparisons, the quality of evidence was down graded due to the high risk of bias and imprecision of the effect estimate. Therefore, more rigorous RCT examining frailty interventions will decrease the risk of bias and imprecision and hence improve the quality of evidence.

This network meta-analysis contributes to the field of aging and frailty, as it is the first frailty network meta-analysis. As, we introduce the network meta-analysis methodology to this field; we expect further adoption of this methodology in the future due to its value of comparing the effect of multiple interventions. Our results identified physical activity and medication management as the most important components of

frailty intervention for older adults. These results will guide the decision of clinicians and policy makers to optimize frailty prevention and management programs.

Chapter 4 describes the rationale and methodology of pilot RCT examining the feasibility of preoperative multi-modal frailty intervention in pre-frail/frail older adults undergoing hip or knee replacement. Prehabilitation represents a shift away from the impairment driven, reactive model of care towards a proactive approach that enables patients to become active participants in their care (12). The concept of prehabilitation is based on the principle that structured and sustained exercise leads to improved cardiovascular, respiratory, and musculoskeletal systems (13, 14).

Various preoperative interventions and specifically exercise have been implemented in different elective surgical patients to improve baseline functional reserve and hence allow the postoperative patient to more quickly reach their minimal functional level (15, 16). Exercise and physical therapy prehabilitation interventions in cardiac and thoracic surgery patients has shown increases in preoperative function and decreases in pulmonary complications, and length of stay (17-19). In abdominal surgical population, several prehabilitation interventions have been examined including exercise, inspiratory muscle training and combinations of the two. A systematic review and meta-analysis included 9 RCTs examining the effect of prehabilitation interventions on postoperative outcomes after intra-abdominal surgeries (20). This meta-analysis showed that prehabilitation consisting of inspiratory muscle training, aerobic exercise, and/or resistance training can decrease all types of postoperative complications after intra-abdominal operations (20). However, the effect on length of stay was unclear due to the

lack of reporting of this outcome. Joint replacement is one of the most common surgical procedures (21). A systematic review examined the effect of preoperative physiotherapy or exercise on post-operative outcomes (21). This review included 22 studies and found that exercise/education slightly reduced postoperative pain and improved physical function measured by the Western Ontario and McMaster Universities Arthritis Index (21).

Since most of the previous prehabilitation interventions composed of exercise and education, the fit joint pilot trial will have a unique contribution to the prehabilitation literature. The fit joint Trial examines an innovative model of care, which will include not only home-based and/or centre-based exercise, but also protein and vitamin D supplementation and medication review and optimization. Another potential advantage of the Fit Joint model of care is being a community-based intervention, while a majority of prehabilitation intervention are based in hospitals or health facilities. This may not be ideal as commuting and cost can be barriers for those high-risk patients most in need of prehabilitation (22). Examining the fidelity and feasibility of the fit joint model of care is a critical step before examining its effectiveness on postoperative outcome, health services use and mortality in joint replacement population and potentially to other surgical populations. This work also may contribute to the field of aging. The inclusion of frail older adults in therapeutic clinical trials is hampered by difficulties in defining and recruiting this population. The exclusion of frail older adults from RCTs due to several reasons (such as multi-morbidity) may question the generalizability of their results on older adults. The fit joint trial will also examine the feasibility of recruiting frail/prefrail

older adults in RCTs and hence increase the generalizability of our results on frail surgical population.

Currently we completed recruitment for this pilot RCT. After successful completion of this trial in Hamilton Ontario, a stakeholder meeting (including patients, physiotherapists orthopaedic surgeons, geriatricians, kinseologists, research scientists and policy makers) will be arranged to discuss any feedback about this new model of care and how it can be optimized. We aim to pilot the same model of care in a second joint replacement centre to test the study processes in a second site in preparation for a multi-centre national trial. This chapter contributes to care of frail older adults by testing a prehabilitation intervention in frail older adults undergoing joint replacement. Optimizing the preoperative care of frail older adults may improve the post-operative outcomes and decrease surgical complications.

In chapter 5, we were successful to identify older adults with informal caregivers' role in primary care setting. However, there were no differences between caregivers and non-caregivers in the study outcomes at 6-month follow-up.

Frailty in older caregivers is associated with high caregiver burden and diminished quality of life (23); therefore, optimizing caregivers' health and increasing their functional ability in primary care settings may be beneficial. However, this chapter did not show improvement in caregivers' quality of life or social support, which may indicate that caregivers would benefit more from intervention tailored to their individual needs. Other study limitations include lack of statistical power and short follow up period. Additionally, the potential effect of supporting caregivers using TAPESTRY

approach on care recipients was not measured. It was shown that the wellbeing of caregivers is associated with increasing the care recipients' access to healthcare services and consequently their quality of life (24).

Other caregiver interventions have been examined in other populations. A systematic review and meta-analysis pooled 30 studies and examined the effectiveness of support groups for caregivers of people with dementia on multiple caregivers' outcomes (25). Support groups showed a significant positive effect on caregivers' burden, psychological well-being, depression and social outcomes (25). Another systematic review examined the effect of web-based interventions on caregivers of people with cancer on the physical, social, psychological outcomes (26). Six studies were included (3 RCTs and 3 other study designs) and showed a beneficial effect on caregiver burden, social and psychological outcomes. However, more high-quality research is needed to prove the efficacy of the web-based interventions (26). Corry et al conducted a systematic review of systematic reviews to evaluate the effectiveness of interventions to support caregivers of people with selected chronic conditions (27). They included eight systematic reviews and showed that education and support programme interventions improved caregiver quality of life and information-giving interventions improved caregiver knowledge for stroke caregivers (27). However, more large-scale high quality studies are needed to further estimate the effect of these interventions across caregiver groups (27).

A variety of caregiver's interventions have been examined, but interventions to optimize their health and integrating them to the medical and social support system are lacking. Chapter 4 address this gap in the literature as caregivers often have chronic

medical conditions, neglect their own health, and are less likely to engage in preventive health measures (28).

Our strategy was successful in identifying older adults with a caregiver's role in primary care settings. The future direction for this work will be examining this strategy of identifying caregivers with or without high burden in other primary care settings. Since the caregivers' needs were not met in this study (shown by lack of effect on caregiver's quality of life and social support), a survey of caregivers visiting primary care clinic is needed to know their expectations and needs. A survey of the interdisciplinary team about their educational needs to support caregiver is required. This survey should be followed by education program to primary care interdisciplinary team about the available resources to support caregivers with high burden. Since the wellbeing of caregivers is associated with increasing the frail care recipients' quality of life (24), We aimed to improve the care for frail older adults by identifying and supporting their caregivers. This chapter contribution was introducing a model to identify caregivers of frail older adults in a primary care setting and provide the required support.

In chapter 6, the fracture rating scale (FRS) was predictive of one-year hip and all fractures in older adults living in Long-term care (LTC) in three Canadian provinces. Hip fracture is a common and major event in LTC residents (49%) that leads to disability, hospitalizations and death (29, 30). Given the life expectancy of LTC residents (16), it is challenging for LTC staff to identify residents with high fracture risk and implement the appropriate strategy (31). As the FRS tool will identify those at risk, the implementation of fracture prevention recommendation in LTC will be increased (32). As there are effective non-pharmacological and pharmacological interventions to prevent fractures,

implementing the FRS in LTC across Canada is expected to decrease the incident of hip and all factures. Ultimately FRS implementation may lead to decreased healthcare spending by optimizing LTC residents' functional ability and keeping them partially independent.

This chapter contributes to the field of aging and care for vulnerable elderly by developing and validating the FRS tool, which is tailored to older adults living in LTC. It is expected that the LTC population is increasing and hence the impact and benefit of the FRS tool will also increase. The FRS is embedded in the RAI-MDS 2.0, which is completed within 14 days of a resident entering a home. Thus, the FRS can be easily and regularly implemented in LTC without burden on the LTC staff who are at a significant risk of burnout (33). The LTC staff burnout is caused by the growing number of older adults requiring LTC admission, excessive staff workloads due to complex conditions (34) and inadequate LTC staffing levels (35). As we demonstrated the FRS' validity, we suggest it can be used for LTC resident care planning across Canada and possibly internationally.

The next step after validation of the FRS tool is to develop knowledge translation and implementation strategies to increase the uptake of the FRS tool by the LTC staff. To ensure that residents identified as "at risk" using the FRS receive treatment, an electronic Clinical Assessment Protocol (CAP) will be developed and implemented. The Fracture Risk CAP will automatically produce recommendations for residents based on their fracture risk and will inform clinical decision-making as part of the person-centered care planning process to fill the gap of fracture prevention in LTC. This chapter contribute to the care planning of frail older adults living in the LTC by introducing a fracture

prediction tool tailored and validated for this population. Implementing the FRS tool will improve fracture prevention and consequently morbidity and mortality in frail LTC residents.

Frailty definition includes declining in physical and cognitive function. Rehabilitation science is well positioned to address the frailty syndrome and its related issues and help older adults to regain their functional level. In the context of the world health organization international classification of functioning model, frailty as a health condition may modify older adults' body function and structure (e.g. physiological reserve), activity (daily living activity), and participation (community participation). We expect that treating or reducing frailty may improve body function, activity and participation. This rehabilitation science thesis focuses on prevention and treating frailty in older adults and supporting their caregivers.

7.2 Conclusion

To summarize, this thesis aims to contribute to the clinical care of frail older adults in different settings. The research studies outlined in this thesis concluded 1) the first systematic review and network meta-analysis considering the direct and indirect effect of frailty interventions, found that physical activity and physical activity with nutritional supplementation and medication management are the most effective frailty interventions. The quality of the evidence of this review was low and very low, 2) the Fit Joint RCT will inform the planning and designing of multi-modal frailty interventional studies in hip and knee replacement patients, 3) TAPESTRY approach was successful in identifying people with caregivers role in a primary care setting. There was no difference

between caregivers and non-caregivers in the TAPESTRY approach effect on quality of life, social interaction, hospitalizations and ED visits, 4) the FRS is a validated tool to be used across Canada to predict hip and all fractures in LTC residents.

In this thesis, we addressed several knowledge gaps in frailty and caregivers' literature (as mentioned in chapter 1). As the number of interventions targeting frailty increased, a network meta-analysis was needed to determine the most effective frailty intervention (chapter 2 and 3). Frailty is common in people going for hip and knee replacement; therefore it is critical to determine if a multi-modal frailty intervention is feasible in this population (chapter 4). We examined a primary care model to identify and support caregivers, as primary care team is well positioned to support caregivers (chapter 5). Finally, we validated a fracture prediction tool in LTC resident across Canada, as predicting and preventing fractures in LTC may delay frailty progress (chapter 6). This tool addressed the gap of fracture prediction and prevention in frail LTC residents.

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