Université de Montréal

Social Isolation, Frailty, and Health Outcomes among Community-Dwelling Older Adults: A Longitudinal Study in Québec

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Résumé

Introduction : L'isolement social est un problème de santé publique qui est lié à des résultats de santé négatifs. Cependant, le niveau d'association entre l'isolement social et la santé reste inconnu. Cette association peut être influencée par des facteurs biologiques associés à l'âge, tels que la fragilité. L'objectif général de cette thèse était d'examiner les interrelations entre l'isolement social, la fragilité et les résultats de santé physique, mentale et cognitive chez les personnes âgées au Québec.

Méthodes : Les données proviennent des trois phases de l'étude longitudinale FRéLE, une étude de population auprès de 1643 personnes âgées de 65 ans et plus vivant à domicile dans la province de Québec au Canada. S'appuyant sur la théorie de Berkman, nous avons mesuré l'isolement social par la participation sociale, les réseaux sociaux et le soutien social provenant de différents liens sociaux tels que les amis, la famille nucléaire et la famille élargie. Nous avons opérationnalisé la fragilité en utilisant le phénotype de fragilité de Fried. Les résultats de santé comprenaient l'incapacité physique, la comorbidité, la dépression et la fonction cognitive. Pour atteindre notre objectif, premièrement nous avons effectué un examen de la portée afin de synthétiser la littérature existante sur l'interrelation entre l'isolement social, la fragilité et la santé ainsi que leurs modérateurs et médiateurs. Deuxièmement, nous avons réalisé une série de modèles de régression multivariés pour examiner si la fragilité joue un rôle modérateur sur les relations entre l'isolement social et la santé dans un premier temps. Troisièmement, nous avons réalisé une série de modèles de croissance pour examiner l'effet modérateur des changements de la fragilité sur les associations entre les changements de la relation sociale et la santé en deux ans.

Résultats : Les résultats de l'examen de la portée ont révélé que la fragilité était fortement liée à la mauvaise santé. Cependant, peu d'études ont trouvé une association entre l'isolement social et la santé. En outre, l'association entre le soutien social et les résultats de santé était plus significative que celle des réseaux sociaux et la participation sociale (étude 1- Chapitre 4). Conformément aux résultats de l'examen de la portée, l'analyse transversale a démontré que l'isolement social, plus précisément ou particulièrement le soutien social est lié à la santé mentale et cognitive plutôt qu'à la santé physique chez les personnes âgées. L'analyse de modération a montré que les personnes âgées fragiles qui recevaient du soutien social de leurs amis, participaient à des activités sociales

et qui avaient des amis et des fratries étaient en meilleure santé mentale et cognitive que les robustes (étude 2- Chapitre 5). L'analyse de modération longitudinale a révélé que les changements dans la fragilité ont un effet modérateur sur l'association entre les changements dans la participation sociale, le soutien social ainsi que les contacts sociaux avec les amis sur les changements dans la santé cognitive et mentale (étude 3- Chapitre 6).

Conclusion : Cette étude longitudinale suggère que le soutien social et la qualité de la relation jouent un rôle compensatoire dans l'amélioration de la santé mentale des personnes âgées fragiles dès le début et au fil du temps. Les résultats éclairent davantage le rôle central des amitiés et de la participation sociale dans l'amélioration de l'état de santé des personnes âgées sur deux ans.

Mots-clés *: Isolement social, réseaux sociaux, soutien social, participation sociale, fragilité, modérateur, longitudinale, personnes âgées, vieillissement*

Abstract

Introduction: Social isolation is a public health issue that is linked to various adverse health outcomes. However, the strength of the association between social isolation and health remains unknown. This association may be influenced by biological factors related to increasing age, such as frailty. Hence, the overall aim of this dissertation was to examine the interrelationships between social isolation, frailty, and physical, mental, and cognitive health outcomes among community-dwelling older adults in Québec.

Methods: Data came from three waves of the FRéLE longitudinal study, a population-based study among 1643 community-dwelling older adults aged 65 and over in the province of Québec in Canada. Based upon Berkman's theory, we measured social isolation through social participation, social networks, and social support from different social ties, namely friends, nuclear, and extended family. We assessed frailty using Fried's frailty phenotype. Health outcomes included disability, comorbidity, depression, and cognitive function. To achieve our overall goal, we first conducted a scoping review to map and synthesize the existing evidence on the interrelationship between social isolation, frailty, and health outcomes and their possible moderators and mediators. Second, we performed a series of multivariate regression models to examine whether frailty cross-sectionally moderated the relationships between social isolation and health outcomes. Third, we performed a series of latent growth models to examine the moderating role of changes in frailty on the associations between changes in social relationships and health outcomes.

Results: The results of the scoping review revealed that frailty was strongly linked to poor health outcomes; however, few studies found an association between social isolation and health outcomes. In addition, social support had a more significant association with health outcomes than with social networks and social participation (Study 1- Chapter 4). In accordance with the results of the scoping review, the cross-sectional analysis demonstrated that social isolation, particularly social support, is linked to mental and cognitive health rather than physical health among older adults. The moderation analysis demonstrated that frail older adults who received social support from friends, participated in social activities, and had friends and siblings were in better mental and cognitive health than robust peers (Study 2 - Chapter 5). The longitudinal moderation analysis revealed that

changes in frailty moderated the association between changes in social participation, support from friends, nuclear, and extended family members, and social contacts with friends were associated with greater changes in cognitive and mental health among older adults (Study 3 - Chapter 6).

Conclusion: This longitudinal study suggests that social support and the quality of the relationship have a compensatory role in improving mental health among frail older adults at baseline and over time. The findings further elucidate the pivotal role of friendships and social participation in enhancing health status among older adults in two years.

Keywords*: Social isolation, Social networks, Social support, Social participation, Frailty, Longitudinal, Moderator, Aging*

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List of Acronyms and Abbreviations

ADL: Activities of daily living

AFC-QC: Age-Friendly Cities in Québec

AIC: Akaike's Information Criteria

ANOVA: Analysis of Variance

BIC: Bayesian Information Criterion

BMI: Body-Mass Index

CHARLS: China Health and Retirement Longitudinal Study

CHS: Cardiovascular Health Study

CLSA: Canadian Longitudinal Study on Aging

CSHA: Canadian Study of Health and Aging

ELSA: English Longitudinal Study of Ageing

EPESE: Hispanic Established Populations for the Epidemiologic Study of the Elderly

FCI: Functional Comorbidity Index

FI-CGA: Frailty index derived from comprehensive geriatric assessment

FRéLE: Fragilité, une étude longitudinale de ses expressions / Frailty: A longitudinal study of its expressions

GDS-15: 15 item Geriatric Depression Scale

GFI: Groningen Frailty Indicator

IADL: Instrumental Activities of Daily Living

IMIAS: International Mobility in Aging Study

NSHAP: National Social Life, Health, and Aging Project

LASA: Longitudinal Aging Study Amsterdam

LGM: Latent Growth Curve Model

LMS: Latent Moderated Structural

MAR: Missing at Random

MCAR: Missing Completely at Random

MNAR: Missing Not at Random

MoCA: Montreal Cognitive Assessment

ML: Maximum Likelihood

NuAge: Étude longitudinale québécoise sur la nutrition comme déterminant d'un vieillissement réussi/ Québec Longitudinal Study on Nutrition and Successful Aging

PASE: Physical Activity Scale for the Elderly

PF: Physical Functioning

PR: Participation Restrictions

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: Randomized Controlled Trial

SD: Standard Deviation

SEM: Structural Equation Modeling

SHARE: Survey of Health, Ageing and Retirement in Europe

SES: Socioeconomic Status

SOF: Study of Osteoporotic Fractures

TFI: Tilburg Frailty Indicator

TILDA: Irish Longitudinal Study on Ageing

TLSA: Taiwan's Longitudinal Study on Aging

WHAS: Women's Health and Aging Studies

WHO: World Health Organization

To Rose and all frail and isolated older adults

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Chapter 1 – Introduction

"Strong social ties are good for one's health. The consequences of neglecting this fact become especially apparent in older age. It is thus urgent that more attention be given to social isolation as a potent killer". Lubben (2017)

Social isolation and frailty are growing public health concerns with important implications for the health of aging populations. Perhaps, the most compelling argument that social isolation poses a substantial public health risk was put forth by Holt-Lunstad et al. (2010) that social isolation has a more significant health risk than smoking and obesity.

1.1 Social isolation

Industrialization and modernization have produced several striking and characteristic demographic changes including the decline of formal marriage and childbearing, a rise in rates of divorce, and increasing life expectancy worldwide, particularly in European and North American countries (Carr, 2019; Djundeva et al., 2018; Mair, 2019). As a result, the number of older adults who lack a partner/spouse, child or kin, and, therefore, age alone is rising (Carr, 2019; Mair, 2019). The proportion of older adults living alone tends to increase with age. In 2016, nearly one in three older adults lived alone in Québec compared to one in four across Canada (Charpentier & Kirouac, 2019). The frequency of participation in community activities with family and friends is also lowest among older adults in Québec compared to other provinces of Canada (Naud et al., 2019). Consequently, these older adults are more likely to live with a lower level of social support and fewer social contacts, a condition which in some cases can lead to social isolation (Carr, 2019; Mair, 2019). Older adults with smaller personal networks have a lower likelihood of participating in social activities. This situation may result in social inequality where those who have better access to social resources can create better living conditions than those with less (Hortulanus et al., 2006). It has been estimated that 24% of older Canadians need more informal contacts, and approximately one in five Canadians aged 65 or over feels lonely or isolated. The prevalence of social isolation ranges from 6% to 43% among Canadian community-dwelling older adults versus 7% to 17% worldwide (Dickens et al., 2011; Gilmour, 2012; Keefe et al., 2006; Menec et al., 2019).

One of the assumptions underlying aging research is that older adults are particularly vulnerable to social isolation as they age due to the impact of predictable events related to social and physical aging (Wethington & Pillemer, 2014). Certain subgroups of older adults are more at risk of social isolation and loneliness than others due to physical health conditions, illness, the death of loved ones, or other life events (Davies et al., 2021; Duppen et al., 2019). Maintaining meaningful relationships is central to the health and well-being of older adults. In this vein, a broad range of social relationships is critical, including informal relationships with friends, neighbors, children, other family members, and intimate relationships (Carstensen, 2006; World Health Organization, 2015). Evidence has demonstrated the protective effects of social support, frequency of social contacts, and social ties against adverse health outcomes among older adults (Holt-Lunstad et al., 2017). Conversely, social isolation has been associated with increased risks of depression (Santini et al., 2016), cognitive decline (Okura et al., 2017), disability (Janke et al., 2008), cardiovascular diseases, higher blood pressure, a weakened immune system, inflammatory reactivity, negative health-related behaviors, poorer biological responses (Cacioppo & Hawkley, 2003; National Academies of Sciences & Medicine, 2020), and premature mortality in older adults (Holt-Lunstad et al., 2015).

Social isolation is a risk factor for mortality and a broad array of adverse health outcomes. However, other risk factors may influence the relationship between social isolation and health. Modeling risk factors for health outcomes might enhance our ability to better understand for whom social isolation might mostly influence physical, mental, and cognitive health status (Berkman, 2014; Holt-Lunstad & Smith, 2016). There is substantial evidence that demographic factors (i.e., age, gender, ethnicity, socioeconomic status (SES)) intervene in the relationships between social relationships and health (Das, 2013; Domènech-Abella et al., 2017; Hämmig, 2019; Holt-Lunstad et al., 2015; Holt-Lunstad et al., 2010; Maes et al., 2019). Recent evidence suggests that the deleterious health effects of social isolation are particularly strong among people over 65 years of age, those with low SES, and minorities (Cacioppo & Hawkley, 2003; Röhr et al., 2021).

Current evidence also supports plausible biological mechanisms that may explain the strength or direction of the effect of social isolation on health (Ditzen & Heinrichs, 2014; Hennessy et al., 2009; Uchino, 2006). The mechanisms can be explained by the fact that socially isolated adults are more likely to passively cope with stressors and stressful conditions, reporting greater vascular

resistance and blood pressure. Someone experiencing isolation may feel mistrust and alienation toward others that activates a biological defense mechanism (Cacioppo & Hawkley, 2003; National Academies of Sciences & Medicine, 2020). Isolated older adults have weakened immune systems that put them at risk for some diseases and they may lack the inflammatory response needed to heal from injury or illness.

Stressors could increase levels of frailty, a key biological mechanism. Frailty is an age-related physiological vulnerability to various life stressors (Peek et al., 2012; Walston et al., 2006). Pre-frailty is the silent precursor to frailty that can lead to frailty when external stressors occur in older adults (i.e., acute illness, injury, or psychological stress) (Dent et al., 2016). The evidence for specific impacts of social isolation on health in at-risk populations such as frail older adults is sparse. Understanding whether biological alterations may be modified could have profound effects on both research and health policy approaches to developing effective strategies to improve population health (Berkman, 2014).

1.2 Definition of social isolation and loneliness

Social isolation is different from loneliness, and the distinction between the two conditions is raised in many research studies. Social isolation is defined as a low quantity and quality of contact with others, whereas loneliness is a subjective feeling from limited social contact and rooted in one's perception of the quality of contact. Socially active persons with extensive social networks may feel lonely, while socially isolated persons with a small number of social contacts may not necessarily feel lonely and may feel sufficiently embedded (Cornwell et al., 2008; De Jong Gierveld, 2006; Grenade & Boldy, 2008; National Academies of Sciences & Medicine, 2020). Social isolation can be measured by a broad range of structural and functional aspects. Social network size and social participation are structural network features and receiving little social support is an important functional aspect of social isolation.

- Social networks refer to the web of social relationships surrounding an individual and the characteristics of those social ties.
- Social support pertains to various types of assistance that people receive from their social networks, including instrumental, emotional, informational, and appraisal support (House et al., 1985; Kawachi & Berkman, 2000). Instrumental support involves the provision of

tangible aid and services that directly meet the immediate need of the person such as food, clothing, cooking, getting groceries, or paying bills. Emotional support refers to the amount of affection, love, caring, empathy, and respect from an intimate partner, children, friends, and relatives. Informational support is related to giving feedback, suggestions, and opinions, or helping in decision making. Appraisal support pertains to the provision of information that is useful for self-evaluation purposes (Berkman & Glass, 2000; House et al., 1988).

- Social participation refers to a person's active involvement in activities that provide interactions with others in society or community and express interpersonal interactions outside the family environment. Community involvement such as belonging to social or religious groups, getting together with friends and relatives, volunteering, attending social functions, and participating in social roles and leisure activities are examples of social participation (Berkman, 2014; Levasseur et al., 2022; Levasseur et al., 2010).

1.3 Current public health concerns and health policy responses

Geriatrics and gerontological scholars have increasingly voiced concern about social isolation and loneliness in late life and their impacts on health (Berg-Weger & Morley, 2020; Holt-Lunstad et al., 2017). Accordingly, public health agencies and governments promote reducing social isolation and loneliness and strengthening social engagement and connectedness among older populations as an important public health goal (Freedman & Nicolle, 2020). As such, social isolation has been considered one of the priority areas by the National Seniors Council in Canada (Council, 2015). The Québec Government has also identified social engagement and social participation of older adults as one of its priorities in the 2018–2023 Action Plan, A Québec for All Ages (Coté et al., 2012). At the international level, the UK and Japan have recently appointed a Minister for Loneliness to tackle social isolation and loneliness in later life through community action, practice, research, and health policy (Freedman & Nicolle, 2020). In addition, the World Health Organization (WHO) approach to healthy aging underlines the importance of maintaining social relationships in older age. Social relations are an important component of healthy aging because meaningful and positive interactions can yield resources, such as trust and social support. Strong social support networks can enhance longevity and quality of life in later life, and thus protect

against functional decline and promote physical and social resilience in older age (World Health Organization, 2015).

As a policy response to demographic aging, the WHO has created a Global Network for Age-Friendly Cities and Communities to promote physical, leisure, and social activities that are accessible and inclusive (World Health Organization, 2015). Age-Friendly cities and communities foster healthy and active aging and enable well-being throughout life. Social participation and social inclusion are among the features of this initiative to alleviate social isolation and loneliness. The Age-Friendly Cities in Québec (AFC-QC) were launched in 2008 along with other provinces of Canada, aiming to improve the quality of life of older adults by intervening in different aspects of social inclusion (Garon et al., 2014). The AFC-QC is a community-building approach, compatible with the WHO's active aging concept (World Health Organization, 2002) and the bottom-up approach from the Madrid International Plan of Action on Aging (United Nations, 2006). This initiative emphasizes the participation of older adults in all stages of the approach to ensure a relevance between the needs of older adults and measures to be implemented. Social participation, inherent in the active-aging approach of the WHO, constitutes the cornerstone for understanding the development of AFC-QC (Garon et al., 2016). In line with this program, the research studies have underlined the importance of the participation of older adults in social activities on their mental well-being (Santini et al., 2016; Santini et al., 2020) and physical health (Kristensen et al., 2019). According to the WHO Report on Aging and Health (2015), making progress on healthy aging requires a much better understanding of age-related issues. One of the age-related health conditions is frailty (Bandeen-Roche et al., 2006).

1.4 Frailty and health outcomes

Global aging demographic projections estimate that there will be two billion people aged 65 years or older worldwide by 2050 (World Health Organization, 2017). The proportion of older adults in the Canadian population surpassed the proportion of youth in 2015, and the greatest number of older adults will reside in Québec and Ontario by 2030 (Statistics Canada, 2019). In 2036, 23%–25% of the total Canadian population will be over 65 years old, and one person out of three older adults will be 80 years or over (Bohnert et al., 2015). Both gerontological and geriatric evidence has illustrated the increase in risks of frailty with advancing age (Duppen et al., 2019; Fried et al.,

2001). Frailty is typically more prevalent in women than in men (Gordon & Hubbard, 2020) and is observed in 12%–24% of older adults across the world (O'Caoimh et al., 2021). Approximately 7.8% of Canadian community-dwelling older adults aged 65 and older are physically frail (Kehler et al., 2017). With an increasingly older population, chronic diseases, disability, and adverse health outcomes will exert a burden on individuals, family members, and the public. Accordingly, it is urgently required to identify individuals most vulnerable to poor health outcomes and prevent and ameliorate adverse health outcomes in such individuals. Consequently, it is needed to delay the onset of vulnerabilities and fortify resilience in these vulnerable persons. Relatedly, frailty has gained attention in the past decades for its promise for identifying vulnerable older adults and its potential to meet the identified needs (Bandeen-Roche et al., 2020).

Not only can older persons expect to live much longer than previous generations, but they are also more prone to dwindling social connections. For example, globalization and global connectivity make it easier for younger generations to migrate to urban areas. This may result in older family members being left in rural areas without social networks or support. Furthermore, due to changes in family structure and dramatic falls in fertility, the relative number of younger people in a family is much lower than in previous decades (World Health Organization, 2015). Consequently, family support is less available than for previous generations of older adults (Wethington & Pillemer, 2013). While intrinsic factors such as genetics and frailty contribute to adverse health outcomes, there is growing recognition of the effects of social factors on frailty, and consequently on health outcomes (Freedman & Nicolle, 2020).

Although the concept of frailty is broadly defined and has evolved in the scientific literature, there is an ongoing debate regarding its optimal definition and concept (Bergman et al., 2007; Hoogendijk et al., 2019). Frailty is generally defined as a state of increased vulnerability to external stressors (Dent et al., 2016; Morley et al., 2013). There are two main approaches to conceptualizing physical frailty in the field of gerontology and geriatrics. The first approach is the phenotype of frailty, proposed and validated by Fried (2001), operationalized in the Cardiovascular Health Study (CHS) among community-dwelling older adults aged 65 and over. In this approach, frailty refers to a biological syndrome derived from cumulative declines in different physiological systems, resulting in a loss of reserves and resistance to external stressors. The five characteristics of the phenotype of frailty are unintentional weight loss, fatigue, weakness, slowed performance, and low

physical activity. Any three of these five characteristics define a person as frail (Fried et al., 2001). Physical frailty is characterized by slow and incomplete recovery after new acute illness, injury, or psychological stress, indicating that total physiological reserves diminish and become insufficient for the maintenance and repair of the aging body (Lang et al., 2009). Accordingly, physical frailty may lead to increased risks of adverse health outcomes such as falls, hospitalization, disability, and mortality (Clegg et al., 2013; Fried et al., 2001). The second approach is the frailty index proposed by Mitnitski and Rockwood (2001) that is based on an accumulation of age-related deficits, including symptoms, signs, abnormal laboratory values, functional impairments, diseases, and disabilities. This approach sees frailty not as a specific clinical syndrome but as an age-related state of poor health status (Mitnitski et al., 2001).

The differences between frailty as a clinical syndrome and frailty as a state of health, though real, are exaggerated. Both approaches are informative at the group and population levels, providing essential and complementary insights. Both views share genetic determinants and have strong social determinants and consequences. Another common feature of the two approaches is that each sees frailty as rooted in aging. Notably, not all people age at the same rate, and not every one the same age has the same risk of mortality. Both approaches use more than one criteria to define frailty and predict higher risks of poor health outcomes. Once frailty is characterized, the effort can be made to explore the antecedents of differential aging. Antecedents can be risk factors for differential aging, such as genetic influences or social vulnerability, or can be features of aging such as loss of the ability to resist stress (the idea of robustness) or recover from functional decline (the idea of resilience). Most importantly, a common unifying definition of frailty includes both robustness and resilience. The loss of robustness or resilience results from the reduction in physiological reserve (Andrew et al., 2008; Howlett et al., 2021; Kuchel, 2018; Li et al., 2015; Ukraintseva et al., 2016). Psychological resilience refers to a person's potential ability to adapt in the face of threats or minor stressors (Whitson et al., 2018). In a systematic review, Whitson et al. (2016) state that "physical resilience is defined as a characteristic at the whole person level which determines one's ability to resist or recover from functional decline following health stressors" (p. 493). Physical resilience is partly constrained by underlying physiologic reserve across organ systems and is influenced by genetics, environment, and psychosocial factors. Both physical and psychological resilience manifest as an individual's ability to respond to late-life stressors (Whitson et al., 2016).

Many other frailty tools were thereafter developed based on these two main approaches (Aguayo et al., 2017; McIsaac et al., 2019). The FiND questionnaire (Cesari et al., 2014), the study of osteoporotic fractures (SOF) index (Luciani et al., 2013), and the Beaver Dam Eye Study Index (Klein et al., 2003) are examples of tools based on the phenotype of frailty conceptual model (Aguayo et al., 2017). Examples of some commonly used and validated frailty tools based on the accumulation of deficit model include the Comprehensive Geriatric Assessment (Jones et al., 2004), the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (Rockwood et al., 2005), and the Long Term Care Survey Frailty Index (Kulminski et al., 2007). The Geriatric Advisory Panel of the International Academy of Nutrition and Aging proposed the FRAIL scale (fatigue, resistance, ambulation, illnesses, loss of weight) based on the combination of these two approaches (van Kan et al., 2008).

Alternatively, Gobbens et al. (2010) proposed the "Multidimensional Model" that describes frailty as a dynamic state of loss affecting one or more domains of functioning including cognitive, physical, and social. There are other similar multidimensional tools used to identify frailty in older adults. For example, the Edmonton Frail Scale (Rolfson et al., 2006) and the Groningen Frailty Indicator (GFI) (Peters et al., 2012) evaluate physical, cognitive, social, and psychological domains, and the Tilburg Frailty Indicator (TFI) focuses on physical, psychological, and social domains (Robbert J Gobbens et al., 2010).

Apart from the definition of frailty, identifying which frailty measure is most suitable for clinical settings is a continuous heated discussion among scholars. Most importantly, a frailty measure should be able to accurately identify frailty. As suggested by Clegg et al. (2013), the frailty measurement should be able to reliably predict clinical outcomes and response to potential treatments, supported by a biological theory. It should be also simple to apply (Bandeen-Roche et al., 2006; Clegg et al., 2013; Dent et al., 2016). The phenotype of frailty meets some of these criteria as its foundation is based on a biological theory and can predict clinical outcomes. For example, some of the Fried criteria (i.e., grip strength) are not routinely used for patient assessment (Dent et al., 2016).

This dissertation focuses on the phenotype of frailty for several reasons. The Fried phenotype of frailty is the most coherently articulated approach to frailty to date (Bergman et al., 2004) and has been widely cited in research publications and clinical practice (Bouillon et al., 2013; Duppen et

al., 2019). In addition to its relative simplicity, the operational definition by Fried et al. (2001) has shown a good predictive validity for adverse health outcomes in groups of community-dwelling older adults aged 65 years and over (R. Gobbens et al., 2010). In contrast to the frailty index and multidimensional measurements of frailty, the phenotypic definition excludes characteristics such as social, cognitive, and psychological domains, disability, or complex comorbidity (McDermid & Bagshaw, 2014), allowing researchers to examine the association of specific dimensions of health with social isolation and frailty. Indeed, the role of cognitive abilities and psychosocial milieu in the frailty concept remains under debate. According to Bandeen-Roche et al. (2020), cognitive and psychosocial vulnerabilities are important but unique conditions that should be measured separately from each other and from physical frailty. This view is partially supported by findings of a previous population-based study that different domains of frailty, including nutrition, physical activity, mobility, strength, energy, and mood, appear to aggregate together except for the cognition domain (Sourial et al., 2010). Therefore, one could assess risks or harms from concurrent vulnerabilities in different domains (Bandeen-Roche et al., 2020). In addition, a systematic review and meta-analysis of 48 research studies on the co-existence of frailty and multimorbidity have illustrated that frailty and comorbidity are two related conditions, and the majority of frail older adults are multimorbid; however, few older adults with multimorbidity are frail (Vetrano et al., 2019). Given that social functioning is one of the components of several multidimensional measurements of frailty and this dissertation is inspired by Berkman and Krishna's theory (2014) on the impact of social isolation on health outcomes, the application of multidimensional models of frailty is irrelevant. Research illustrated that social components of frailty did not predict poor health outcomes (Gobbens et al., 2012a) . Frailty is one of the determinants of health that occurs when multiple physiological systems decline (Dent et al., 2016). This specific status of frailty and physiological processes may make frail older adults more vulnerable to diseases such as depressive symptoms, falls, dementia, chronic diseases, disability, and mortality. Given the physiological features of physical frailty and based on Berkman and Krishna's theory (2014), social isolation may impact frailty, one of the determinants of health, and health outcomes. Therefore, the phenotype of frailty is more appealing for use in this dissertation than other types of frailty.

1.5 Social isolation, frailty, and health outcomes

Both social isolation and frailty are often associated with older age (Fried et al., 2001; Wenger & Burholt, 2004) and are linked to a myriad of physical, mental, and cognitive health problems (Zhang et al., 2018). A number of studies have reported associations between small social networks, less social support, and low levels of social activities with frailty (Buttery et al., 2015; het Veld et al., 2015; Jürschik et al., 2012; Vaingankar et al., 2017) with consistent evidence that frail older adults have a higher prevalence of morbidity and rates of mortality than robust older adults (Hayashi et al., 2020; Liao et al., 2018). However, it appears that associations between these variables may vary according to the measures used and types of social ties. For example, the results of a cross-sectional study from Korea have shown that social contact with friends rather than with family members and neighbors was associated with frailty (Chon et al., 2018). Conversely, a cross-sectional study from Ireland found no relationship between frequency of contact with friends or neighbors and frailty (Schnittger et al., 2012). The results of cross-sectional studies in China and Canada highlighted the beneficial effect of social contact with friends on cognitive health and quality of life (Bélanger et al., 2016; Wang et al., 2015). In other cross-sectional studies from Spain and Latin America, perceived social support from children had a positive impact on the health status of older adults (Bélanger et al., 2016; Zunzunegui et al., 2009). Evidence also indicates that there is a link between having children and psychological well-being (Dykstra, 2015). These nuances suggest the possibility of different impacts of social network types on frailty and health outcomes.

Empirical evidence is limited, and findings are equivocal on the interrelationships between social isolation, frailty, and health outcomes. Three cross-sectional studies (Dent & Hoogendijk, 2014; Hermsen et al., 2014; Kamiya & Kenny, 2017) examined the effects of social isolation and physical frailty on adverse health outcomes. They found frailty was linked to disability, falls, and mortality; however, social isolation was not associated with adverse health outcomes. By contrast, a cross-sectional study (Zhang et al., 2018) and a longitudinal study (Li & Hsu, 2015) found that social support and frailty were independently associated with falls and cognitive function, while social participation was not linked to frailty and cognitive function. The results of a cross-sectional study from Japan (Hayashi et al., 2020) and a longitudinal study from the Netherlands (Hoogendijk, Smit, et al., 2020) on the combined effects of frailty and social isolation on adverse health outcomes

revealed that frail and isolated older adults were at the greatest risk of mortality and falling compared to frail non-isolated, isolated robust, and robust socially active peers. These discrepancies suggest that frailty might intervene in the relationship between social isolation and health and make isolated older adults more vulnerable to adverse health outcomes. This is the case, for example, in a longitudinal study (Liao et al., 2018) that examined the effect of social support and frailty on mortality. The results have shown that robust older adults who provided social support to their family members had a lower risk of mortality compared to frail older adults.

One of the main reasons why we know little about social isolation is the inconsistent use of the concept of social isolation and its operationalization. Previous researchers have identified a wide range of social isolation indicators that pose health risks, including infrequent participation in social activities, having a small social network, and lack of social support. However, different aspects of social isolation are rarely studied together in frailty research, which makes it difficult to determine which aspects of isolation are most deleterious for health. Given that these aspects are measured in different ways, meaningful comparisons between the findings of different studies are also limited. It is thus unclear which aspects (structural versus functional) are more problematic than others.

In sum, knowledge gaps in the scientific literature have shown that few studies considered the effects of different types of social ties, such as friends, children, and family members, on frailty and health outcomes. In addition, most of the previous studies have been cross-sectional and have included either only structural or functional aspects of social isolation among older adults. The majority of studies have suggested a need for the incorporation of both structural and functional aspects of social isolation through longitudinal studies to better understand which aspects of social isolation can increase or reduce the incidence of frailty and adverse health outcomes among older adults. In addition, research studies have mostly focused on physical health and less attention has been paid to mental and cognitive health outcomes. There is a scant longitudinal study on the interrelationship between social isolation, frailty, and adverse health outcomes and whether frailty intervenes in the relationship between social isolation and health. Longitudinal studies allow us to understand how late-life social factors influence the trajectories of frailty, and consequently, health outcomes. Longitudinal studies also permit investigating continuity and change over time and exploring what predicts changes. To this end and to address knowledge gaps in the literature, the overall aim of this dissertation was to examine the interrelationship between structural and

functional aspects of social isolation, the phenotype of frailty, and physical, mental, and cognitive health outcomes among community-dwelling older adults in Québec.

1.6 Statement of purpose and specific objectives

The main aim of this doctoral research study was to examine the moderating role of changes in frailty on the relationship between changes in social isolation/relationships and changes in health outcomes among community-dwelling older adults in Québec. To achieve this goal, we first reviewed the existing research studies on the relationship between social isolation, loneliness and physical frailty; the interrelationship between social isolation, loneliness, frailty, and health outcomes; as well as the possible moderators and mediators in these relationships. The results of the scoping review provided us with an overview of the available research evidence on the relationship between social isolation, physical frailty, and health outcomes, and gaps in research studies. We were not able to investigate the role of loneliness on frailty and health outcomes in the second and third research studies due to the nature of secondary data. Second, we analyzed cross-sectional data (baseline) to be familiar with the dataset and have better insight into the associations between variables of interest. In line with the results of our scoping review, we examined the moderating role of frailty on the cross-sectional relationship between social isolation and health outcomes. The results of the cross-sectional study gave us an idea about the moderating role of frailty on the relationship between social isolation, and physical, mental, and cognitive health outcomes. Based on these results, we built our hypothesis for the longitudinal study (baseline and follow-up 1-2). Central to our hypothesis is that changes in frailty moderate the association between changes in social relationships and changes in health outcomes.

Specifically, this doctoral research study sought:

1. To document and synthesize the existing evidence on the effects of social isolation and loneliness on frailty and health outcomes and the potential moderation and mediation pathways related to health outcomes among community-dwelling older adults (Chapter 4- Study 1).
2. To examine whether the relationship between social isolation/relationships and health outcomes varied based on frailty status among community-dwelling older adults in Québec.

2.a. To examine the moderating role of frailty on the cross-sectional relationship between social isolation and health outcomes among community-dwelling older adults in Québec (Chapter 5- Study 2).

2.b. To examine whether changes in frailty moderated the association between changes in social relationships and changes in health outcomes among community-dwelling older adults in Québec (Chapter 6- Study 3).

1.7 Structure of the dissertation

The dissertation contains seven chapters, including this introduction. Chapter 2 presents details on the literature related to social isolation, physical frailty, and health outcomes among community-dwelling older adults, with a focus on social isolation theories and frailty frameworks. Further, this chapter provides a comprehensive understanding of how and under which mechanisms frailty plays a moderator role on the pathway from social isolation to health outcomes. Chapter 3 presents the data sources and methods employed. Chapter 4 is related to a scoping review of the literature which is the first study of this dissertation published in the *Archives of Gerontology and Geriatrics*. The goal of this review was to lay out the state of research and knowledge gaps on 1) the effects of social isolation and loneliness on physical frailty and the possible moderators and mediators on these relationships; 2) the effects of social isolation, loneliness, and physical frailty on health outcomes; 3) the moderating roles of frailty or social isolation and loneliness on the pathway to health outcomes among community-dwelling older adults; and 4) the implications for public health policies and practices (Study 1). More specifically, the findings of this review construct a platform for analyzing the cross-sectional and longitudinal associations between variables of interest. Chapter 5 outlines the cross-sectional results on the effect of social isolation on frailty and physical, mental, and cognitive health as well as the moderating role of frailty on the pathway from social isolation to health (Study 2). The second study is published in the special issue related to the "Prevention and Management of Frailty" in the *International Journal of Environmental Research and Public Health*. The cross-sectional study generated the hypotheses for the longitudinal study. Chapter 6 presents the longitudinal results on the moderating role of changes in frailty on the pathway from changes in social relationships to health outcomes (Study 3). This manuscript will

be submitted to a scientific journal. Lastly, Chapter 7 presents the dissertation's contributions to the scientific literature and provides an overall conclusion on the findings of this dissertation.

Chapter 2 – Literature Review and Conceptual Framework

2.1 State of knowledge

This section reviews cross-sectional and longitudinal studies published on the interrelationship between social isolation, physical frailty, and health-related outcomes among community-dwelling older adults. More specifically, I first present original research studies on the relationship between structural and functional aspects of social isolation and health outcomes. Then, I lay out the studies on the relationship between social isolation and physical frailty as well as those on the relationship between social isolation, frailty, and health outcomes, from 2001, the publishing year of the phenotype of frailty, up to December 2021. The results of some of these studies are discussed in detail in Study 1 (Chapter 4) and summarized here.

2.1.1 Social isolation and health

The structural and functional characteristics of social isolation have important effects on adverse health outcomes (Berkman & Glass, 2000; Erin York Cornwell & Linda J Waite, 2009; Shankar et al., 2011). John Cassel (1976) and Sidney Cobb (1976) highlighted the salient roles of social support from social ties on health outcomes. In this view, social ties might provide essential social support during illness through either helping a person to cope with the stressful experiences and recover more quickly from an illness or enabling individuals to reduce risky health behavior (i.e., alcohol consumption and cigarette smoking) and maintain healthy habits (Berkman, 2014; Berkman et al., 2000; Cassel, 1976; Lubben, 2017). Individuals' social support networks directly impact how they interact with their environments. Social ties (e.g., family members, friends, spouse, and neighbors) can play important roles in older adults' lives and reduce their feeling of isolation. Having an extensive social network might not be necessary to achieve a rewarding social network, but rather the rewards of a social network are greatest when individuals have high-quality relationships with others (Chatters et al., 2018; National Academies of Sciences & Medicine, 2020).

Research evidence has demonstrated that social isolation could predict poor health outcomes such as disability, depression, cognitive impairment (Buttery et al., 2015), comorbidity (Eck & Riva,

2016; Victor & Yang, 2012), and mortality (Naito et al., 2021) among older adults. A comprehensive meta-analysis of 148 research studies measuring the structural, functional, or combined aspects of social relationships, highlighted the effects of social isolation on mortality (Holt-Lunstad et al., 2010). A recent longitudinal study, using the Irish Longitudinal Study on Ageing (TILDA), illustrated that high loneliness and few social networks were associated with increased all-cause mortality risk among community-dwelling older adults (Kuiper et al., 2016). Likewise, several recent prospective studies, systematic reviews, and meta-analyses have replicated these findings, demonstrating that a lack of social connections was significantly associated with increased risk for premature mortality (Holt-Lunstad et al., 2015; Lennartsson et al., 2021; Rico-Uribe et al., 2018; Shor & Roelfs, 2015; Tanskanen & Anttila, 2016).

A longitudinal study, using data from the China Health and Retirement Longitudinal Study (CHARLS), investigated the association between social isolation and loneliness with functional ability, including activities of daily living (ADL) and instrumental activities of daily living (IADL). This longitudinal study found that social isolation, rather than loneliness, was related to functional impairment over four years among older women but not older men (Guo et al., 2021). Another longitudinal study, using the National Social Life, Health, and Aging Project (NSHAP) data, found that social networks were not significantly associated with functional impairment in community-dwelling older adults (Guida et al., 2020). A longitudinal study, using the same dataset, found a bidirectional association between social networks and depression among community older adults (Santini et al., 2020). Likewise, a longitudinal study from China provided evidence that social contact with children and social participation was significantly associated with a decreased risk of depression among older adults (Wang et al., 2020).

The results of a recent systematic review and meta-analysis on the longitudinal relationship between social isolation and cognitive function in later life have shown that different aspects of social isolation, including social networks and social participation, were associated with cognitive decline among older adults. However, there is wide variation in approaches to measuring social isolation across 61 included studies which may contribute to inconsistencies in the results (Evans et al., 2019). Another systematic review and meta-analysis of longitudinal studies replicated these findings, demonstrating that structural, functional, and a combination of structural and functional aspects of social isolation were associated with cognitive decline (Kuiper et al., 2016).

Nevertheless, no firm conclusions can be drawn about the strength and magnitude of the associations and the relative importance of the different aspects of social isolation. The discrepancies in the results were due to the type of social relationship measurement and methodological quality of included studies.

2.1.2 Social isolation, frailty, and health outcomes

In general, few studies have investigated the interrelationship between social isolation, frailty, and health-related outcomes. Kamiya and Kenny (2017) used a multidimensional measurement of social isolation, including social networks, social support, and social participation. The results showed that social isolation was linked neither to frailty nor to mortality; however, frailty was associated with mortality. Dent and Hoogendijk (2014) reached the same results and revealed no association between social isolation, including social networks and social support, and health outcomes, though frailty was linked to disability, hospitalization, and mortality. Furthermore, Dent and Hoogendijk (2014) looked at the direct effect of frailty on social isolation and found no association between these variables.

A cross-sectional study (Malini et al., 2016) reported no link between social support, frailty, and fear of falling. By contrast, a cross-sectional study (Zhang et al., 2018) found that both social support and frailty were independently associated with falls. Likewise, a cross-sectional study has demonstrated a significant association between social participation with frailty and falls among Malaysian community-dwelling older adults (Risbridger et al., 2021). A cross-sectional study from the Netherlands (Hermsen et al., 2014) found that frailty was linked to poor health outcomes including participation restrictions and functional limitations; though social support was only related to participation restrictions. The results of a longitudinal study, using the Taiwan Longitudinal Study of Aging (TLSA), revealed no link between social participation and cognitive function, whereas social support and frailty were independently linked to cognitive function among older women (Li & Hsu, 2015).

2.1.3 Combined effects of social isolation and frailty on health

Two recent studies examined the combined effects of social isolation and frailty on health outcomes. A cross-sectional study from Japan investigated the combined effects of frailty and social isolation on fear of falling among older adults (Hayashi et al., 2020). This study categorized

the participants into four groups: 1) robust older adults without social isolation, 2) non-isolated frail older adults, 3) isolated robust older adults, and 4) frail and isolated older adults. The results demonstrated no evidence of falling among non-isolated frail older adults and isolated robust peers. However, a combination of frailty and social isolation was significantly associated with falling. More specifically, the risk of falls was higher among frail isolated older adults than non-isolated frail older adults and isolated robust peers (Hayashi et al., 2020).

Hoogendijk et al. (2020), using the Longitudinal Aging Study Amsterdam (LASA) dataset, investigated the combined effects of the phenotype of frailty and social isolation on mortality in community-dwelling older adults. Social isolation is measured through social networks and social support. They created four groups in regard to social isolation and frailty, as suggested by Hayashi et al. (2020). The results of this longitudinal study have shown that frail older adults were at a higher risk of mortality compared to robust older adults without any of these conditions. However, the highest risk of mortality was observed in older adults with the combination of frailty and social isolation (frail isolated older adults) over time. These results highlighted that social isolation in frail older adults may have serious consequences in adverse health outcomes.

In sum, these two recent studies have reported that the combination of social isolation and frailty is linked to adverse health outcomes (Hayashi et al., 2020; Hoogendijk, Smit, et al., 2020). Overall, the results of these studies have illustrated that social isolation, in and by itself, was not associated cross-sectionally and longitudinally with poor health outcomes. The association appeared when social isolation is combined with frailty. This indicates that the relationship between social isolation and frailty with health remains equivocal. Relatedly, the relationship between frailty and social isolation may be bidirectional, such that higher social isolation may lead to physical frailty, and/or physical frailty may lead to higher social isolation (Hayashi et al., 2020).

2.1.4 The unidirectional and bidirectional relationship between social isolation and frailty

2.1.4.1 Social isolation and frailty

Several cross-sectional studies found an association between a lack of social networks (Chen et al., 2015; het Veld et al., 2015; Jürschik et al., 2012; Vaingankar et al., 2017) and low social support (Buttery et al., 2015; Luger et al., 2016) with frailty. By contrast, other cross-sectional studies

illustrated no association between social support and frailty (Chen et al., 2014; Gale et al., 2012; Jürschik et al., 2012). In regard to social participation, two longitudinal studies demonstrated a link between less social activities and developing frailty over time (Etman et al., 2012; Hsu & Chang, 2015). Likewise, the results of a longitudinal study from Japan, using the Japanese version of the phenotype of frailty, revealed that exercise-based social participation and social networks with neighbors were associated with less frailty progression among community-dwelling older adults aged 75 years and over (Takatori & Matsumoto, 2021). In line with this study, another longitudinal study found participation in sports clubs and voluntary activities significantly decreased the risk of progression from non-frailty to frailty among Chinese community-dwelling older adults over two years (Xie & Ma, 2021). Several cross-sectional studies replicated this finding on the relationship between social participation and frailty (Chen et al., 2014; Chen et al., 2015; Kwan et al., 2019).

Two cross-sectional studies and one cohort study (Chon et al., 2018; Schnittger et al., 2012; Uno et al., 2021) have examined the effect of different types of social ties, including children, friends, family, and neighbors, on frailty. The results of a cross-sectional study from Korea (Chon et al., 2018) revealed that social contact with friends was significantly associated with physical frailty; however, contact with family and neighbors was not linked to frailty. Likewise, the results of a one-year prospective cohort study from Japan, using the Nagoya Longitudinal Study for Healthy Elderly dataset, have revealed that contact with friends but not with family members was associated with an increased risk of developing prefrailty (Uno et al., 2021). In contrast, a cross-sectional study from Ireland reported no relationship between social contact with friends and neighbors and developing frailty (Schnittger et al., 2012).

Two longitudinal studies have examined the effect of social isolation on the phenotype of frailty. Jarach et al. (2021) used data from the Survey of Health, Ageing and Retirement in Europe (SHARE) study to test the longitudinal relationship between social isolation and frailty. The findings highlighted the link between social isolation and physical frailty over two years. By contrast, Ding et al. (2017), using the English Longitudinal Study of Ageing (ELSA) database, found no link between social isolation and frailty, though emotional support was linked to frailty over time.

One of the hypothesized mechanisms for the association between social isolation and frailty is that social isolation may be linked to the components of frailty. As such, a longitudinal study, using the ELSA data, demonstrated that social isolation was significantly associated with a decrease in gait speed, a marker of frailty, especially among older adults with a low socioeconomic status after six years (Shankar et al., 2017). Likewise, a cross-sectional study found an association between social isolation and gait speed among community-dwelling older adults (Merchant et al., 2020). A longitudinal study, using data from the CHARLS, found that social isolation is positively associated with decreased grip strength among older men, not women (Yu, Steptoe, Niu, et al., 2020). Other potentially important mechanisms are nutritional deficiencies and low physical activity. Isolated older adults are more likely to be inactive and such inactivity and low physical activity increase the risk of being frail (McPhee et al., 2016; Peterson et al., 2009; Shankar et al., 2011; Song et al., 2015). Prior studies and reviews have shown the link between social isolation and weight loss (Bloom et al., 2017; Martin et al., 2005; O'Connell et al., 2020). Another recent longitudinal study, using the SHARE dataset, has examined the effects of the combination of low physical activity, low protein intake, and poor social networks on the phenotype of frailty among older adults. The results of this study have demonstrated that older adults with a combination of two of these risk factors had a higher risk of developing frailty compared with those with none or one of these risk factors over 11 years (Haider et al., 2020).

2.1.4.2 Frailty and social isolation

Hoogendijk et al. (2016), using the LASA dataset, examined the association between physical frailty and social functioning among community-dwelling older adults, cross-sectionally and longitudinally over three years. To the best of our knowledge, this is the only study that explicitly investigated the effect of frailty on social isolation. Social functioning refers to social networks and emotional and instrumental social support. The cross-sectional results revealed that pre-frail and frail older adults had a smaller social network size compared to non-frail older adults. Longitudinal results demonstrated physical frailty was not associated with the size of social networks and social support over time. The authors interpreted these results by questioning the direction of the association between frailty and social relationships. The reason may lie in the fact that older adults with small social networks are more likely to become frail in later life. Hence, Hoogendijk et al. (2016) suggested future longitudinal studies should consider the effect of social

relationships on frailty over time to determine whether social relationships can buffer frailty. They also suggested future studies could further investigate the mechanisms that mediate the relationship between social relationships and health.

2.1.4.3 Bidirectional relationship between social isolation and frailty

Two longitudinal studies, using the ELSA data, have investigated the bidirectional association between social isolation and frailty. Gale et al. (2018) found that social isolation was not related to frailty in the whole sample, albeit a high level of social isolation was associated with physical frailty in men. Their results on the association between frailty and social isolation have shown that frailty was not linked to social isolation over time (Gale et al., 2018). Maltby et al. (2020) have examined the effects of unidimensional and multidimensional measurements of social isolation on frailty and vice-versa. The multidimensional measurement of social isolation includes three dimensions, namely social isolation from children, family members (i.e., parents and siblings), and a wider social network (i.e., friends and social organizations). The unidimensional measure is based on the inclusion of the five items used in the multidimensional measurement of social isolation suggested by Gale et al. (2018). The results have shown that neither unidimensional nor multidimensional social isolation predicted a significant change in physical frailty over 4 years. However, frailty predicted social isolation from a wider social network over time (Maltby et al., 2020).

2.1.5 Moderation

Two cross-sectional studies (Dent & Hoogendijk, 2014; Mulasso et al., 2016) and two longitudinal studies (Hoogendijk et al., 2014; Liao et al., 2018) examined the effects of social isolation and frailty on health outcomes among community-dwelling older adults. Dent and Hoogendijk (2014) examined the interaction effects of frailty, social networks, and social participation on health outcomes, including hospitalization, discharge to a higher level of care, and mortality. The results revealed that only frail older adults with a low level of social activity had a higher likelihood of mortality and discharge to a higher level of care than frail and non-isolated older adults. Another cross-sectional study (Mulasso et al., 2016) found that isolated and frail older adults had a higher level of disability compared to non-isolated and frail older adults. A longitudinal study using the LASA dataset found no buffering effect of social support against functional decline and mortality

in frail older adults (Hoogendijk et al., 2014). The results of a longitudinal study from Taiwan (Liao et al., 2018) showed that non-frail and pre-frail male older adults who provided social support to their family members had a lower risk of mortality than frail older adults who did not provide social support to their family members over time. However, this study did not explicitly examine the interaction effect of social support and frailty on mortality. The results further indicated that there was no association between receiving family support and mortality among frail older adults.

2.1.6 Conditional process model (moderated mediation model)

A cross-sectional study from China examined the mediator and moderator roles of different types of social support in the relationship between physical frailty and depression among community-dwelling older adults (Jin et al., 2020). The results have shown that emotional and instrumental support mediated and moderated the relationship between frailty and depression, but not informational support.

2.1.7 Synopsis of the results and discussion

Overall, the results of the research articles on the relationship between social isolation and frailty highlighted that the number of studies in this research area is recently growing. In addition, more studies tend to focus on the multidimensional measurement of social isolation. Almost half of the studies (17/32) reported the effect of social isolation on frailty, while one cross-sectional study showed the impact of frailty on social isolation. The results of the comparison between cross-sectional studies and longitudinal studies have revealed that 45% of cross-sectional studies (11/24) illustrated an association between social isolation and frailty, while six longitudinal studies out of eight reported this association.

In general, two longitudinal studies, using the ELSA dataset, have investigated the bidirectional effects of social isolation on frailty (Gale et al., 2018; Maltby et al., 2020). Both found no link between social isolation and frailty. Similarly, Gale (2018) found frailty was not linked to social isolation over time; whereas Maltby (2020) reported that frailty was associated with the lack of social contact with friends.

This literature review highlights the fact that most of the studies have examined the effects of social isolation on frailty, but not frailty on social isolation. Evidence from longitudinal studies seems to

suggest that social isolation predicts frailty. Evidence on whether frailty increases the risk of social isolation is sparse, and few studies have explicitly explored this relationship. Hoogendijk et al. (2016; 2014) have exclusively investigated the effect of frailty on social isolation. These pieces of evidence led us to examine the effect of social isolation on frailty, which is more established in the scientific literature and has been extensively studied. In addition, Berkman and Krishna's theory (2014) pointed out the direct impact of social isolation on health outcomes. Consequently, frailty as an indicator of health status cannot precede social isolation in this research study. Hence, based on Berkman and Krishna's theory and prior studies, the focus of this study is on social isolation as a focal independent variable.

The results are ambiguous and have not been fully understood when the effects of both social isolation and frailty were examined on health. Most of these studies have shown that frailty is linked to adverse health outcomes, but few studies found a relationship between social isolation and poor health outcomes. In this line, the results of Hayashi's (2020) and Hoogendijk's studies (2016; 2014) illustrated that the combination of social isolation and frailty is linked to adverse health outcomes, whereas social isolation is not associated with health outcomes. This indicates that it is plausible that frailty alters the relationship between social isolation and health and makes isolated older adults more vulnerable to poor health outcomes.

Among studies that examined the moderation role of social isolation on the pathway from frailty to health, less than half found a significant association of moderation. One recent cross-sectional study has examined the mediating and moderating role of social support on the pathway from frailty to health (Jin et al., 2020). No study has so far explored the mediating or moderating role of physical frailty on the relationship between social isolation and health outcomes among community-dwelling older adults. In sum, knowledge gaps in the scientific literature demonstrate that a few studies examined the effects of social isolation and frailty on health outcomes, and little is known about the role of frailty as a moderator in the relationship between social isolation and health outcomes among older adults. To address these research gaps, this thesis mainly aimed to examine the moderating role of frailty on the pathway from social isolation to health.

2.2 Conceptual Framework

The theoretical questions examined in this section are: How are changes in social isolation related to changes in health outcomes? And does this relationship vary based on changes in frailty among older adults?

2.2.1 Social Isolation Perspective

The theoretical part of this thesis is inspired by the works of Berkman and colleagues. By integrating diverse sociological theories, Berkman and Glass (2000) proposed an overarching conceptual model of how social networks impact health. More recently, Berkman and Krishna (2014) have developed a more comprehensive conceptual framework linking social networks, social support, and social participation to a wide array of health outcomes.

To analyze a wider boundary of social relationships around individuals than traditional relations based on family and kinship, Barnes (1954) and Bott (1957) suggested the social network theory. These social anthropologists introduced the initial and basic idea of the social network, where the social network is a system of social relations among people, including kinship, friendship, neighborhood, and acquaintanceship. A network of ties forms a group for carrying out social activities (Barnes, 1954; Berkman & Glass, 2000; Mitchell, 1974). Social participation determines to what degree a person is integrated into society and feels attached to the community (Berkman & Glass, 2000; Kawachi & Berkman, 2000). The social network theory emphasized that social relationships between persons ramify through their society. Indeed, this theory implies that the social structure of the network shapes individuals' behavior (Barnes, 1954; Berkman & Glass, 2000; Mitchell, 1974).

The British psychoanalyst John Bowlby (1969) developed the attachment concept in which individuals need to tie to social groups. Bowlby's attachment theory posits that intimate bonds in early childhood play a critical role in the development of healthy behavior in children and form a secure base for later attachment and relationships (Bowlby, 1982). More recently, empirical research points out that this theory can successfully apply to adults. As such, the evidence has illustrated that adults have attachment needs much like those of children. These needs could be met through adults' relationships with intimate partners, friends, and family members. From this point of view, difficult early interactions may result in later relational isolation, leading to anxiety and

depressive symptoms. Today, the principle and perspective of this theory apply usefully to the treatment of mental health disorders (Bettmann, 2006).

Thereafter, American sociologists extended this theory to a quantitative perspective. In this theory, the characteristics of the network at the social level are more important than the characteristics of the individual. This focus on the network indicates that social contacts between individuals are not random. These social contacts, however, are based on several factors including, geographic locations, demographic characteristics (age, race, gender), and the characteristics of the individual (socioeconomic position, occupation) (Berkman & Glass, 2000; Berkman et al., 2000). Nevertheless, the social network theory has been criticized for focusing on the structural aspect of networks. The reason is that the structure of a person's social network (i.e., numbers of close friends and relatives, and membership in voluntary organizations) provides little information about the quality, amount, and nature of social interactions (Erin York Cornwell & Linda J. Waite, 2009; Valtorta et al., 2016).

In response to this criticism, several social scientists focused on the functional aspects of social relations rather than the structural aspects. Major contributors were Kahn and Antonucci (1980), who elaborated on the convoy model. According to this model, social relationships vary based upon their quality (i.e., positive and negative), structure or quantity of relations (i.e., frequency of contact), function (i.e., exchange, aid, affirmation), and also personal characteristics such as age, race, gender, and socioeconomic status. In this vein, social relationships are conceptualized as a multidimensional feature (Antonucci et al., 2014; Kahn & Antonucci, 1980). Furthermore, Cassel (1976) and Cobb (1976) highlighted the important role of social support on physical health outcomes. These investigators along with Berkman and Glass (2000) speculated the need to focus on the structural aspects of social networks in which social support is provided (Berkman & Glass, 2000). Hence, it is necessary to include personal networks and social participation (structural aspect) as well as social support (functional aspect). Accordingly, social isolation is an umbrella term that encompasses the structural and functional aspects of how individuals connect to each other (National Academies of Sciences & Medicine, 2020). House (1985) proposed to distinguish between these two aspects of social isolation: social networks and social support. Social networks pertain to the structure of social ties and the characteristic patterns of social ties, including friends, family members, neighbors, or other important persons in one's life. Social participation refers to

being part of a social group in which people can have personal engagement, intimacy, and friendship. Social support refers to the provision of emotional, instrumental, appraisal, and informational support through different types of social ties. However, there is some variation in the type, frequency, intensity, and extent of support provided and all social ties are not supportive (Berkman & Glass, 2000).

The common features in structural and functional aspects are that social isolation refers to a reduced scope of the personal network, a smaller and less heterogeneous personal network, few social activities, and less supportive relationships (Hortulanus et al., 2006). In this vein, social isolation broadly pertains to a state in which an individual lacks social engagement with others, socially supportive relationships, and has few social network ties (Berg & Cassells, 1992; National Academies of Sciences & Medicine, 2020; Nicholson, 2009). Along with these social theorists, Berkman and Krishna (2014) highlighted the impact of social isolation on health in their underpinning conceptual model, emphasizing that the lack of diverse social ties, social support, and social disengagement are linked to poor health outcomes.

2.2.2 Frailty concept

In an attempt to distinguish between "physiologic age" and "chronological age," geriatricians have introduced the concept of "physiologic reserve." Our body is a complex biological system that can resist and adapt to multiple external stressors. The complexity of a system determines the system's ability to adapt to baseline changes and resiliency to deleterious failure. Illness can reduce the ability of a system to detect changes in the baseline state and impose limitations on the ability of the system to adapt to those changes. Both physiologic aging and illness may result in loss of complexity in different organ systems. Many of these changes are closely linked to adverse health outcomes such as disability, hospitalization, falls, and death. Loss of complexity leads to a reduction in responses to health stressors and a diminished threshold for decompensation. Once a critical threshold level is exceeded, the system cannot maintain a steady state, leading to an accelerated dysregulation. This theoretical critical threshold is called "physiologic reserve." The phenotypic expression of this process is frailty (McDermid & Bagshaw, 2014). The frailty process represents a transitional state in the dynamic progression from robustness to functional decline. During this process, physiological reserves diminish and become insufficient for the maintenance and repair of the aging body (Lang et al., 2009).

There is consensus that frailty is an age-related state of vulnerability to poor health outcomes that reflects the multisystem physiological change. A plausible expectation is that frailty and resilience are correlated, such that frail older adults have low resilience. Additionally, both concepts highlight the key role of stressors in influencing health outcomes in later life. Two individuals of the same chronological age may respond differently to the same stressor. Accordingly, the ability to identify frailty or predict resilience could provide useful insights into how to optimize health for both individuals (Whitson et al., 2018).

Physical frailty theoretically results from declines in physiological reserves of the aged body that leads to decreased energy to respond to stressors and a diminishment in the ability to maintain hemostasis. Hence, frail older adults have reduced stress tolerance due to the decreased physiological reserves in the skeletal muscles, bones, and immune systems (Chhetri et al., 2021; Strandberg & Pitkälä, 2007; Wade et al., 2017). Given the physiologic vulnerability inherent in having frailty, it is possible that the stress of isolation could result in poor health status for frail older adults compared to robust older adults. One view of the mechanism is that social isolation could increase negative thoughts and reduce resilience which leads to higher levels of stress and anxiety and, ultimately, a higher likelihood of development and progression of physical illness among isolated older adults than their non-isolated peers (Davies et al., 2021; Shankar et al., 2017). This hypothesis could be strengthened through the concept of the physiologic reserve. The underlying mechanism is that social isolation is itself a stressor that leads to poor health and the main feature of frailty is vulnerability to stressors due to lowered physiological reserves (Cacioppo & Hawkley, 2003; Fried et al., 2001). Additionally, the concept of the physiologic reserve could provide a better insight into the plausible link between frailty and adverse health outcomes such as disability and comorbidity (Chhetri et al., 2021). The findings of the Cardiovascular Health Study (CHS) provided support for the assumption that frailty leads to disability due to its key features of muscle weakness, decreased endurance, and slowed performance (Fried et al., 2001). According to Fried (2001), physical frailty, disability, and comorbidity are distinct clinical entities that can arise independently, though they are related.

The physiological reserve that underlies frailty may not achieve disease status. Hence, some older adults are frail without having a specific life-threatening disease (Rockwood & Mitnitski, 2007). For example, many common chronic disease conditions such as cardiovascular, pulmonary, and

inflammatory diseases can trigger or accelerate the biological decline in physiological systems that underlies frailty. However, frailty often exists independently of disease or disability and this concept lies at the heart of frailty. This can support the concept of an independent underlying physiological etiology that is driving frailty and its related health outcomes (Fried et al., 2001; Theou et al., 2015; Walston et al., 2006). This indicates that not all older adults with disabilities and comorbidities are frail and not all frail older adults have disabilities or comorbidities.

Bergman et al. (2004) developed a Canadian working framework for understanding frailty that offers a pathway linking frailty to poor health outcomes in older populations. At the heart of this model is the phenotype of frailty approach. However, this model added two other components to the frailty model, namely cognitive decline and depressive symptoms. Unlike the Canadian working framework, this thesis focuses on the original five components of the phenotype of frailty. Based upon Bandeen-Roch's conceptual framework (2020), we distinguish between physical frailty and cognitive and psychosocial vulnerability. In line with the phenotype of frailty approach (Fried et al., 2001), the Canadian working framework distinguishes between frailty, disability, and comorbidity. This supports the hypothesis that physical frailty has an underlying etiology that is probably independent of chronic diseases and disability (Bergman et al., 2004; Fried et al., 2004; R. Gobbens et al., 2010). Additionally, this model demonstrates a relationship between frailty and adverse health outcomes that coheres with previous systematic reviews and meta-analyses (Chu et al., 2021; Vermeiren et al., 2016).

2.2.2.1 The choice of control variables

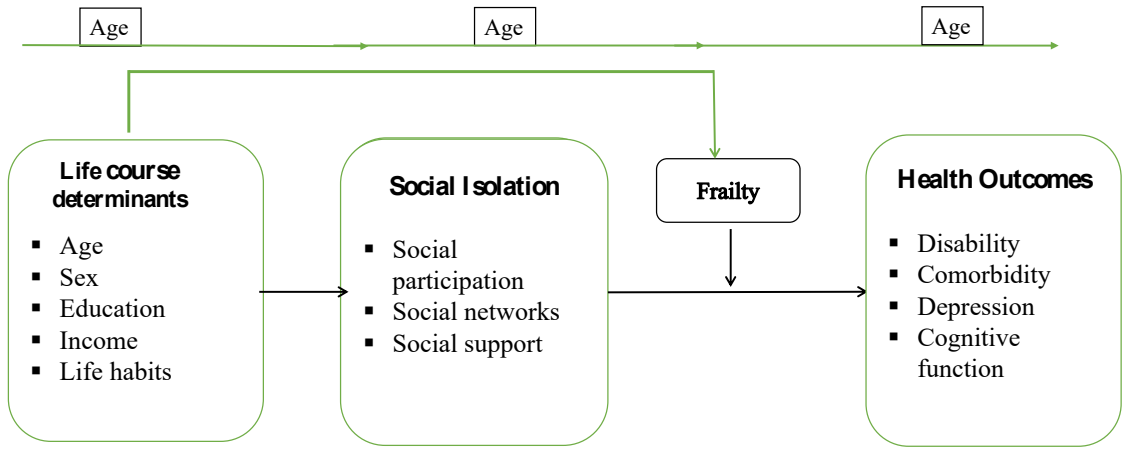
Building on the Canadian working framework, Gobbens et al. (2010) developed an integral model of frailty in which life course determinants, including sleeping patterns, smoking, alcohol consumption, socioeconomic factors (i.e., education and income), and socio-demographic factors (i.e., age and gender) might influence frailty and adverse health outcomes. Likewise, empirical research supports the link between lifestyle factors (Cacioppo et al., 2002; Jung et al., 2021; Shankar et al., 2011) and frailty among community-dwelling older adults. Further, prior studies have shown the associations between socioeconomic factors (i.e., education level and annual income) and sociodemographic factors (i.e., age, sex) with frailty (Collard et al., 2012; Jung et al., 2021; Jürschik et al., 2012; Serra-Prat et al., 2016) and social isolation (Santini et al., 2016; Victor & Yang, 2012). The impact of socio-demographic and socio-economic factors on health is also

highlighted in Berkman's theory (2014). This evidence led us to select the above-mentioned variables as covariates in our conceptual model.

2.2.3 The adapted conceptual framework

Through the lens of Berkman's theory (2014), Bergman's frailty frameworks (2004), Gobbens' integral model (2010) of frailty, and prior studies, we have developed a conceptual framework (Figure 1) on how social isolation impacts frailty and adverse health outcomes among community-dwelling older adults. This conceptual framework focuses on the concept of social isolation from Berkman and Krishna's conceptual model (2014), incorporating various types of social network ties (i.e., friends, nuclear and extended family members), social support, and social participation. Berkman's conceptual model has been used in numerous studies among community-dwelling older adults (Ahmed et al., 2018; Bélanger et al., 2016; Zunzunegui et al., 2004). The validity of Gobbens' integral model is demonstrated among community-dwelling people aged 65 years and older (Gobbens et al., 2012b).

Figure 1. The conceptual framework of the moderating role of frailty on the relationship between social isolation and health outcomes among community-dwelling older adults



Covariates: Life course determinants
Independent variables: Social isolation
Moderator and Mediator: Frailty
Dependent variables: Health outcomes

The framework in Figure 1 shows the pathway from which structural and functional aspects of social isolation, including social networks, social support, and social participation have a direct impact on adverse health outcomes. Frailty mainly moderates the relationship between social isolation and health outcomes. In this vein, the strengths of the impact of communicating with social ties, receiving social support from different ties, and participating in social activities on health status are higher among frail older adults than robust peers. The mechanism is that frail older adults experiencing a decrease in total physiological reserves have less resilience to recover from an illness compared to robust older adults. Therefore, increased social relationships may play a compensating role for frail older adults who have low physiological reserves. However, robust older adults have sufficient physiological reserves, and consequently, the effects of social isolation on health outcomes will be attenuated, and they will tend to stay in better health status and not experience poorer health outcomes. In line with previous research studies, Berkman's theory (2014), and Bandeen-Roch's study (2020), we consider disability, comorbidity, depression, and cognitive impairment as adverse health outcomes of frailty and social isolation. The predictors and consequences of frailty from Bergman's (2004) and Gobbens's (2010) frameworks have been adopted, whereas the focus of this conceptual framework is on the five original components of Fried's (2001) phenotype of frailty. Based upon Gobbens's (2010) framework, Berkman and Krishna's (2014) theory, and previous studies, the covariables are socio-economic and sociodemographic factors (i.e., sex, age, annual income, education), and life habits (i.e., smoking, alcohol consumption, and sleep disturbance) that may influence both social isolation and frailty. To this end, drawing upon Berkman and Krishna's (2014) social theory and prior empirical research studies, this dissertation aims to test the following research questions and hypotheses:

2.2.3.1 Research questions and hypotheses

As mentioned in Chapter 1, the central objective of this thesis was to examine the moderating role of frailty on the relationship between social isolation/relationships and health outcomes among community-dwelling older adults. We first examined the cross-sectional moderating effect of frailty on the relationship between social isolation and health outcomes (Objective 2a). Then, we tested the moderating role of changes in frailty on the pathway from changes in social relationships to changes in health outcomes among older adults (Objective 2b).

2.2.3.1.1 Moderation

1.1 Does frailty moderate the cross-sectional relationship between social isolation and health outcomes among older adults?

Hypothesis 1.1: Socially isolated and frail older adults will be more likely to experience a higher level of depressive symptoms, cognitive impairments, functional limitations, and chronic diseases than socially isolated and robust older adults.

1.2 Do the relationships between changes in social relationships and changes in health outcomes vary according to changes in frailty status among older adults?

Hypothesis 1.2: Increased changes in social relationships will result in greater changes in physical, mental, and cognitive health among older adults with changes toward frailty compared to those with changes toward robustness.

Chapter 3 – Methods

In this chapter, I provide details on the methodology used in each objective of this dissertation, namely the scoping review and the cross-sectional and longitudinal studies. I also discuss the rationale for applying specific procedures and techniques in each study.

3.1 Scoping review

This doctoral research study started with a scoping review. The first objective was to document and analyze the effects of social isolation and loneliness on frailty and adverse health outcomes and their potential moderators and mediators among community-dwelling older adults across the world (Study 1- Chapter 4).

A scoping review aims to map the relevant literature and key concepts on a broad topic area and to identify knowledge gaps in the existing research literature. In general, this type of review is useful when a body of research has not been comprehensively reviewed and when the research area is large and diverse and has a complex nature that precludes conducting a precise systematic review (Arksey & O'Malley, 2005; Peters et al., 2015). The key difference between a systematic review and a scoping review is that a systematic review generally focuses on a well-defined and specific research question that can apply to the specific study design, whereas a scoping review typically addresses a broader research question that can apply to a greater range of study designs (Arksey & O'Malley, 2005).

The strength of the scoping study is that it provides a rigorous and transparent method for synthesizing research evidence and mapping existing research evidence. This method is often undertaken to identify research gaps, synthesize and disseminate research findings, and propose recommendations for research, practice, and policy. In addition, the methodological focus of a scoping study shifts away from expert knowledge of a particular field associated with the traditional literature review toward an approach that emphasizes analytic skill to review different studies' designs. The drawback of the scoping study is that, unlike systematic reviews, this type of review does not require a quality appraisal of the included research studies (Arksey & O'Malley, 2005; Peters et al., 2015).

The rationale for conducting a scoping review before performing quantitative analyses in this dissertation was to better understand research gaps by reviewing both cross-sectional and longitudinal studies to achieve in-depth and broad insights on the interrelationships between social isolation, frailty, and health outcomes, and the potential moderating or mediating role of frailty on the relationship between social isolation and health. The overall methodology is summarized below, and full details are provided in Study 1.

3.1.1. Study design

The scoping review on the effects of social isolation and loneliness on frailty and health outcomes was based on the methodological framework proposed by Arksey and O'Malley (2005). The focus of the scoping review was mainly on the original five stages, including identifying the research questions and relevant research studies, selecting the research studies, charting the data, and synthesizing and reporting the results. Consultation with stakeholders and policymakers is an optional step that was not considered in this scoping review.

3.1.2. Review questions

The research questions of the scoping review were as follows:

1) What evidence exists on the effects of social isolation and loneliness on frailty and their possible mediators and moderators among community-dwelling older adults?
2) What evidence exists on the effects of social isolation, loneliness, and frailty on adverse health outcomes among community-dwelling older adults?
3) What evidence exists on the moderating and mediating role of frailty on the relationship between social isolation/loneliness and health outcomes or the moderating and mediating role of social isolation/loneliness on the relationship between frailty and health outcomes among community-dwelling older adults?
4) What are the limitations and gaps in the research studies?

3.1.3. Search strategy to identify relevant studies

Six databases were searched for relevant literature: Medline, Embase, CINAHL Plus, Scopus, Web of Science and PsycINFO. The search strategies were developed and validated in consultation with a public health librarian at the Université de Montréal, using keywords related to "social isolation,"

"loneliness," "frailty," and "older adults" and their synonyms. An example of the search strategy is presented in Appendix A of Study 1. Original papers published in English and French from 2001 to June 2018 were searched and updated until July 2019. The publication date limitation was chosen because the phenotype of frailty proposed by Fried was developed in 2001. Reference lists from included studies were hand-searched for additional studies.

3.1.4. Selection criteria

The inclusion criteria were as follows:

1) Original research studies in English and French published between 2001 to July 2019
2) Research studies focused on community-dwelling older adults 60 years and over
3) Research studies focused on the phenotype of frailty
4) Research studies that measured loneliness and/or structural and functional aspects of social isolation, including social networks, social support, and social participation, based on Berkman and Krishna's (2014) conceptual framework.

The articles were excluded if they were review papers or editorials, and if they did not report any findings on the phenotype of frailty, social isolation, loneliness, and their measurements. No restrictions were placed on the country of origin, type of health outcomes, and study designs.

3.1.5. Data extraction

The approach to searching for studies for a scoping review followed three steps. The first step was an initial limited search of a selection of relevant databases (n=4001), followed by a screening of the title and abstract of the articles across all included databases based on the inclusion and exclusion criteria (n=1893) and removing the duplicates (n = 2113). Second, full texts of articles that met the inclusion and exclusion criteria (n=61) were assessed and selected for data extraction in the scoping review. Third, the reference list of all identified articles and update alerts from the electronic database were searched for additional studies (n=5). Lastly, 26 articles were included. For the selection process, I initially screened research articles based on their titles and abstracts and reviewed all full-text papers retrieved. Any doubt regarding the article selection process was substantively resolved in consultation with my supervisor.

The following information was extracted from each retrieved article: authors, publication year, country of origin, objectives, study population, study design, sample size, the prevalence of frailty, duration of the longitudinal studies, the measurements for frailty, social isolation, and loneliness, the type of adverse health outcomes, and key findings relevant to the review questions.

3.2. Quantitative research methods

Drawing on the results of the scoping review (Study 1- Chapter 4), we performed cross-sectional (Study 2 - Chapter 5) and longitudinal studies (Study 3- Chapter 6). This section provides the methods and techniques applied in these two mentioned studies based on the dissertation's objectives.

3.2.1. Study design and population

Data were from the longitudinal FRéLE study (Fragilité, une étude longitudinale de ses expressions/ Frailty: A longitudinal study of its expressions) which was conducted from 2010 to 2012 among community-dwelling older adults aged 65 and over in the province of Québec in Canada. Three different databases (Béland et al., 2005; Huntley et al., 1993; Zunzunegui et al., 2004) were used to estimate the appropriate sample size in each category of the phenotype of frailty for estimating sample size. The results revealed that a sample stratified by gender (men and women) and age (65–74, 75–84, and 85 and over) with 270 in each of the six subgroups was needed to identify the distribution of frailty status over time (Béland et al., 2018; Provencher et al., 2017).

A total of 4915 older adults were randomly selected from the Régie de l'Assurance Maladie du Québec (RAMQ) list of whom 4483 were identified as eligible for the study. Of these, 2141 participants gave permission, and finally, 1643 participants signed a consent form and completed the baseline questionnaire. The participants of the study represented a subset of three areas, as follows: a metropolitan area (Montréal), an urban area (Sherbrooke), and a rural town area (Victoriaville). The participants were excluded from the interview if they 1) had hearing impairment, 2) were admitted to a long-term care center, 3) were hospitalized, 4) participated in the Longitudinal Study on Nutrition and Successful Aging (NuAge) in Sherbrooke or Montréal, and 5) were not able to clearly understand either French or English to answer the questionnaire during the face-to-face interviews. No one with cognitive impairment was excluded. The data were

stratified by gender, area, and age groups to have enough participants presenting in each category of the phenotype of frailty. The preliminary results demonstrated that the sociodemographic characteristics and health status of FRéLE participants represented some of the characteristics of the community-dwelling older population across the province of Québec (Béland et al., 2018; Provencher et al., 2017).

3.2.2. Data collection

Data were collected over two years through a face-to-face interview in three-time points (T0-T1-T2). The interviews took place in the respondent's home with trained health professionals. The average time of the interview was 90 minutes (Béland et al., 2018; Provencher et al., 2017). Response rates were 99.82% at the first interview (N= 1640), 84% at the second interview (N=1379), and 74.38 % at the third interview (N=1222). In this dissertation, the data from baseline (T0) were used for the cross-sectional analysis, and the data from the first, second, and third time points (T0-T1-T2) were used for the longitudinal analysis.

3.2.3. Ethical considerations

The Research Ethics Committee of the Jewish General Hospital provided the ethical approval for the FRéLE study (January 12, 2010). The Research Ethics Committee of the Integrated Health and Social Services University Network for West-Central Montréal approved this doctoral research study, and this approval has been renewed every year (#CODIM-MBM-17-146- October 10, 2021). The Health Research Ethics Board of the Université de Montréal approved the present dissertation for the duration of three years, and the ethical approval has been renewed twice (#17-162-CERES-D-17-08-2021) (Appendix B).

3.2.4 Measurements

3.2.4.1 Independent variables – Social isolation

According to Berkman and Krishna's (2014) theoretical model, we measured social isolation by social participation, social networks, and social support from different social ties, including friends, nuclear family (i.e., children and an intimate partner/spouse), and extended family (i.e., siblings

and grandchildren). The indicators of social networks and social support used for our analysis were the same as those validated by Ahmed et al. (2018).

- **Social networks**: The indicators of social networks were the four questions validated by Ahmed et al. (2018), which asked for each social tie, namely friends, children, and extended family. The examples of questions asked about contacts with children were: "How many children do you have?"; "How many children do you see at least once a month?"; "How many of them do you speak to by phone at least once a month?"; "How many children do you have a very close relationship with?" These questions were not asked about an intimate partner because they usually had daily contact. Responses ranged from 1 to 5: Never, rarely, sometimes, frequently, and always. Scores were summed, and higher scores indicated higher social contacts.

- **Social support**: The indicators of social support were the five questions from Ahmed et al. (2018) social support scale asked for each social tie, namely friends, nuclear, and extended family members. The examples of questions asked about social support from children were: "Do you help your children from time to time?"; "Do you feel that you are loved and appreciated by your children?"; "Do your children listen to you when you need to talk about your problems or preoccupations?"; "Do you feel that you play an important role in your children's lives?"; "Do you feel useful to your children?" Responses ranged from 1 to 5: Never, rarely, sometimes, frequently, and always. Scores were summed, and higher scores indicated higher social support.

The absence of social ties: Some participants in the FRéLE study lacked one or more social ties, including friends, children, grandchildren, siblings, and partner. In order to resolve this issue, we created a binary variable for indicating the absence of social ties as suggested by McDonough and Walters (2001) and Béland et al. (2005). Accordingly, we assigned a score of zero to the participants who had social ties (i.e., having children) and a score of one to the participants who lacked social ties (i.e., having no children). The absence of social ties was a time-invariant variable as the number of participants' networks did not often increase or decrease over two years. Furthermore, we created a continuous variable for each social network and social support indicator by multiplying the continuous social variable by its related-dichotomous variable (i.e., social

network-children × no children). The dichotomous and continuous variables were used simultaneously in our equations (Béland et al., 2005; McDonough & Walters, 2001).

Social participation: A 12-item scale of social participation consisted of membership in community organizations, participation in religious or community-based activities, family activities, volunteering, playing music, painting, shopping, and going to restaurants, libraries, and sport and recreation centers (Statistics Canada, 2010). Responses ranged from 1 to 5: almost every day, at least once a week, at least once a month, at least once a year, and never. Scores were summed, with higher scores indicating lower social participation. In the longitudinal analysis, we reversed the scale so that higher values represented a higher level of social participation.

Reliability: Table 1 shows the Cronbach alpha internal consistency estimates for social participation, social networks, and social support for each tie.

Table 1 Cronbach alpha estimations for social variables

Social variables	T0	T1	T2
Social participation	0.69	0.67	0.66
Friends			
Social network	0.70	0.80	0.75
Social support	0.72	0.67	0.65
Nuclear family			
Social network-Children	0.87	0.90	0.88
Social support-Children	0.72	0.71	0.72
Social support-Partner	0.73	0.74	0.74
Extended family			
Social network-Grandchildren	0.74	0.71	0.71
Social network-Siblings	0.75	0.79	0.79
Social support- Family	0.70	0.73	0.72

3.2.4.2. Moderator – Phenotype of frailty

The controversial debate is whether frailty is a clinical syndrome or not. A medical syndrome is a set of symptoms and signs or multiple manifestations that occur in combination, and no single manifestation is sufficient to identify those with the syndrome (Lang et al., 2009; Walston et al.,

2006). Bandeen-Roche et al. (2006) analyzed the internal validity of the phenotype of frailty and evaluated the degree to which the five criteria of frailty phenotype aggregate into a medical syndrome based on data from a combined sample of women aged 70-79 from the Women's Health and Aging Studies (WHAS) I and II. Frailty is a syndrome if there are at least two or more classes. Bandeen-Roche et al. (2006) performed a latent class analysis and identified three classes, each with a specific score on the five frailty criteria. The prevalence of each criterion increased progressively across classes, suggesting an increase in frailty status. Their findings support the internal validity of the phenotype of frailty vis-à-vis the stated theory defining frailty as a clinical syndrome and justifying the categorization of frailty as robust, prefrail, and frail (Bandeen-Roche et al., 2006).

Frailty was assessed using five criteria of the phenotype of frailty. For the cross-sectional analysis, we used the multi-categorical scale proposed by Fried (2001). Participants were categorized as frail, pre-frail, and robust. Participants were deemed as physically frail in the presence of three or more of these criteria, as pre-frail in the presence of one or two of the five frailty indicators, and as robust if none of these characteristics were observed. For the longitudinal analysis, we used the continuous scale of frailty proposed by Béland et al. (2020), constructed by using factor mixture models. It is a 5-point Likert scale with higher scores suggesting less frailty. The continuous variable is normally distributed with the following means and standard divisions in three-time points (T0: 20±8.6, T1: 21.4±9.1, T2: 21.2±9.3). The details for each criterion of frailty are described in Provencher et al. (2017) and summarized here. First, the continuous scale is presented, followed by the multi-categorical scale.

Weight loss was a self-reported unintentional weight loss of 10% or ≥ 4.5 kg body weight in the last 12 months (Fried et al., 2001). For the cross-sectional study, we used a dichotomous variable separating participants with and without weight loss. Weakness was measured by grip strength, using the Martin vigorimeter (Jones et al., 1991). The mean of three trials was taken for each hand (in kilopascals). For the cross-sectional study, the lowest quintile (20% of the population) by sex and Body-Mass Index (BMI) was applied to indicate weak grip strength (<45.00 kPa for men and <30.33 kPa for women). Exhaustion was assessed using a four-item measure of vitality from the SF-36 (Ware Jr & Sherbourne, 1992). It is a continuous 5-point Likert scale, ranging from 0 to 100. For the cross-sectional study, the lowest quintile (20% of the population) was identified for the

total sample (≤ 46.9). Slowness was assessed with gait speed. Slow gait was defined based on the time to walk 15 feet (4,572 m). The threshold values are based on gender and standing height. For the cross-sectional study, the cut-offs varied from 47 cm to 80 cm for women and 56 cm to 82 cm for men (Guralnik et al., 1994). Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) (Washburn, 2000; Washburn et al., 1993). The score ranged from 0 to 400, with higher scores indicating higher levels of physical activity. For the cross-sectional study, the cut-offs (20% of the population) for low physical activity were identified for each gender (≤ 28.2 for women and ≤ 33.5 for men).

Béland et al. (2020) examined the construct validity of the phenotype of frailty as a syndrome in the FRéLE study. Concordant with the WHAS study, they performed a latent class analysis to evaluate whether the five criteria of the phenotype of frailty aggregated into a syndrome. First, Béland et al. dichotomized the five criteria of frailty according to the Bandeen-Roche et al. (2006) procedure and compared their results with the three classes of the frailty model (frail, prefrail, and robust) in the WHAS study. They obtained the same results as in the WHAS study and rejected the hypothesis of homogeneity, indicating that the FRéLE sample is an acceptable starting point to test the frailty measurement model validity. The WHAS study merely examined frailty classes based on the one-class model null hypothesis. In addition to this hypothesis, Béland et al. (2020) used a continuous measurement of Fried's (2001) frailty with five components and tested the null hypothesis of more than one categorical class. The findings of the continuous scale of frailty suggested that individuals were not heterogeneous between classes. Unlike the WHAS study, frailty is not defined as a syndrome in the FRéLE sample but rather an indicator of distinct health status. According to these results, physical frailty is considered in the longitudinal study as a marker of health status, not a clinical syndrome. Of note, this continuous scale was not available for the cross-sectional study as it was not yet constructed. As a result, we used the categorical scale of frailty proposed by Fried (2001), which was the best option at that time.

Theoretically, the Fried (2001) frailty phenotype refers to a clinical syndrome, resulting from the reduction of individuals' physiologic reserve. Methodologically, frailty is defined as a determinant of health status in the FRéLE study by Béland et al (2020), which is in line with the health-based conceptual frameworks of frailty proposed by Bergman et al (2004) and Gobben et al (2010). This specific feature of frailty as a health status allowed us to examine the interactions between social

isolation/relationships and frailty on multiple health outcomes. It means that frailty as one of the determinants of health could manifest in the relationships between social isolation/relationships and health outcomes among older adults.

The reasons for using the continuous scale of frailty in the longitudinal analysis were as follows: First, the correlations between the continuous scale of frailty and health outcomes were stronger than the correlations between the categorical scale of frailty and health outcomes. Second, unlike the continuous scale of frailty, we did not observe changes in frailty with the multi-categorical scale over time. Third, Béland et al. (2020) demonstrated in their study that Fried's (2001) frailty criteria did not meet the Bandeen-Roche criteria for identifying it as a syndrome.

3.2.4.3 Health outcomes

Disability was assessed by the Katz (1963) scale of ADLs and the Lawton (1969) scale of IADLs. Activities of daily living comprised the following items: bathing, grooming, dressing, eating, using the toilet, walking, getting out of bed, getting up from a chair, and cutting nails. Instrumental ADLs were as follows: meal preparation, telephoning, using transportation, shopping, doing errands, housekeeping, taking medications, and handling finances. For the cross-sectional analysis, we binarized the participants into two groups according to whether they performed ADLs or IADLs without help (score 0) or were unable to perform ADLs or IADLs (score 1). Participants with a score of one were classified as experiencing functional limitations in ADLs or IADLs. For the longitudinal analysis, as recommended by Spector and Fleishman (1998), we combined ADLs and IADLs items into one single scale, indicating a count variable. The scores for this scale ranged from 0 to 9, with higher scores indicating difficulties in performing ADLs or IADLs.

Comorbidities were assessed by the Functional Comorbidity Index (FCI), a validated scale for older adults (Groll et al., 2005). Chronic conditions were arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, coronary artery disease, heart failure, myocardial infarction, neurological diseases, stroke, peripheral vascular disease, diabetes, gastroduodenal pathology, depression, anxiety or panic disorders, visual and hearing impairment, degenerative disc disease, obesity, and cancer. We included cancer in this study because it was one of the comorbidities in the Cardiovascular Health Study conducted by Fried (2001). The scores ranged from 1 to 19

points, with high scores indicating higher comorbidities. The diagnosis of each disease was verified by doctors. In the longitudinal analysis, we reversed the scale of chronic diseases so that higher values indicated fewer chronic conditions and better health outcomes.

Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS-15). This item measures the past week's experience of fifteen indicators of depressive symptomatology (responses yes/no). The scores ranged from 0 to 15, with higher scores indicating higher depressive symptoms (Sheikh & Yesavage, 1986). We reversed the depression scale in the longitudinal analysis so that higher values indicated better mental health. The Cronbach alpha internal consistency estimates for the GDS were 0.75 in T0 and 0.78 in T1and T2.

Cognitive function status was evaluated by the Montreal Cognitive Assessment (MoCA) which has high reliability and internal consistency. Scores ranged from 0 to 30 points, with higher scores suggesting better cognitive function (≥25) (Nasreddine et al., 2005). In the FRéLE study, 66 participants had a lower cognitive status and were excluded from the MoCA screening test. As suggested by Béland et al. (2018), we censored these participants to the left in the cross-sectional analysis. We created a continuous scale for measuring cognitive function in the longitudinal analysis.

3.2.4.4 Covariates

We examined sociodemographic characteristics: age, sex, annual income, education, and life habit indicators, i.e., sleeping patterns, smoking, and alcohol consumption. These variables were time-invariant in the longitudinal analysis.

3.3. Statistical analysis

This section provides the statistical techniques for performing moderation analyses in the cross-sectional and longitudinal studies. The focus of the cross-sectional study was on the multi-categorical moderation analysis (Hayes, 2017). In the longitudinal analysis, moderation analyses were conducted with the continuous variable of frailty. The objective of the longitudinal study was to examine the moderating role of changes in frailty on the pathway from changes in social relationships to changes in health outcomes.

3.3.1. Descriptive analysis

Descriptive statistics were used to describe the characteristics of the participants in three waves. Continuous and count variables were summarized as means and standard deviation, and categorical variables were displayed as frequencies and percentages (Supplementary Table 2-Study 3). Furthermore, we estimated the intercept and slope parameters from growth models for all time-varying variables (Table 1- Study 3). For the cross-sectional study, we conducted analysis of variance (ANOVA) and chi-square tests to determine differences in baseline characteristics by frailty status (Table 1- Study 2).

3.3.2. Cross-sectional moderation analysis

We started with the cross-sectional moderation analysis (Study 2). The cross-sectional moderation analysis addressed the following research question:

1.1 Does frailty moderate the cross-sectional relationship between social isolation and health outcomes among community-dwelling older adults in Québec?

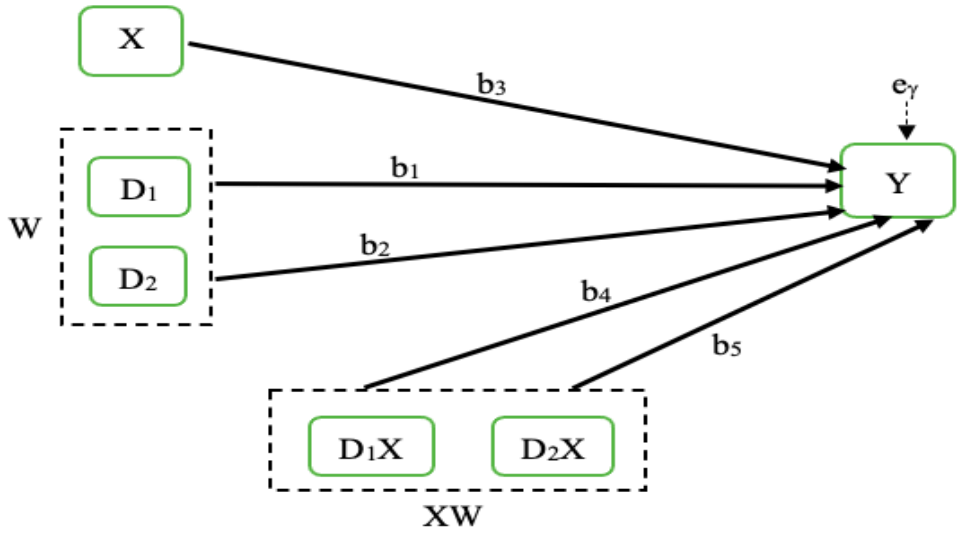
First, we performed a series of simple regression models (Models 1) to test the association between each type of social tie (i.e., friends, children, extended family, and an intimate partner) with frailty and each health outcome (i.e., disability (ADLs and IADLs), depression, chronic diseases, and cognitive function). According to the methodology proposed by McDonough and Walters (2001) and Béland et al. (2005), we added dichotomous variables, representing the absence of social ties, along with the continuous social isolation variable (the product of the dichotomous variable and the continuous variable) for each type of social tie to all equations. We included those social isolation variables significantly associated with frailty and health outcomes in Models 1 into Models 2. Second, we conducted a series of multiple regression models (Models 2) to examine the effects of social isolation on frailty and health outcomes. In the final model, we added all health outcomes simultaneously into the multiple regression models.

Figure 2 presents the statistical multi-categorical moderation model. Frailty as a moderator (W) was a multi-categorical variable representing three categories (frail, pre-frail, and non-frail) and social isolation variables (X) were continuous and binary variables. According to Hayes (2017), we used a system of coding based on g − 1 variables, representing the g categories of frailty (g =

3). We categorized participants into frail (D_1) and prefrail (D_2) with reference to the non-frail group. Social isolation (X) and frailty (W) were centered at their means to simplify the interpretation of the results (Hayes, 2017).

To examine the interaction hypothesis (Hypothesis 1.1 - Chapter 2), we entered the following interaction terms (social isolation× frailty, no social ties× frailty) into the simple regression models (Models 1) to assess whether the association of social isolation with adverse health outcomes differed according to frailty status. If the interaction between social isolation× frail, social isolation× pre-frail (see b_4 or b_5 in Figure 2), no social tie× frail, or no social tie× pre-frail differs from zero, then the relationship between X and Y varies in three groups of frailty. Interactions were entered one by one into the simple regression models, and statistically significant interactions were retained and introduced in the multiple regression analyses. We compared the models with interactions with the models without interactions, using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), adjusted BIC, and chi-square tests. All models were adjusted for covariates. We built all multivariate regression models using 5000 bootstrapped samples /Monte Carlo integration to calculate 95% confidence intervals. Missing data were minimal (less than 3% (n=56)) and handled through mean imputation and regression imputation. Statistical significance was set to $p<0.05$ throughout all analyses. All regression analyses were carried out using Mplus version 8 (Muthén & Muthén, 2017).

Figure 2. A statistical diagram of moderation model with a multi-categorical variable



Notes: X: social isolation (independent variable); Y: health outcome (dependent variable); W: frailty (moderator); D_1: frail; D_2: Pre-frail; e: residual; D_1X and D_2X are the interaction of frailty and social isolation; b3 represents the relation between health and social isolation; b_1 and b_2 illustrate the relation between health and frailty; b_4 and b_5 indicate the interaction between frailty and social isolation. For visual clarity, dichotomous social isolation variables and covariates are not shown.

3.3.3. Modeling changes

The complexity of the body and mind and its potential for change and development over time provide possibilities for variations in individuals' health status. One of the main objectives of developmental science is to describe for whom individuals' health status changes over time (Nesselroade & Baltes, 1979; Ram & Grimm, 2007). The first rationale for conducting longitudinal studies is the identification of intra-individual change (within-person) or measuring the same individual repeatedly, allowing us to identify if and how specific attributes of the individual change over time. The second rationale is the identification of inter-individual differences (between-individual) in intra-individual differences or estimates of whether different individuals change in different ways (Grimm et al., 2016).

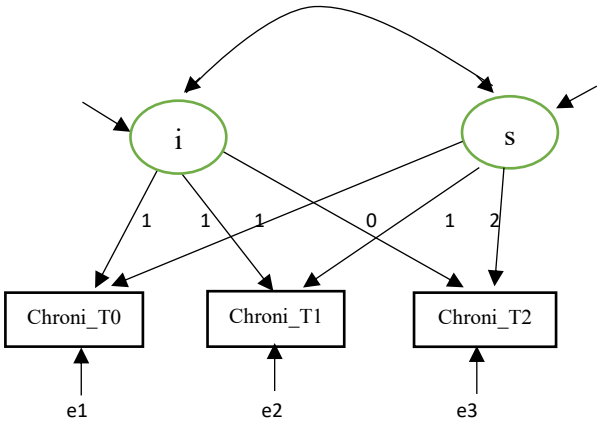
Based on the results of the cross-sectional moderation analysis, we set up a longitudinal study. We conducted a series of Latent Growth Curve Models (LGMs) within the framework of Structural Equation Modeling (SEM). Growth curve modeling is an analytic technique for estimating within-individual (intra-individual) change across repeated measurements and between-individual (inter-individual) variations in those changes over time (Grimm & Ram, 2009; Grimm et al., 2016). Traditional approaches to studying change such as ANOVA and multiple regression analysis focus on inter-individual variability and mean changes. In response to this analytical limitation, analysts have introduced new analytic methods to examine individual differences over time, including random-effects ANOVA, multilevel modeling, and hierarchical linear modeling. In these approaches, individual differences are captured by random coefficients; however, statistical modeling is limited to a single outcome. Latent growth analysis considers both factor means and variances, referring to individual differences. The LGM provides greater flexibility in the measurement of change, notably random changes in measurement error (Duncan & Duncan, 2009; Preacher et al., 2008). Additionally, growth models avoid the inflation of Type I error related to the repeated measures analysis of variance. (Curran et al., 2010; Duncan & Duncan, 2009). The intraindividual change over time is parsimoniously described by two parameters: 1) an individual's initial level of ability (intercept), and 2) an increase or decline in performance across multiple

measurements (slope). These parameters allow us to understand whether individuals follow different paths of development.

In the longitudinal study, variables were measured at three time points. The time intervals between occasions were equal over time (1 year). The independent variables were time-varying indicators, including social networks, social support, and social participation. The absence of social ties was time-invariant because the number of social ties (i.e., children, friends, etc.) did not change over 1 to 2 years in the FRéLE sample. The intervening variable, frailty, was a time-varying indicator. Likewise, health outcomes such as comorbidity, depression, and cognitive function were time-varying variables. However, the slope of disability was low and unstable and did not allow for an analysis of moderation terms involving changes. Accordingly, we tested the intercept of disability, not the slope.

Change in each of these variables over the three time periods was modeled using growth modeling. As an example, observed scores for chronic conditions (Chroni_T0, Chroni _T1, Chroni_T2) at the three time points are presented in Figure 3. A growth model includes two parameters, including the intercept (i) and the slope (s). The intercept represents the initial status at the first time point (baseline). The slope is the growth rate, representing the pattern of change over time. The coefficients are fixed at a value of 1 for the intercept, and at 0, 1, and 2 for the slope (Béland et al., 2018; Muthén & Muthén, 2017). The double-headed arrow shows a covariance between intercept and slope parameters.

Figure 3. Path diagram of a growth model for one variable



Notes: i: intercept (Initial status), s: slope (Growth rate), e: residual, Chroni_T0: chronic conditions at baseline, Chroni__T1: chronic conditions at time point 1, Chroni__T2: chronic conditions at time point 2. For simplicity, covariates are not shown.

We estimated changes between variables of interest, using intercepts and slopes (Béland et al., 2018; Muthén & Muthén, 2017). Here is an example of one of the univariate LGMs:

1) The regression of the slope of chronic conditions (sChroni) on the slope of social networks with friends (sSN-FR)

2) The regression of the slope of chronic conditions (sChroni) on the intercept of social networks with friends (iSN-FR)

3) The regression of the intercept of chronic conditions (iChroni) on the intercept of social networks with friends (iSN-FR)

It is worth noting that the second and third steps are not the main focus of the growth models and are control steps.

3.3.4. Moderation analysis

The longitudinal moderation analysis is based on the following research question:

Do the relationships between changes in social relationships and changes in health outcomes vary according to changes in frailty status among community-dwelling older adults in Québec?

We performed the latent moderated structural equations (LMS) approach to estimate the interaction terms in LGMs, under the assumption of normality (Klein & Moosbrugger, 2000; Wen et al., 2014). This approach has advantages in minimizing the convergent problems and generally results in less biased estimates for both coefficients and standard errors (Wen et al., 2014). Of note, the distributions of all change scores were almost normal in this longitudinal study (See Figures 1.3-Study 3).

To test the longitudinal moderation hypothesis (Hypothesis 1.2 - Chapter 2), we tested changes in health outcomes on the interactions between changes in social relationships and changes in frailty (Models 1). We created the following interaction terms with the Mplus XWITH command. These regressions were sensitive to interactions between the intercepts of social variables (binary and continuous) and the intercept and the slope of frailty. We thus examined the following analyses

and included the significant interaction terms from these analyses in the previous model (Models 1) for exploring interactions between changes in social relationships and frailty on changes in health outcomes.

1. We regressed the intercepts of all health outcomes (disability, depression, cognitive function, and comorbidity) on the interactions between the intercepts of social variables (continuous and binary) and frailty.
2. We regressed the slopes of health outcomes (depression, cognitive function, and comorbidity) on the interactions between the intercepts of binary social variables and frailty.
3. We regressed the slopes of health outcomes on the interactions between the intercepts of binary social variables and the slope of frailty.

The interactions involving intercepts at baseline (steps 1-2) are included as control variables and are not the subject of the moderation hypothesis. The interactions that were statistically significant in the univariate LGMs were included in multivariate LGMs. Convergence problems are mainly associated with estimating the interaction terms in LGMs (Wen et al., 2014). As suggested by Kim et al. (2018) and to minimize these convergence problems, we estimated multiple sets of starting values for residual variances and other terms from a series of sub-models that were together producing a saturated model. Convergence problems and the complexity of models might also increase with a large number of interaction terms (Kim et al., 2018). Therefore, we applied the two following solutions. First, we estimated the LGMs separately for social variables, including friends, nuclear family, extended family, and social participation. However, health outcomes were simultaneously entered into the multivariate LGMs. Second, the inclusion of binary and continuous indicators of social relationships together resulted in recurrent convergence problems in models involving changes. Therefore, we considered only binary indicators of social ties for testing the intercepts of the interaction effects except for social participation. Social participation had no related binary indicator, precluding convergence problems in estimating model parameters. To calculate a likelihood ratio to test for the significance of the interaction effects, we compared the models without interaction with the models with interaction, using the AIC, BIC, and adjusted BIC.

Only statistically significant coefficients in the univariate LGMs were retained in the multivariate LGMs. We compared the log-likelihood, number of parameters, and BIC values in all LGMs. The lower the BIC value, the better the model (Muthén & Asparouhov, 2008). In the moderation analysis, the estimations for slopes of social networks with siblings and children were unstable due to the small residual variances (Okada, 2017). Hence, we did not report the results. All LGMs were adjusted for time-invariant covariates. The Poisson regression models were used for disability as a count variable. The significance level was set at $p \leq 0.05$. We estimated all LGMs with the Maximum Likelihood (ML) estimator in Mplus version 8 (Muthén & Muthén, 2017).

3.3.5. Missing data

Missingness is inherent in longitudinal research studies where a loss to follow-up is roughly problematic (Palmer et al., 2012). Missing data are often classified into three types: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). The missingness is not related to participant characteristics in MCAR. In this type of missing data, participants with missing values constitute a random subset of the study population, and participant characteristics are similar between subjects with and without missing data. However, the main reason for missingness in MAR is related to known participant characteristics. In this approach, missingness is a function of covariates and observed outcomes. Lastly, the most complicated type of missing data is MNAR, where the missingness is related to unknown participant characteristics. This indicates that the missing data have a relationship with other missing data (de Goeij et al., 2013).

In the current study, the number of missing data was 264 (16.1%) in T1 and 421 (30.5%) in T2. We handled the missingness in T1 and T2 by performing a pattern-mixture model based on the MNAR assumption in the latent growth framework using the Mplus program (Muthén et al., 2011). This approach is used to estimate a growth model for the outcome with binary dummy dropout indicators used as covariates. We created dummy variables for dropout occasions in T1 and T2, defined as two latent subgroups of subjects. One dummy variable is related to dropout patterns, and another is related to the outcome trajectories. We regressed the intercept and slope growth factors of all independent and dependent variables on the dropout indicators. In all LGMs, there was no missing data for covariates at baseline. Estimation is performed using maximum likelihood with the EM algorithm (Muthén & Asparouhov, 2008)

Chapter 4 – Scoping review

Study 1. Effects of Social Isolation, Loneliness, and Frailty on Health Outcomes and their Possible Mediators and Moderators in Community-Dwelling Older Adults: A Scoping Review

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Authors' contributions to the article:

Fereshteh Mehrabi developed the idea for the article, designed and implemented the search strategies, extracted, synthesized the data, drafted, and revised the manuscript.

François Béland developed the idea for the article and contributed to the writing of the manuscript.

Both authors read and approved the final manuscript.

Research Highlights

- Frailty is linked to loneliness rather than to social isolation.
- Evidence supports that frailty is a strong predictor of poor health outcomes.
- Few studies found a relationship between social isolation and adverse outcomes.
- Social isolation and loneliness may moderate the effect of frailty on health.

4.1. Abstract

Background/Objective: Over the past decade, the quantity and quality of social relationships in later life have become one of the main challenges facing an aging society. Our aims were to map and synthesize the literature addressing the effects of loneliness, three aspects of social isolation, including social networks, social support, and social participation, and frailty on health outcomes and their mediators and moderators among older adults.

Methods: We conducted a scoping review and searched for articles published in English and French from 2001 up to 2019 in the following databases: Medline, Embase, CINAHL Plus, Scopus, Web of Science and PsycINFO.

Results: Our database search initially resulted in 4001 articles of which 1832 were excluded; 26 were eligible. Most of the included studies revealed associations between social isolation, loneliness, and frailty. The majority of studies found evidence of associations between frailty and their adverse outcomes; however, only few studies found a relationship between social isolation and health outcomes. In spite of the established link between frailty and adverse outcomes, no study looked at how social isolation and loneliness can alter adverse outcomes of frailty. No study investigated the role of frailty or social isolation and loneliness as a mediator on the pathway related to health.

Conclusions: Evidence is limited in examining the role of frailty or social isolation and loneliness as a moderator and mediator. Longitudinal research combining both social isolation and loneliness are warranted to explore whether social isolation or loneliness has more deleterious effects on frailty and health outcomes.

Keywords: Social isolation, Loneliness, Frailty, Health outcomes, Aging

4.2 Introduction

Over the past decade, the quantity and quality of social relationships in later life have become one of the main challenges facing an aging society (Valtorta et al., 2018b). Globally, up to 50% of older adults are at risk of social isolation and about one third of those aged 60 years and over experience loneliness in later life (Landeiro et al., 2017). Several national campaigns have been set up across Europe, North America, and Australia to alleviate social isolation and loneliness among older adults including, the Monalisa initiative in France (https://www.monalisa-asso.fr), the Coalitie Erbij in the Netherlands (https://www.samentegeneenzaamheid.nl), the campaign to end loneliness in the United Kingdom (http://www.campaigntoendloneliness.org.uk), the RISE campaign in Canada (https://rise-cisa.ca), Connect2affect in the United States (https://connect2affect.org) (Valtorta et al., 2018b), and the Australian coalition to end loneliness (https://www.endloneliness.com.au). One of the motives of these campaigns is the growing body of literature on the association between social isolation and health (Cummings, 2002; Fitzpatrick et al., 2005; Merz and Huxhold, 2010). It is well established that socially involved older adults are more likely to be healthy, live longer and report positive well-being outcomes in comparison to isolated older adults (Keller et al., 2003; Vozikaki et al., 2017). Several aspects of social isolation have been shown to account for poor health outcomes in older adults (Cornwell and Waite, 2009; Fokkema et al., 2012; Hawton et al., 2011; Li and Zhang, 2015). In particular, lack of social support and social disengagement or feelings of loneliness are closely linked to cardiovascular diseases (Shankar et al., 2011), dementia (Dröes et al., 2017; Kuiper et al., 2015), depression (Okura et al., 2017; Santini et al., 2016; Sherman, 2003), cognitive decline (Kim et al., 2017; Okura et al., 2017), disability (Janke et al., 2008; Kelley-Moore et al., 2006), and mortality (Clausen et al., 2007; Holt-Lunstad et al., 2015; Teguo et al., 2016). Taken together, these social factors might influence the onset, trajectory, or outcomes of frailty, one of the dimensions of health, in older populations (Peek

et al., 2012). Furthermore, research has suggested that loneliness is contributing to the development of frailty among older adults (Gale et al., 2018; Herrera-Badilla et al., 2015).

Frailty is defined as a state of loss of reserve capacity, deriving from cumulative declines in multiple physiological systems which can lead to vulnerability and poor health outcomes (Clegg et al., 2013; Fried et al., 2001) such as cognitive decline (Auyeung et al., 2011), dementia (Kulmala et al., 2014), depression (Mezuk et al., 2012; Nascimento et al., 2016), hospitalization (Dent and Hoogendijk, 2014), disability (Provencher et al., 2017), falls and premature death (Fried et al., 2001). In a landmark study, Fried et al. (2001) proposed the "Frailty Phenotype Approach" which focuses on physical frailty and defines frailty as the presence of three or more of the following criteria: unintentional weight loss, exhaustion, low grip strength, slowness, and low physical activity. In this approach, frailty is a distinct entity from disability and comorbidity, although overlapping with both (Bergman et al., 2004; Fried et al., 2004; Gobbens et al., 2010b). Relatedly, not all older adults with disabilities are frail, nor all frail older adults have disabilities. Based on the Fried's phenotype of frailty, Bergman et al. (2004) developed "A Canadian working framework for understanding frailty" in which frailty precedes disability and comorbidity. Disability and comorbidity, though, can be adverse health outcomes of frailty. This working framework offers a set of pathways linking social factors to physical frailty in older populations, suggesting how they affect each other directly or indirectly through mediators and moderators to produce health outcomes. Given the pervasive impact of social isolation and loneliness on frailty and health, an intriguing challenge is to explore how social isolation, loneliness and physical frailty are related to health outcomes and what is the role of frailty in the relationship between social isolation, loneliness, and health or what are the roles of social isolation and loneliness on the pathway from frailty to health?

Based on the Bergman conceptual framework and different types of models that have appeared in the retained papers, we identified eight models to illuminate the pathways from social isolation and loneliness to frailty and health outcomes (Figure 1). First, social isolation and loneliness affect frailty (Model 1A) or vice versa (Model 1B). Second and third, mediators and moderators are introduced on the pathway from social isolation and loneliness to frailty (Models 2A-3A) or from frailty to social isolation and loneliness (Models 2B-3B). According to Hayes (Hayes, 2017), we make no distinction between interaction and moderation. Fourth, mediation and moderation

(Models 2-3) are integrated into a single model (Models 4A-4B), commonly known as a conditional process model (Hayes, 2017). Fifth, social isolation, loneliness, and frailty impact health outcomes through three possible pathways such that social isolation and frailty are causally related one with the other (Models 5A-5B) or they are hypothesized to be correlated without implying a causal relationship (Model 5C). Sixth, social isolation, loneliness and frailty are proposed as either focal predictors or mediator variables: A) Frailty is a mediator for social isolation, loneliness, and health outcomes while social isolation and loneliness are focal predictors (Model 6A); or B) Frailty is a focal predictor while social isolation and/or loneliness are mediators of the association between frailty and health outcomes (Model 6B). Seventh, there are two possible moderation pathways related to health outcomes: A) Physical frailty is a moderator of the relationship between social isolation and loneliness, focal predictors, and health outcomes (Model 7A); or B) Social isolation and/or loneliness are moderators between the focal predictor, frailty, on the one hand, and health outcomes on the other hand (Model 7B). Eighth, the conditional process model is the indirect effect of social isolation and loneliness on health through frailty which is moderated (Model 8A) or the indirect effect of frailty on health through social isolation and loneliness which is moderated (Model 8B). The conditional process model can happen in a number of different ways. Only those found in the included studies are considered here.

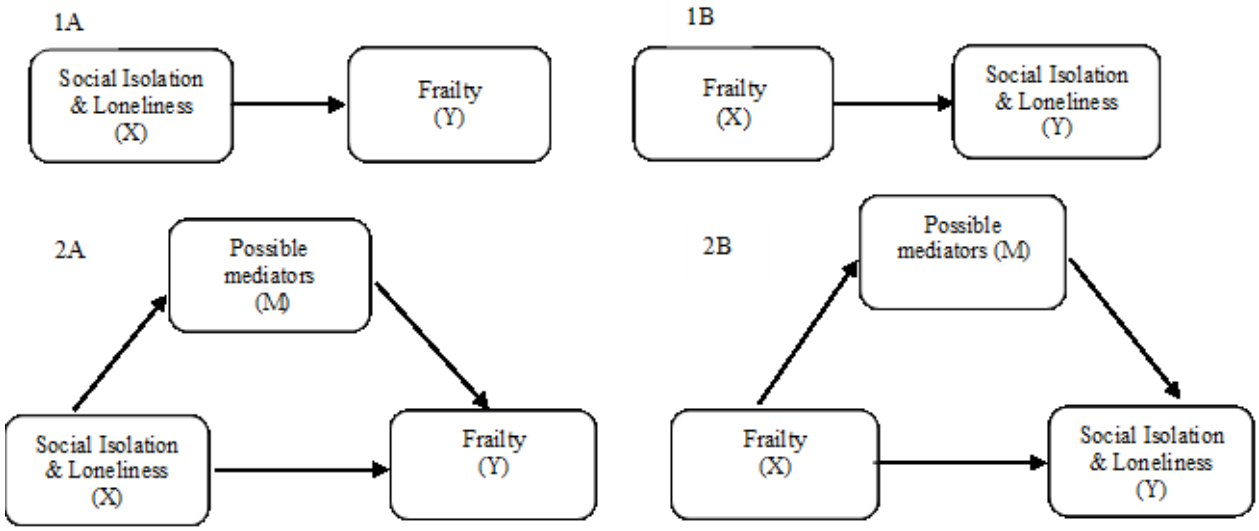
To date, reviews of the relationship between social isolation, loneliness, and health (Courtin and Knapp, 2017; Holt-Lunstad et al., 2010; Kelly et al., 2017; Valtorta et al., 2018b), have yet to focus on frailty. To address this gap, our objectives in undertaking a scoping review were to identify the state of research on the effects of social isolation and loneliness on physical frailty and health outcomes among community-dwelling older adults and to point out gaps in the literature.

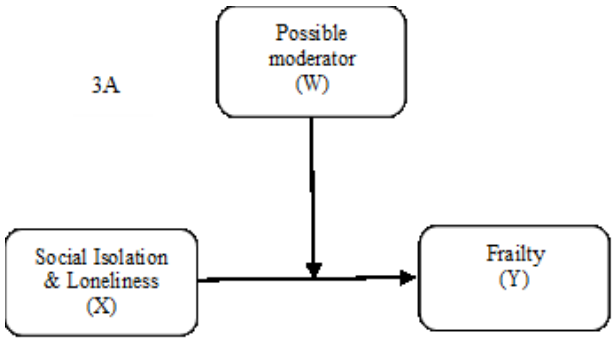
Theoretical perspectives

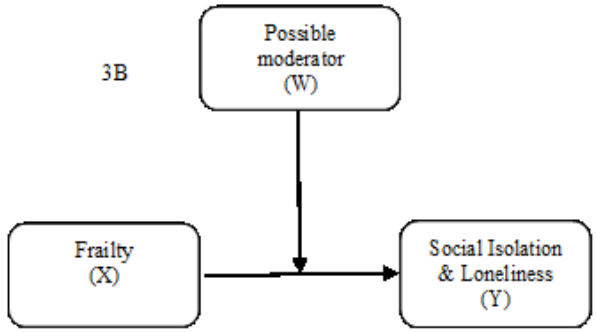
Several sets of theories are proposed to understand the link between social relationships and health. The earliest theories date back to the work of sociologist Emile Durkheim (1973) and psychoanalyst John Bowlby (1969). Most importantly, Durkheim contributed to a general understanding of how social integration impacts suicide. Bowlby proposed the theory of attachment in which individuals need to have close affectional bonds (Berkman et al., 2000). Thereafter, Barnes (1954) and Bott (1957) developed the theory of social networks to explain a

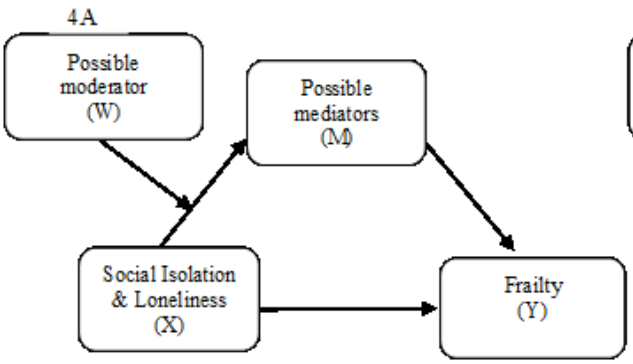
wider boundary of social relationships around individuals than traditional relations based on family and kinship. Social scientists focused not only on social contacts but also on participating in voluntary and religious activities, linking social networks to health outcomes (Berkman & Glass, 2000; Cohen, 1988). However, the social network theory has been criticized for locating the focus on the structural aspect of networks. Most authors agree that using only the quantity of a person's social network provides little information about the quality, amount, and nature of social interactions (Erin York Cornwell & Linda J. Waite, 2009; Valtorta et al., 2016).

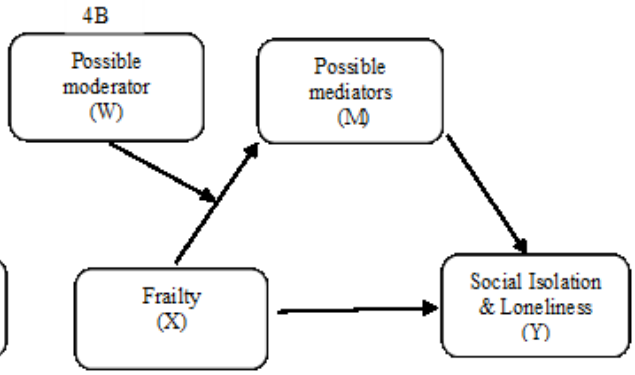
Figure 4. (Study 1. Figure 1) Models of the relationships between social isolation, loneliness, frailty, and health outcomes

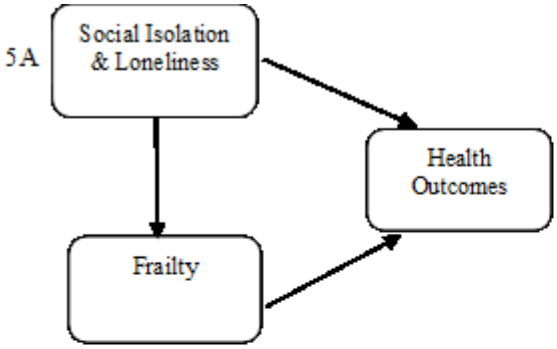


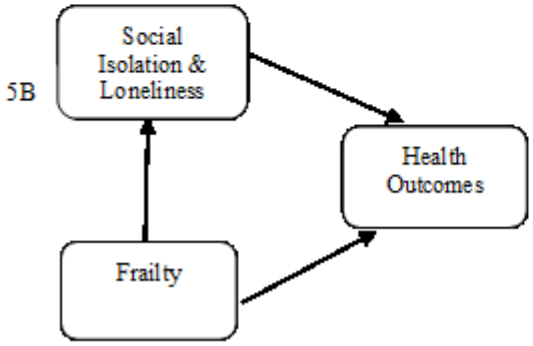

3A
Possible moderator (W)
Social Isolation & Loneliness (X)
Frailty (Y)

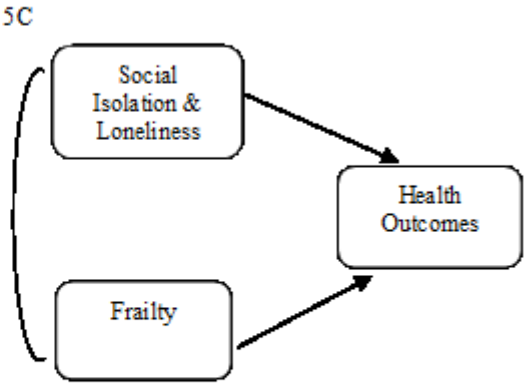

3B
Possible moderator (W)
Frailty (X)
Social Isolation & Loneliness (Y)


4A
Possible moderator (W)
Possible mediators (M)
Social Isolation & Loneliness (X)
Frailty (Y)

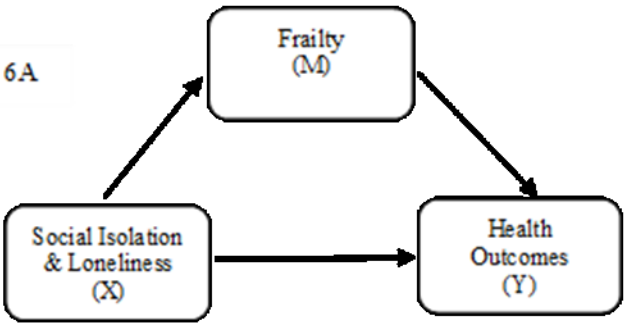

4B
Possible moderator (W)
Possible mediators (M)
Frailty (X)
Social Isolation & Loneliness (Y)


5A
Social Isolation & Loneliness
Health Outcomes
Frailty

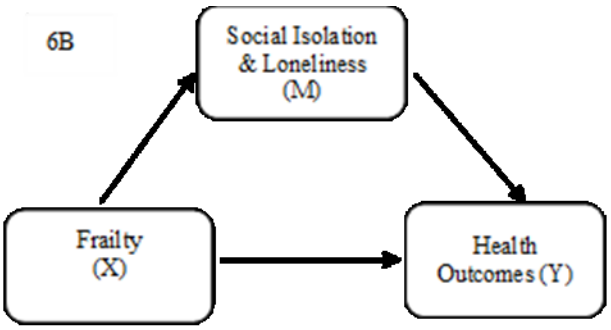

5B
Social Isolation & Loneliness
Health Outcomes
Frailty


5C
Social Isolation & Loneliness
Health Outcomes
Frailty

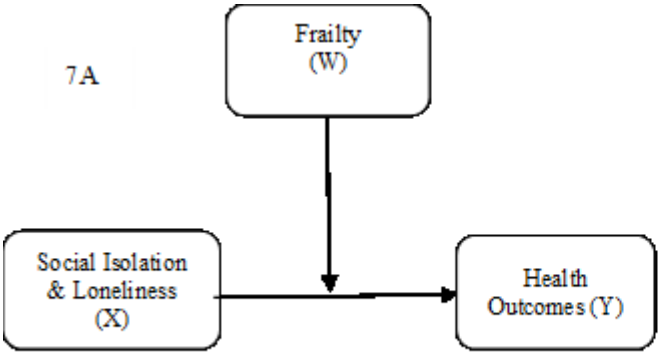
6A


Frailty
(M)
Social Isolation
& Loneliness
(X)
Health
Outcomes
(Y)

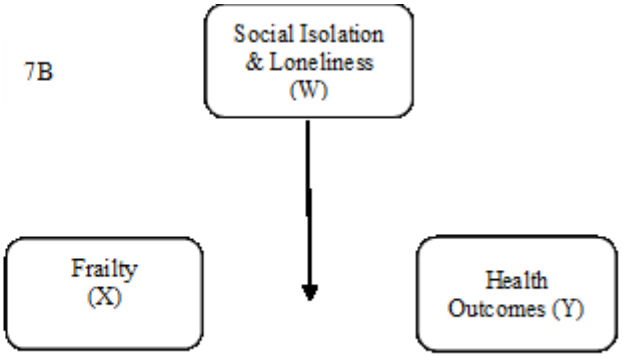
6B

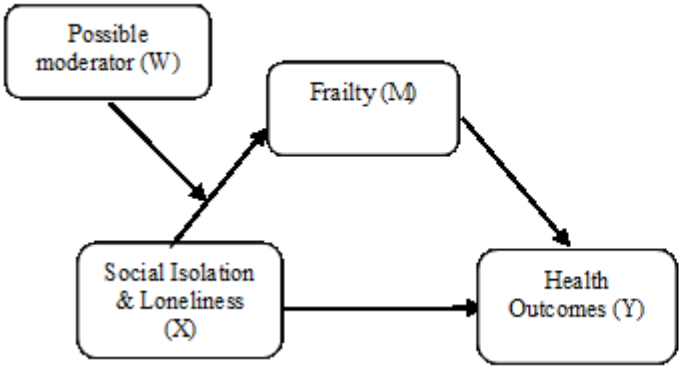

Social Isolation
& Loneliness
(M)
Frailty
(X)
Health
Outcomes (Y)

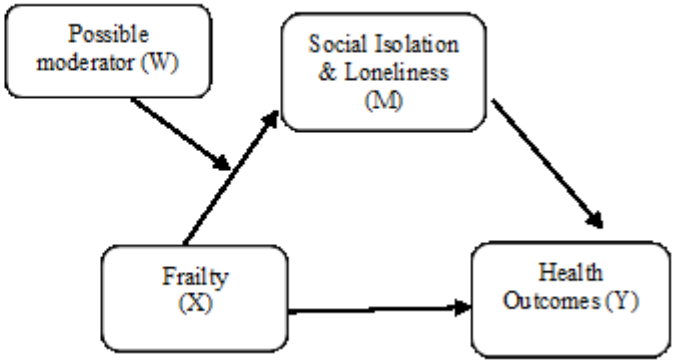
7A


Frailty
(W)
Social Isolation
& Loneliness
(X)
Health
Outcomes (Y)

7B


Social Isolation
& Loneliness
(W)
Frailty
(X)
Health
Outcomes (Y)


Possible
moderator (W)
Frailty (M)
Social Isolation
& Loneliness
(X)
Health
Outcomes (Y)


Possible
moderator (W)
Social Isolation
& Loneliness
(M)
Frailty
(X)
Health
Outcomes (Y)

Meaningful social contacts depend on the degree of support that social ties might provide. In order to have a comprehensive framework, it is important to consider the multiple pathways by which social isolation might impact health.

In reaction to this early work on social relationships, several social scientists focused on qualitative aspects of social relations rather than structural aspects. The most influential theories were the conceptual model of Berkman and Glass (2000) and the rational loneliness theory proposed by Weiss (1973), including emotional and social loneliness. Emotional loneliness is a subjective negative feeling associated with the absence of a close emotional attachment (a partner, a best friend) and social loneliness is related to the absence of a broader group of social contacts (friends, colleagues, and acquaintances). Loneliness is a distinct concept from social isolation, though closely related (Grenade & Boldy, 2008). People with an extensive social network might feel lonely, whereas people with a small network might not feel necessarily lonely and could be satisfied with the quality of their relationships (Erin York Cornwell & Linda J. Waite, 2009; Grenade & Boldy, 2008). More recently, Berkman and Krishna (Berkman, 2014) revised the previous conceptual framework of how social networks impact health outcomes (Berkman et al., 2000) and proposed a more comprehensive conceptual framework linking social networks—particularly those related to social engagement—social support and loneliness to health. In particular, they attempted to integrate loneliness in this recent framework. We used Berkman and Krishna's model (Berkman, 2014) to show how loneliness and three aspects of social isolation, including social network, social participation, and social support, might influence a wide range of health outcomes.

4.3 Methods

Study design

Our study followed the five-stage methodological framework for scoping studies suggested by Arksey and O'Malley (2005): (1) identify the research questions; (2) identify relevant studies; (3) select studies; (4) chart the data; and (5) collate, summarize and report the results. The stages of the review are detailed below.

Identifying research questions

This review is guided by the following research questions:

What evidence exists on the relationship and direction of the associations between social isolation, loneliness, and frailty (Model 1, Figure 1) and mediators and moderators (Models 2–4, Figure 1) in community-dwelling older adults?

What evidence exists on the relationship and direction of the effects of social isolation, loneliness, and frailty on health outcomes (Model 5, Figure 1) and mediator and moderator (Models 6–8, Figure 1) roles of frailty or social isolation and loneliness among community dwelling older adults?

What are the limitations and gaps in the literature?

Identifying relevant studies

We searched a wide range of academic literature databases to identify relevant papers including Medline, Embase, CINAHL Plus, Scopus, Web of Science and PsycINFO. The search terms were developed in consultation with a public health librarian, using keywords related to "social isolation", "loneliness", "frailty", "older adults" and their synonyms. An example of the search strategy is presented in Appendix A.

Selection criteria

Original research articles published in English and French from 2001 up to June 2018 were retrieved, updating by July 2019. The time limit was chosen due to the fact that the year of the publication of a well-known and widely cited operational definition of physical frailty, proposed by Fried (2001), was developed in 2001. Only physical frailty was considered in this paper. Other approaches to frailty such as the "Frailty Index Approach" (Mitnitski et al., 2001) and the "Multidimensional Model" (Robbert JJ Gobbens et al., 2010) were excluded given that they include social functioning, disability, and comorbidity as components of frailty while these characteristics are considered as dimensions of social isolation and health outcomes in this review. We included articles targeting community-dwelling older adults aged 60 and over and we excluded studies in which less than 50% of the sample was older than 60 years or mean age was younger than 60 years. We included one study (Dent & Hoogendijk, 2014) on hospitalized patients in a 20-bed subacute geriatric unit since they might return home after hospitalization. Studies were eligible for inclusion if they identified measurement for loneliness and/or social isolation (namely, social networks, social participation, and social support), as per the Berkman and Krishna framework (Berkman, 2014). Social networks include living arrangements, marital status, number of social ties or

frequency of contact with children, friends, extended family, and neighbors. Social participation includes meeting with family and friends, participation in voluntary or religious activities, being a member of community groups, or attending social groups. Social support includes emotional support, satisfaction with support, negative social interactions, instrumental support, appraisal, informational support, sharing personal experiences and feelings, giving feedback, or helping in decision-making, and support with daily tasks or general ratings of social support (Berkman, 2014; Berkman & Glass, 2000; Kelly et al., 2017). Loneliness includes items such as feeling lonely or isolated, not feeling part of a group, or not having people one can talk to (Berkman, 2014) (Table 1). No restrictions on methodological design or geographical location were applied. We considered the design of the retained studies as longitudinal if frailty status and social isolation were observed over time. For the selection process, the first author (FM) initially screened papers based on their title and abstract and then reviewed the full text of selected papers. Any doubt regarding paper selection was resolved through discussion or with the help of the co-author (FB). Due to the fact that reporting guidelines for scoping reviews do not currently exist (Pham et al., 2014), the recommendation of Pham et al. (Pham et al., 2014), the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2015), was used to conduct the selection process (Appendix B).

Data charting

An Excel data extraction form was developed to guide the collection of information and themes relevant to the research questions. The following descriptive data were extracted from each article: 1) authors, affiliation of the first author, title, year, country; 2) details regarding the nature and scope of the articles (research questions or objectives or hypotheses, sample size, study design, the prevalence of frailty, statistical methods, and how social isolation, loneliness, and frailty were measured); 3) results and discussion regarding the relationship and direction of the associations between social isolation, loneliness and frailty, the relationships between social isolation, loneliness, frailty and health outcomes and mediators and moderators on the pathways related to health outcomes based on Models 1 to 8 in Figure 1; 4) strength, limitations, implications and gaps. The main characteristics of the retrieved studies are summarized in Table 2**.**

Table 2 (Study 1. Table 1) Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Published between 2001 and 2018 2. Focused on physical frailty 3. Focused on loneliness and/or at least one of the three dimensions of social isolation, including social networks, social participation, and social support 4. Community dwelling older adults aged 60 years and over 5. Written in English or French	1. Not assessed physical frailty 2. Not assessed any of the three aspects of social isolation (social networks, social participation, and social support) or loneliness 3. Book reviews, editorials, review articles

4.4 Results

Characteristics of included studies

The electronic search strategies initially yielded 4001 articles. Five additional publications were identified from database update alerts (Chon et al., 2018; Kwan et al., 2019; Liao et al., 2018) and by manually searching the reference lists of the studies found through a database search (Gale et al., 2012; Kamiya & Kenny, 2017). After duplicated were removed (n=2113), the title and abstract of 1893 articles were screened and 1832 articles were excluded based on the inclusion and exclusion criteria. Full texts of 61 articles were assessed of which 26 articles published in English met the inclusion criteria and were finally selected for data extraction in this scoping review. Thirty-five articles were excluded because i) they were review papers, not research papers (n=2), ii) they did not report any findings regarding social isolation and loneliness or their measurement (n=8), and iii) they did not report any results on physical frailty or its measurement (n=25) (Appendix C). The flow of articles from identification to final inclusion is displayed in the PRISMA flowchart in Figure 2.

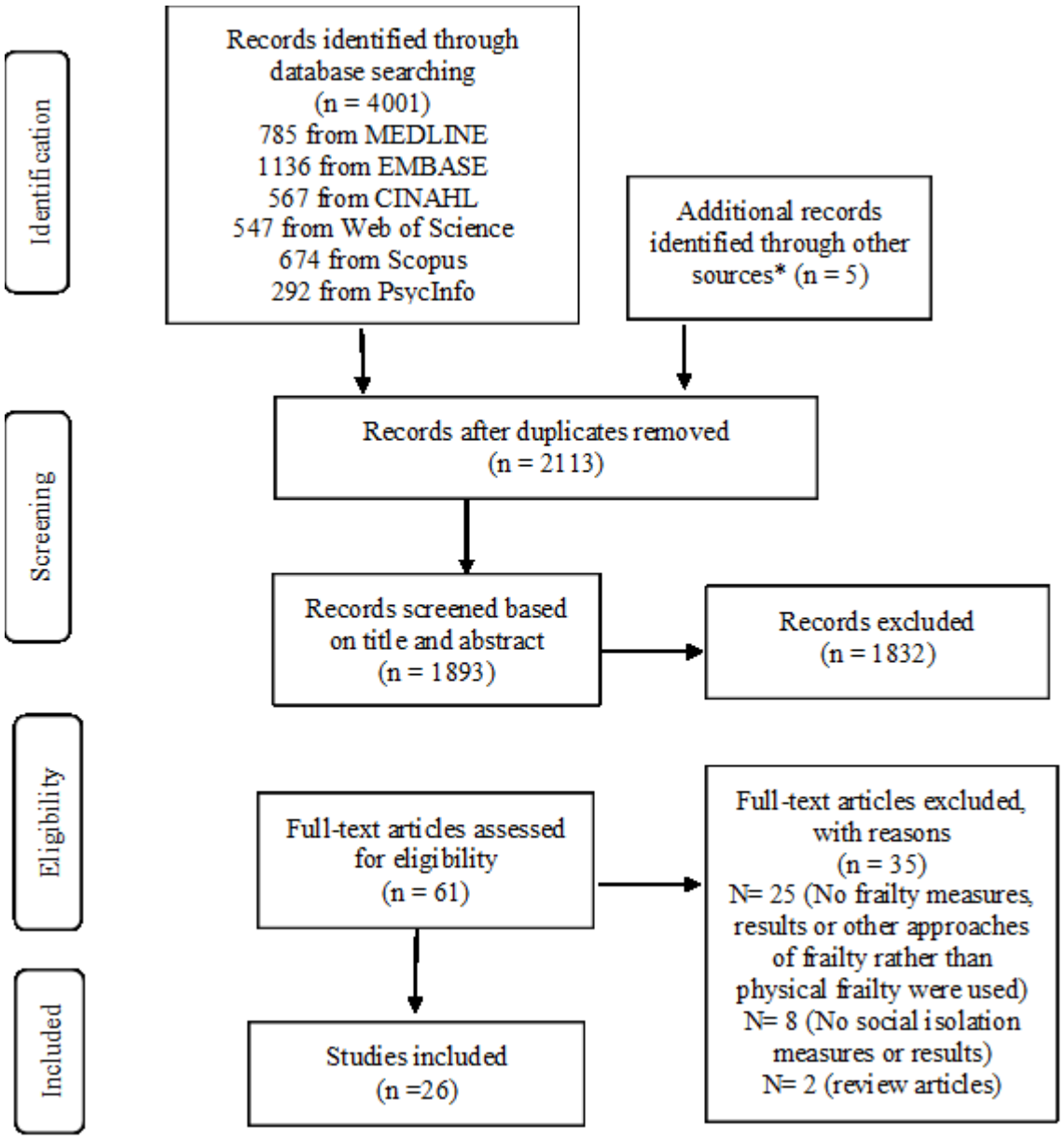


Figure 5 (Study 1. Figure 2) PRISMA flow chart of studies selection process

*Three additional studies included through update alerts and two added through the reference list.

Table 3 (Study 1. Table 2) Characteristics of included studies on social isolation, loneliness, frailty, and health outcomes

First author	Location of study	Sample size, average age of participants	Study design: average length of follow-up (years)	Social isolation aspects and loneliness	Prevalence of frailty	Frailty measurement	Health outcomes	Main findings
Gale (2012)	UK	N=482; M= 64.8; SD= 2.74	Cross-sectional	Social support (negative interactions)	Frail: 4.5% men %,10.1 % women	Fried phenotype	NA	They found no association between perceived social support and frailty; however, negative social interactions were associated with frailty among women.
Jurschik (2012)	Spain	N = 640; M =81.3; SD=5	Cross-sectional	Social networks, social support& social participation	Frail:9.6% Pre-frail: 47%	Modified Fried phenotype	NA	Poor social ties were significantly associated with frailty in the logistic regression model whilst neither social support nor social participation was linked to frailty.
Peek (2012)	USA	wave 2 (n=2438), wave 3 (n=1981), wave 4 (n=1682), wave 5 (n=1167), wave 6 (n = 921); M= 75.14; SD=6.57	Longitudinal, 12	Social support	Frail: 19% (wave 2), 23% (wave 3&4), 28 %(wave 5), 45% (wave 6)	Modified Fried phenotype	NA	Social support protected against frailty for the progressive moderate frailty group.
Ni Mhaolain (2012)	Ireland	N=301; M=75; SD=7.5	Cross-sectional	Loneliness	Frail: 13.3% Pre-frail: 54.2%	Modified Fried phenotype	Fear of falling	Loneliness was not associated with fear of falling in frail older adults in multivariate regression models.
Schnittger (2012)	Ireland	N = 579; M= 72.53; SD = 7.14	Cross-sectional	Social networks	NA	Fried phenotype	NA	Social network support was not associated with frailty.

First author	Location of study	Sample size, average age of participants	Study design: average length of follow-up (years)	Social isolation aspects and loneliness	Prevalence of frailty	Frailty measurement	Health outcomes	Main findings
Chen (2014)	Taiwan	N= 495, M=73.4	Cross-sectional	Social support & social participation	Frail:8.3% Pre-frail: 45.9%	Modified Fried phenotype	NA	In the multinomial logistic regression, the effect of social support on the level of frailty was not significant, however, participation in leisure activities had a significant effect on frailty.
Dent (2014)	Australia	N = 172; M = 85.2; SD = 6.4	Cross-sectional	social participation & social networks	Frail:56% Pre-frail: 37%	Fried phenotype	Mortality, discharge to higher-level care, length of stay & rehospitalization	Results of the logistic regression analyses indicated that frailty was associated with admission to higher-level care, mortality, length of stay and rehospitalization among older adults. They found no evidence of an association between frailty, social participation, and social networks. Frail older adults had increased odd for both mortality and discharge to higher-level care if they had a low level of social activities.
Etman (2014)	11 European countries	N = 14082; 45.9%≤ 64; 54.1 ≥ 64	Longitudinal, 2	Social participation	Frail:8.4%; 11.5% Pre-frail: 39%; 39.8%	Modified Fried phenotype	NA	No social activities increased the likelihood of frailty worsening in the multinomial regression analysis.
Hermsen (2014)	Netherlands	N = 407; M=76.8; SD = 6.3	Cross-sectional	Social support	Frail:18.4%	Modified Fried phenotype	Functional limitations	Less social support was related to participant restrictions whereas frailty was associated with functional limitations in the multivariate regression analysis.
Hoogendijk (2014)	Netherlands	N= 1387; M=69.5; SD=8.2 (functional limitation sample) & 1665 (mortality	Longitudinal, 3	Instrumental &emotional support	Frail: 6.3% & 8.9%	Fried phenotype	Functional decline & mortality	This study did not find any statistically significant interaction effects between social support and frailty on functional decline and mortality.

First author	Location of study	Sample size, average age of participants	Study design: average length of follow-up (years)	Social isolation aspects and loneliness	Prevalence of frailty	Frailty measurement	Health outcomes	Main findings
		sample) ; M=70.4 SD=8.6						
Buttery (2015)	Germany	N = 1843; Range (65-79)	Cross-sectional	Social support	Frail: 2.3%(men); 2.8%(women) Pre-frail: 36.9% (men) ;40.4% (women)	Modified Fried phenotype	NA	Poor social support was significantly associated with frailty in adjusted multinomial logistic regression models.
Chen (2015)	Japan	N=1527; M=73.3; SD=6	Cross-sectional	Social participation & social networks	Frail:9.3% Pre-frail: 43.9%	Fried phenotype	NA	No engagement in social activities and social contacts were associated with frailty.
het Veld (2015)	Netherlands	N = 8684; M = 74.2; SD = 6.4	Cross-sectional	Social networks & loneliness	Frail:8.7% Pre-frail: 28.1%	Modified Fried phenotype	NA	Social ties and loneliness were associated with frailty.
Hsu (2015)	Taiwan	N = 2306; M = 70.7; SD = 5.1	Longitudinal, 14	Social participation	Frail in 5 waves:12.7%; 15.4%;23.3%; 24.8%;27.9%	Fried phenotype	NA	Social participation was significant for the high risk of frailty group over time.
Li (2015)	Taiwan	N = 3226; M = 62.73; SD = 9.64	Longitudinal, 4	Social support & social participation	Frail: 3.66% Pre-frail: 57.37%	Fried phenotype	Cognitive function	The results of the generalized linear model showed that providing more informational support was related to higher cognitive function but the effect of frailty on cognitive function only showed on females. Participation in social activities was only significant for males.
Luger (2016)	Austria	N = 80; M=82.8	Randomized controlled trial	Social support intervention	Frail:64 prefrail: 35	SHARE-FI	NA	Social support intervention can help to tackle frailty in older aduls living at home.

First author	Location of study	Sample size, average age of participants	Study design: average length of follow-up (years)	Social isolation aspects and loneliness	Prevalence of frailty	Frailty measurement	Health outcomes	Main findings
		SD=8						
Malini (2016)	Brazil	N= 742; M=76.7; SD=7.03	Cross-sectional	Social support	Diminished hand grip strength: 20.6%	Hand grip strength	Fear of falling	Social support and hang grip strength were not associated with fear of falling.
Mulasso (2016)	Italy	N = 210; M = 73.4; SD = 5.9;	Cross-sectional	Social isolation & loneliness	Frail:14%; Pre-frail: 55%	Fried phenotype	Disability	The results of one-way analysis of covariance (ANCOVA) demonstrated that the interaction effects of social isolation, loneliness and frailty on disability were significant.
Ding (2017)	UK	N = 4638; M = 74; SD=6.3	Longitudinal, 2	Social isolation (social networks & social participation); social support	Frail: 33%	Modified Fried phenotype	NA	Poor social support was associated with frailty in the Latent Growth Model (LGM) however social isolation were not. Social isolation moderated the indirect effect of social support through chronic disease by making it stronger.
Kamiya (2017)	UK	N = 4432 in wave 2; M=70.79; SD=7.79	Cross-sectional	Social networks, social support and social participation	Frail: 7.01% Pre-frail: 50.69%	Fried phenotype	Mortality	The results of Multinomial logit model and Cox proportional hazard model showed that frailty was an independent predictor of mortality but none of the social isolation measures were associated with mortality.
Vaingankar (2017)	Singapore	N = 2102; M= 69	Cross-sectional	Social networks (including social participation)	Frail: 5.7% Pre-frail: 40.1%	Fried phenotype	NA	In a backward stepwise logistic regression analysis, poor social networks were significantly associated with frailty.
Chon (2018)	Korea	N= 1200	Cross-sectional	Social networks	Frail: 9%; Pre-frail:48.7%	Fried phenotype	NA	The results of the multinomial logistic regression showed that the frequency of

First author	Location of study	Sample size, average age of participants	Study design: average length of follow-up (years)	Social isolation aspects and loneliness	Prevalence of frailty	Frailty measurement	Health outcomes	Main findings
		Range (70-84)						contact with friends was the most statistically significant with frailty.
Gale (2018)	UK	N = 2817; M =69.3; SD= 6.9	Longitudinal, 2	Social isolation (social networks & social participation) & loneliness	Frail:5.3% Pre-frail: 38.5%	Fried phenotype	NA	High level of loneliness, but not of social isolation was associated with physical frailty. The relationship between loneliness and frailty was bidirectional.
Liao (2018)	Taiwan	N= 2186; M = 73.8; SD = 5.5	Longitudinal, 12	Social support	Frail: 19.9% Pre-frail: 40.5%	Modified Fried phenotype	Mortality	Multivariate Cox regression analysis revealed a significant association between providing family support and lower mortality rates in the pre-frail males and non-frail older adults. Less receiving family support were not associated with mortality among frail older adults.
Kwan (2019)	China	N = 263; M = 77.1; SD = 7.5	Cross-sectional	Social participation	Frail: 22.1% Pre-frail: 45.6 %	Fried phenotype	N/A	In the multiple ordinal regression adjusted for all potential confounders, social participation was negatively associated with frailty.
Zhang (2018)	USA	N = 304; M = 78.4; SD = 6.9	Cross-sectional	Social support	Frail: 53%	Fried phenotype	Falls	Low social support was significantly associated with falls in the univariate logistic regression analysis. Frailty was associated with falls in multivariate logistic regression analysis after adjusting for confounders.

The number of articles increased over time with 80% articles (n= 21/26) published in the last 5 years of our review; the remaining 5 other articles (20%) were published between 2011 and 2013. A total of 64,959 participants were included across the included articles, with the average age ranging from 62.7 (Li & Hsu, 2015) to 85.2 (Dent & Hoogendijk, 2014) years. The included studies spanned 20 different countries, mainly conducted in Europe (14 studies) (Buttery et al., 2015; Ding et al., 2017; Etman et al., 2014; Gale et al., 2012; Gale et al., 2018; Hermsen et al., 2014; het Veld et al., 2015; Hoogendijk et al., 2014; Jürschik et al., 2012; Kamiya & Kenny, 2017; Luger et al., 2016; Mulasso et al., 2016; Ní Mhaoláin et al., 2012; Schnittger et al., 2012), 8 studies in South and East Asia (China, Japan, Korea, Singapore, and Taiwan) (Chen et al., 2014; Chen et al., 2015; Chon et al., 2018; Hsu & Chang, 2015; Kwan et al., 2019; Li & Hsu, 2015; Liao et al., 2018; Vaingankar et al., 2017), 2 studies in the United States (Peek et al., 2012; Zhang et al., 2018) and 2 single studies in Brazil (Malini et al., 2016), and Australia (Dent & Hoogendijk, 2014). Sample sizes varied from 80 to 14,082 and more than half of the articles (69%) were based on secondary analyses of previously collected data (18 studies). The largest sample size in this review was determined in a longitudinal study (2014), using the data of the Survey of Health, Ageing and Retirement in Europe (SHARE), which was nationally representative of 11 European countries including Sweden, Denmark, Germany, the Netherlands, Belgium, Switzerland, Austria, France, Italy, Spain, and Greece (Table 2). The smallest sample was in a Randomized Controlled Trial (RCT).

Study designs included 17 cross-sectional studies (66%) (Buttery et al., 2015; Chen et al., 2014; Chen et al., 2015; Chon et al., 2018; Dent & Hoogendijk, 2014; Gale et al., 2012; Hermsen et al., 2014; het Veld et al., 2015; Jürschik et al., 2012; Kamiya & Kenny, 2017; Kwan et al., 2019; Malini et al., 2016; Mulasso et al., 2016; Ní Mhaoláin et al., 2012; Schnittger et al., 2012; Vaingankar et al., 2017; Zhang et al., 2018), 8 longitudinal studies (31%) (Ding et al., 2017; Etman et al., 2014; Gale et al., 2018; Hoogendijk et al., 2014; Hsu & Chang, 2015; Li & Hsu, 2015; Liao et al., 2018; Peek et al., 2012) with follow-up times ranging from 2 to 14 years, and one RCT (4%) (Luger et al., 2016). However, no qualitative studies were included perhaps due to failure to meet the inclusion criteria required, especially measuring physical frailty.

The frailty phenotype proposed by Fried (2001) was the most popular tool used to measure frailty (n=24). Two remaining studies (Luger et al., 2016; Malini et al., 2016) used hand grip strength and

the SHARE Frailty Instrument (SHARE-FI) (Romero-Ortuno et al., 2010) which was developed based on Fried's criteria. The main health outcomes investigated were mortality (4 studies), falls (3 studies), and functional limitations (3 studies).

According to a systematic review (Collard et al., 2012), the weighted average prevalence of phenotype of frailty and prefrailty among community-dwelling older adults aged 65 and over were 9.9% and 44.2%, respectively. The prevalence of frailty in this review ranged from 2.3% (Buttery et al., 2015) to 66% (Luger et al., 2016) and of prefrailty varied from 28.1% to 57.4% (het Veld et al., 2015; Li & Hsu, 2015). The lowest level of frailty is consistent with findings of the SHARE study that Germany has the lowest prevalence of frailty among European countries (Romero-Ortuno et al., 2013). The highest level of frailty was reported in an RCT study (Luger et al., 2016) in which frail older adults were included in the social support intervention. This sample, thus, was not intended to be representative of an older population.

Social support and social participation were the most commonly measured aspects of social isolation. Sixteen studies used a unidimensional measure of social isolation or loneliness, 10 studies used a multidimensional measure (i.e., a measure that combined 2 or more of 3 dimensions) of which three studies examined both social isolation and loneliness (Gale et al., 2018; het Veld et al., 2015; Mulasso et al., 2016).

Social isolation, loneliness, and frailty

Social networks and frailty (Figures 3.1)

According to Model 1A in Figure 1, the results of four cross-sectional studies revealed that a limited number of social contacts was associated with an increased risk of frailty among older adults (Chen et al., 2015; het Veld et al., 2015; Jürschik et al., 2012; Vaingankar et al., 2017) (Figure 3.1 No. 1–4 [Fig. 3.1.1—Fig. 3.1.4]). Chon et al. (2018) examined the effect of different types of social ties including friends, family, and neighbors, on frailty status (Fig. 3.1.5). The results showed that contact frequency with friends was significantly associated with frailty. The dashed arrows represent no significant association between variables. Conversely, a study from Ireland (Fig. 3.1.6) reported no significant relationship between social network support from friends, neighbors and frailty (Schnittger et al., 2012). The other type of networks such as children and extended family were not examined in this study.

Social support and frailty (Figures 3.2)

According to Model 1A in Figure 1, a cross-sectional study from Germany (Fig. 3.2.1) found that low levels of social support were linked to frailty (Buttery et al., 2015). An RCT study from Austria (Fig. 3.2.2) examined the effects of a physical training and nutritional intervention program compared with social support intervention on nutritional and frailty status in prefrail and frail older adults. The results revealed a decrease in frailty and an improvement in the nutritional status of older adults in both groups after 3 months (Luger et al., 2016). By contrast, two cross-sectional studies (Chen et al., 2014; Jürschik et al., 2012) reported no evidence of an association between social support and frailty (Fig.3.2.3-Fig.3.2.4). A cross-sectional study from England (Gale et al., 2012) found no effects of emotional and instrumental support on frailty, though the risk of frailty increased with the level of negative social interactions in close relations among women (Fig. 3.2.5).

In a longitudinal study (Fig. 3.2.6), using the ESLA data, the lack of emotional support was a predictor of future physical frailty over time (Ding et al., 2017). In another longitudinal study from the United States, using the Hispanic Established Populations for the Epidemiologic Study of the Elderly (Hispanic EPESE) data (Peek et al., 2012), frailty was categorized into three trajectories: low, progressive moderate and progressive high frailty (Fig.3.2.7). The results indicated that emotional perceived support was protective against frailty in the group characterized by progressive moderate frailty who started at a higher level of frailty and had a sharp increase of frailty between waves 5 and 6. However, there was no significant association between social support and frailty for those in the low frailty and progressive high frailty groups over 12 years.

Social participation and frailty (Figures 3.3)

Based on Model 1A in Figure 1, three cross-sectional studies (Fig.3.3.1- Fig.3.3.3) found evidence for a protective effect of social activities on frailty (Chen et al., 2014; Chen et al., 2015; Kwan et al., 2019). However, a cross-sectional study from Spain (Jürschik et al., 2012) reached the opposite conclusion, reporting that a high level of social participation was not associated with a reduced risk of frailty (Fig.3.3.4). Evidence from a longitudinal study (Etman et al., 2014) indicated that less social participation increased the probability of frailty worsening which was defined as changing from a lower to a higher frailty state after two years (Fig. 3.3.5). Likewise, the results of Taiwan's Longitudinal Study on Aging (TLSA) (Hsu & Chang, 2015) revealed that social participation was a protective factor to frailty in older adults who had a high risk of frailty over 14 years (Fig. 3.3.6).

Social isolation and frailty (Figures 3.4)

According to Models 1A and 1B in Figure 1, two longitudinal studies (Ding et al., 2017; Gale et al., 2018), using the ELSA data, examined the effects of social isolation, including social networks and social participation measurements, on frailty. Ding (2017) found no evidence of an association between social isolation and frailty over time (Fig. 3.4.1). Gale et al. (Gale et al., 2018) found baseline physical frailty was associated with increased levels of social isolation two years later at Wave 3, but not at subsequent follow-ups (waves 4–5) (Fig. 3.4.2- Fig. 3.4.3). Indeed, the results of this longitudinal study (Gale et al., 2018) revealed a possible direct effect of frailty on social isolation, but not vice versa.

Loneliness and frailty (Figures 3.5)

A cross-sectional study from the Netherlands (het Veld et al., 2015) found a significant link between loneliness and frailty (Fig. 3.5.1). A longitudinal study from England (Gale et al., 2018), using the ELSA data, reported a bidirectional relationship between loneliness and frailty (Fig. 3.5.2—Fig. 3.5.3).

Mediation (Figure 3.6)

Ding et al. (2017) adopted the pathways from physical, psychological and social predictors to frailty from Bergman's working framework (2004). Based upon the modified version of the Bergman framework, they examined the mediation effect of chronic disease and allostatic load on the pathways from social predictors to frailty, albeit no evidence of mediation was found (Fig. 3.6.1).

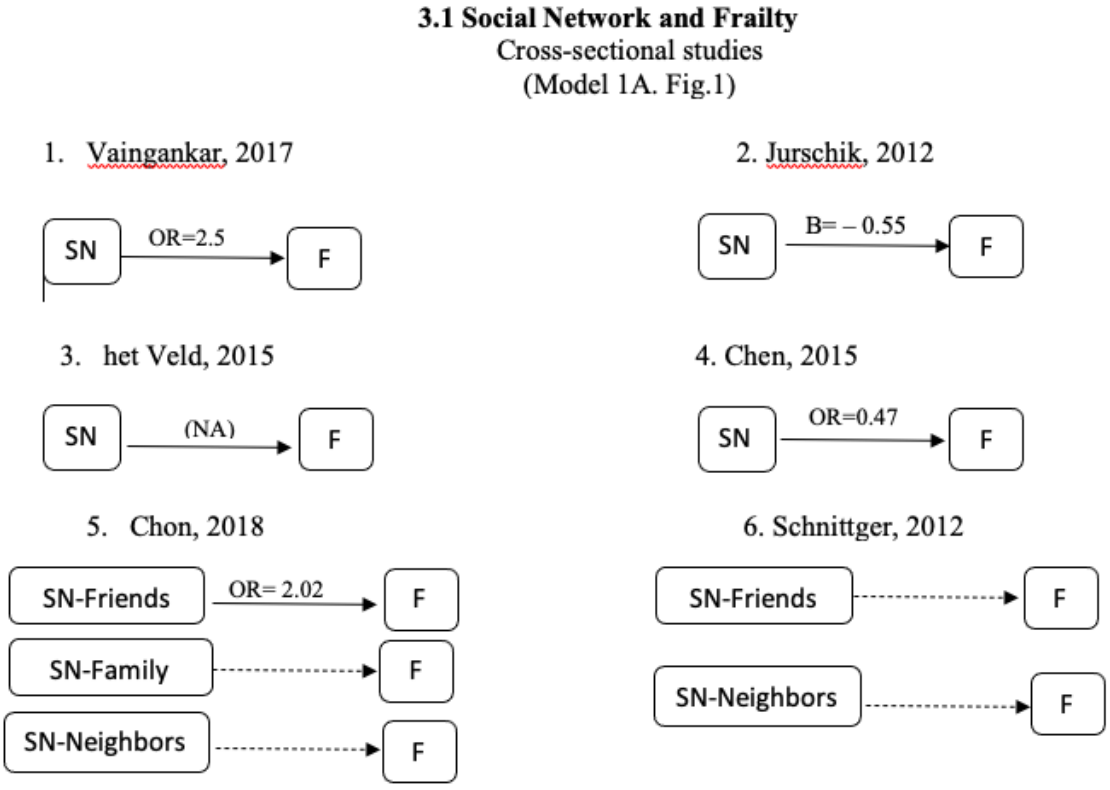
Moderation (Figures 3.7)

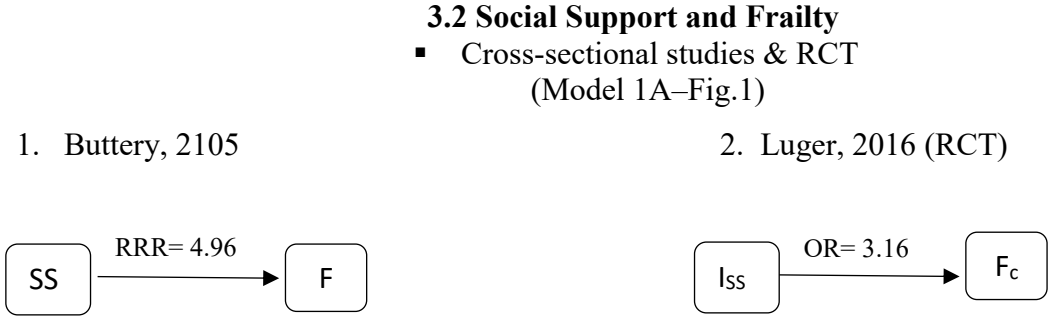
Peek et al. (2012) tested the buffering effect of stressors to examine the hypothesis that social support is protective against frailty among those who are experiencing high stress. However, the interactions of social support and stressors including financial strain, health, and non-health events on frailty among older Mexican Americans were not significant (Fig. 3.7.1). Similarly, Ding et al. (2017) found no evidence of moderation on the pathway from social isolation and social support to frailty (Fig. 3.7.2).

Conditional process model (Figure 3.8)

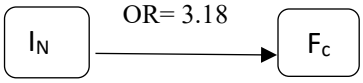
Although Ding et al. **(2017) found** that social isolation was not a predictor of future physical frailty, this social condition moderated the indirect effect of poor social support through chronic disease, reflecting the role of social relations on pathways to frailty (Fig. 3.8.1).

Figure 6 (Study 1. Figure 3) The association of social isolation, loneliness, and frailty in older adults

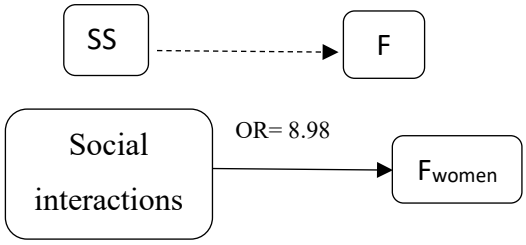




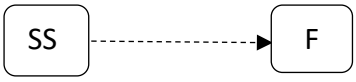
3. Chen, 2014



5. Gale, 2012

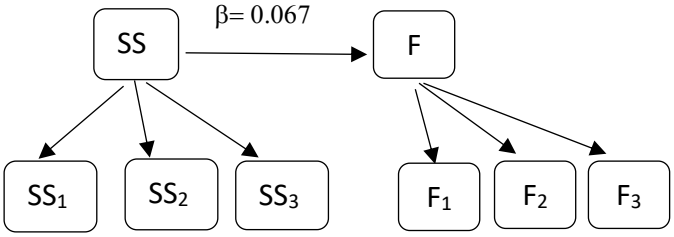


4. Jurschik, 2012

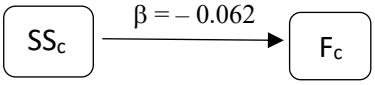


- Longitudinal studies (Model 1A–Fig.1)

5. Ding, 2017



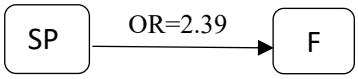
7. Peek, 2012



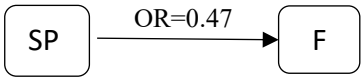
3.3 Social Participation and Frailty

- Cross-sectional studies (Model 1A–Fig.1)

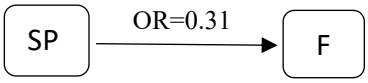
1. Chen, 2014



2. Chen, 2015



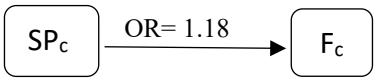
3. Kwan, 2019



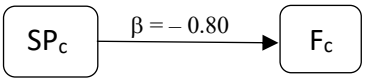
4. Jurschik, 2012

- Longitudinal studies (Model 1A–Fig. 1)

5. Etman, 2014



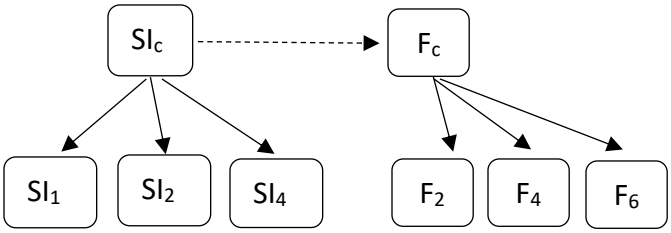
6. HSU, 2014



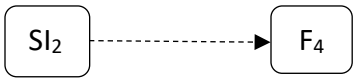
3.4 Social Isolation and Frailty

- Longitudinal studies

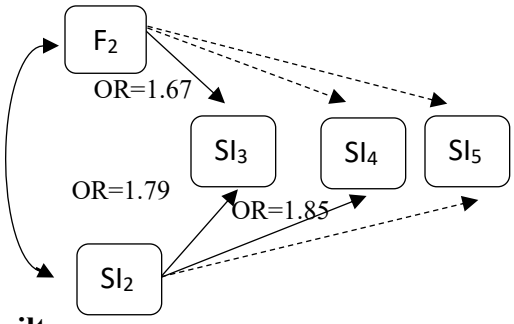
1. Ding, 2017(Model 1A–Fig. 1)



2. Gale, 2018 (Model 1A–Fig. 1)



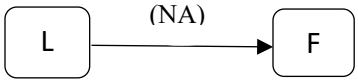
3. Gale, 2018 (Model 1B–Fig. 1)



3.5 Loneliness and Frailty

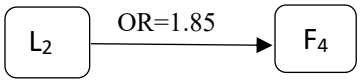
Cross-sectional study (Model 1A–Fig. 1)

1. het Veld, 2015

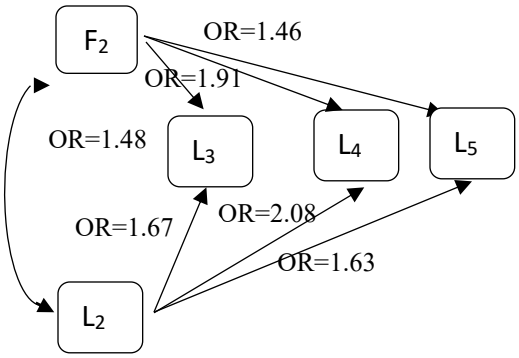


Longitudinal studies

2. Gale, 2018 (Model 1A–Fig.1)



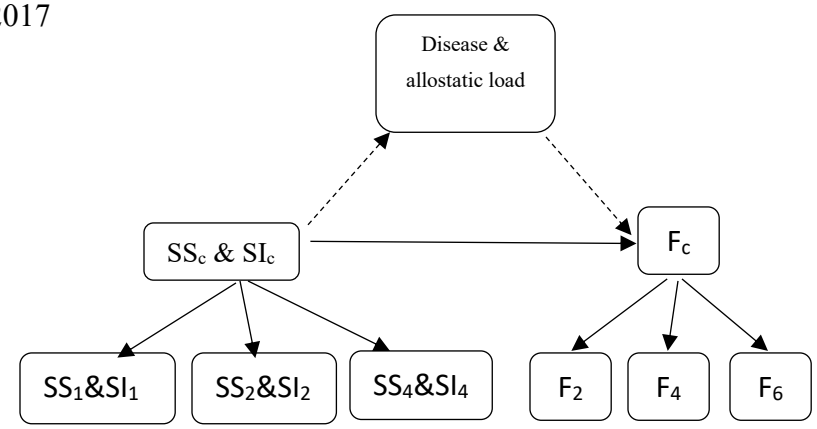
3. Gale, 2018* (Model 1B–Fig.1)



3.6 Mediation (Model 2A–Fig. 1)

- Longitudinal study

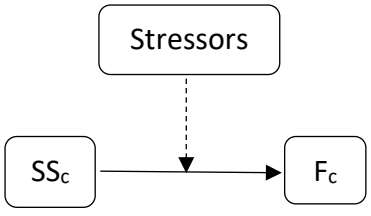
1. Ding, 2017



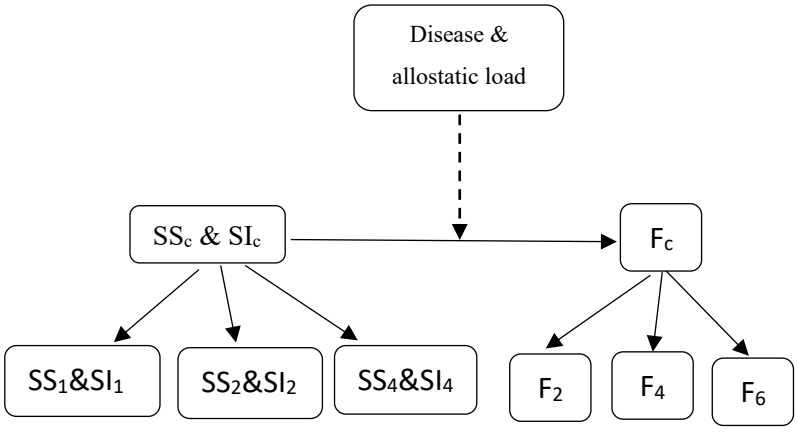
3.7 Moderation (Model 3A–Fig. 1)

- Longitudinal studies

1. Peek, 2012

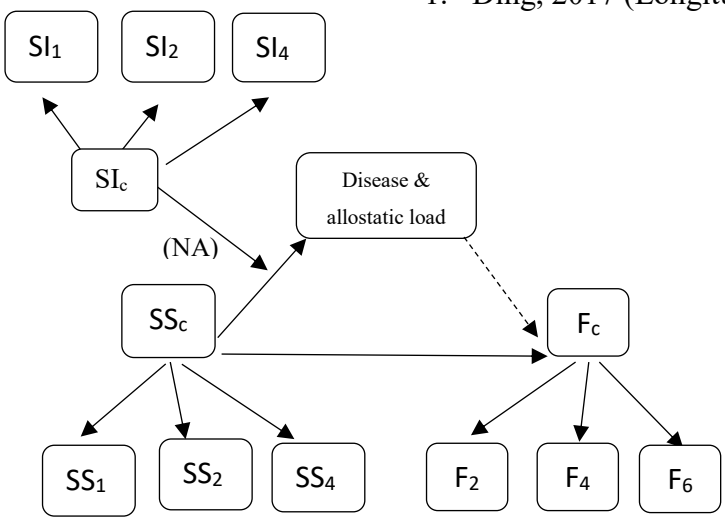


2. Ding, 2017



3.8 **Conditional process model (Model 4A–Fig. 1)**

1. Ding, 2017 (Longitudinal study)



Legends: b: Standardized coefficient; F: Frailty; F_c: Frailty change; L: Loneliness; NA: Not Available; OR: Odd Ratio; RRR: Relative Risk Ratio; SN: Social Networks; SS: Social Support; SS_c: Social Support change; SP: Social Participation; SI: Social Isolation; SI_c: Social Isolation change; * The associations between variables counted three times for Gale (2018).

The effects of social isolation, loneliness, and frailty on health Outcomes

Little attention has been devoted to investigating the effects of social isolation, loneliness, and frailty on health outcomes in the retained literature.

Social networks, frailty, and health (Figures 4.1)

According to Model 5A in Figure 1, a cross-sectional study from the UK (Kamiya & Kenny, 2017) investigated the association between social networks and frailty and whether they were related to mortality (Figure 4.1 No. 1 [Fig. 4.1.1]). The results showed that frailty was an independent predictor of mortality; however, social networks were not linked to frailty and mortality. Based on Model 5B in Figure 1, Dent and Hoogendijk (2014) in their cross-sectional study found that social network was not associated with poor health outcomes and there was no link between a high level of frailty and strong social ties (Fig. 4.1.2). However, Australian frail older adults had a higher likelihood of multiple health outcomes including, admission to higher-level care, long length of stay, rehospitalization, and mortality.

Social support, frailty, and health (Figures 4.2)

Based on Model 5A in Figure 1, a cross-sectional study from England (Kamiya & Kenny, 2017) illustrated that social support was associated neither with frailty nor with mortality while frailty predicted mortality (Fig. 4.2.1). According to Model 5C in Figure 1, the effects of social support and frailty on health outcomes were examined in four studies (Hermsen et al., 2014; Li & Hsu, 2015; Malini et al., 2016; Zhang et al., 2018). A cross-sectional study from Brazil (Malini et al., 2016) reported that low social support and grip strength, as a frailty indicator, were not linked to fear of falling (Fig. 4.2.2). In the cross-sectional study from the Netherlands (Hermsen et al., 2014), the relationship between social support and frailty with functional limitations were independently examined (Fig. 4.2.3). The results indicated that frailty was consistently related to four functional outcomes including Physical Functioning (PF), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), and Participation Restrictions (PR), whereas social support was related only to participation restrictions. The results of a cross-sectional study from the United States (Zhang et al., 2018) revealed that a low level of social support and frailty were independently associated with fall status (Fig. 4.2.4). A longitudinal study from Taiwan (Li & Hsu, 2015) examined the effect of social support and frailty on cognitive decline (Fig. 4.2.5). The results reported a relationship between informational support and higher cognitive function over time, however, the effect of frailty on cognitive function was only significant for female older adults (Li & Hsu, 2015).

Social participation, frailty, and health (Figures 4.3)

According to Model 5A in Figure 1, the results of a cross-sectional study from England (Kamiya & Kenny, 2017) showed that frailty was a predictor of mortality; however, social participation was not linked to frailty and mortality (Fig. 4.3.1). Based on Model 5B in Figure 1, Dent and Hoogendijk (2014) found that frailty was not associated with social activities but with adverse outcomes such as admission to higher-level care, long length of stay, rehospitalization, and mortality. However, there was no association between a high level of social activities and poor health outcomes (Fig. 4.3.2). According to Model 5C in Figure 1, a longitudinal study from Taiwan (Li & Hsu, 2015) examined the effect of social participation and frailty on cognitive decline (Fig. 4.3.3). The results showed the beneficial effect of participating in social activities on cognitive function for males but not for females. Additionally, the effect of frailty on cognitive function was

only significant for female older adults (Li & Hsu, 2015). Similar to the Liao study (Liao et al., 2018), gender inequality in health was highlighted among Taiwanese female older adults in this study.

Mediation

According to Model 6A in Figure 1, one study using the ELSA data (Kamiya & Kenny, 2017) aimed to examine the mediation effect of frailty on the pathway from social isolation to mortality. However, no result regarding this mediation effect was reported, perhaps due to the fact that the direct effect of social isolation on mortality was not significant.

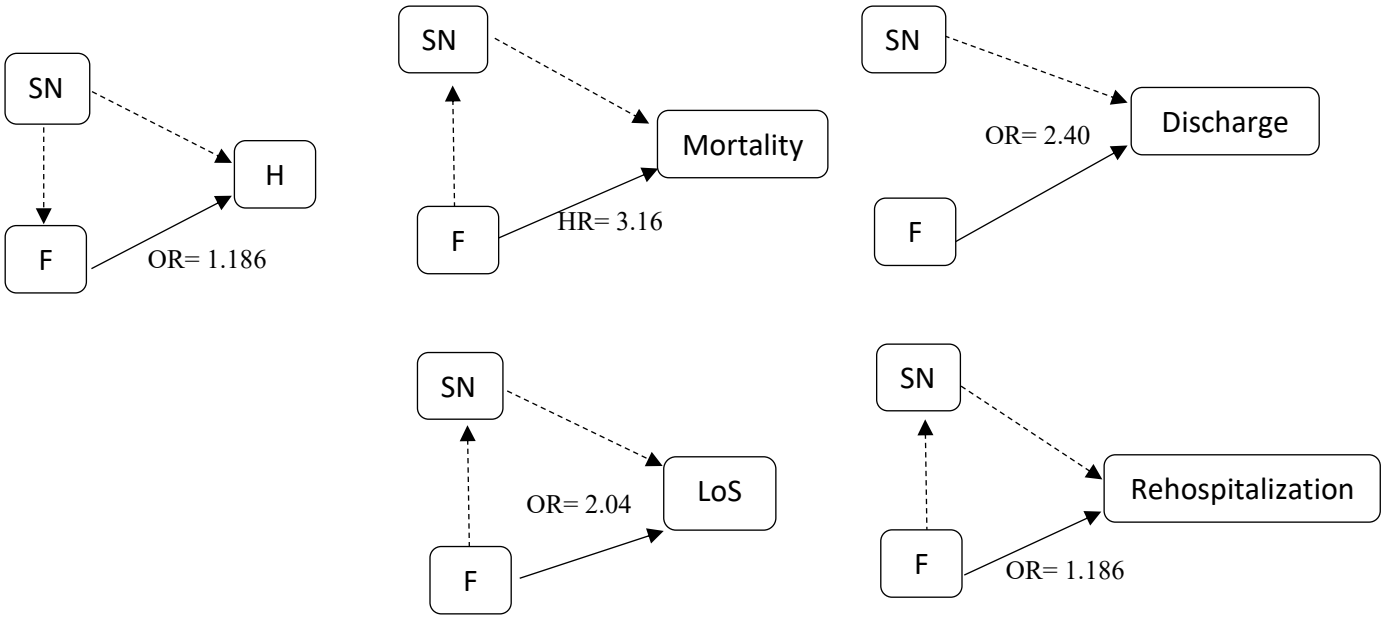
Figure 7 (Study 1. Figure 4) The association of social isolation, loneliness, frailty, and health outcomes in older adults

4.1 Social network, frailty, and health

- Cross-sectional studies

(Model 5A–Fig.1) (Model 5B –Fig.1)

1. Kamiya, 2017 2. Dent, 2014

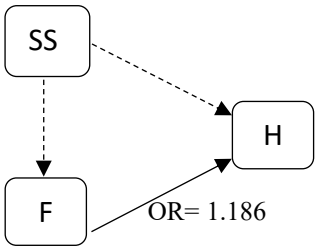


4.2 Social support, frailty and health

Cross-sectional studies

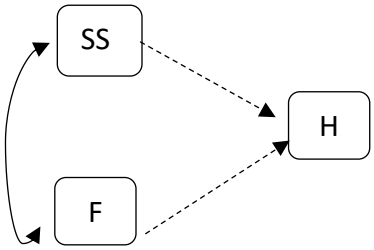
(Model 5A–Fig.1)

1. Kamiya, 2017

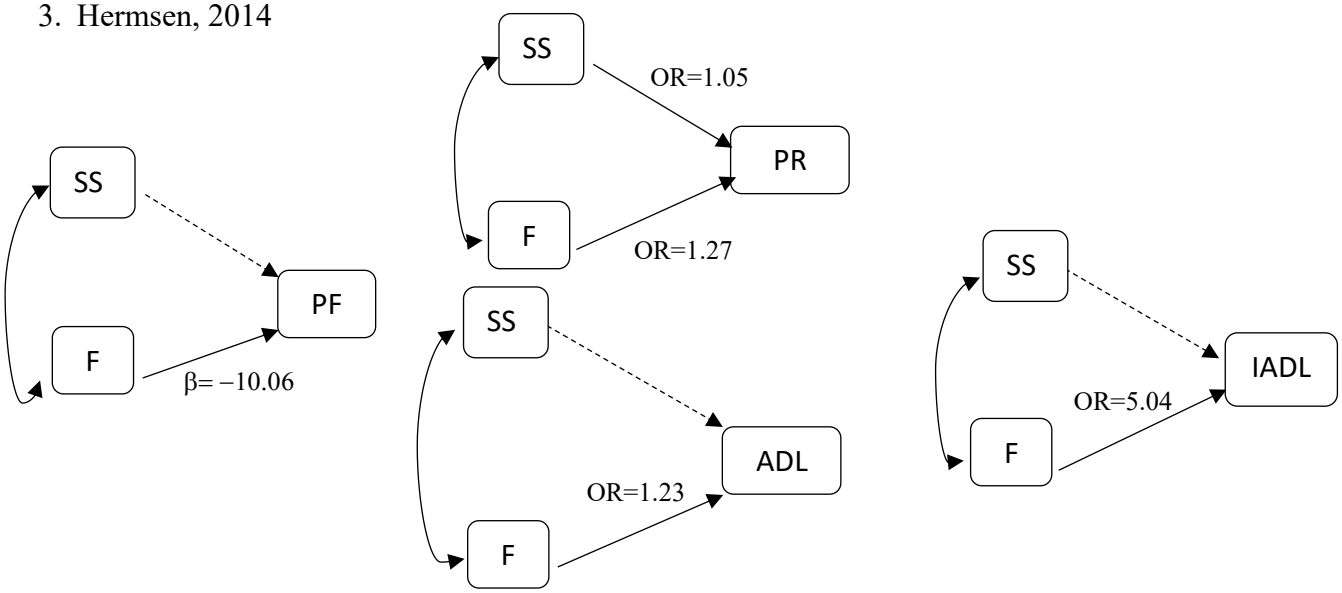


(Model 5C–Fig.1)

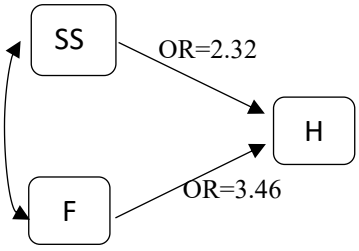
2. Malini, 2016



3. Hermsen, 2014

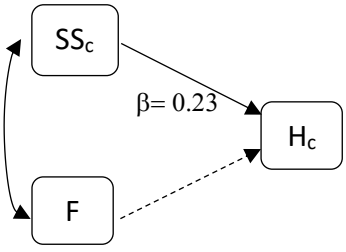


4. Zhang, 2017



Longitudinal study

5. Li, 2015

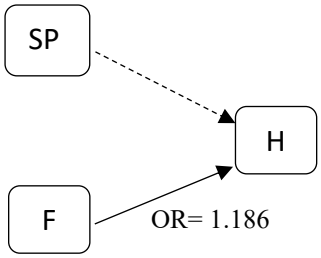


4.3 Social participation, frailty and health

- Cross-sectional studies

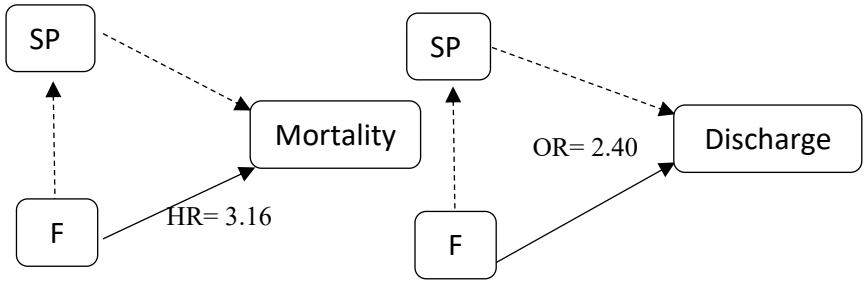
Model 5A–Fig.1

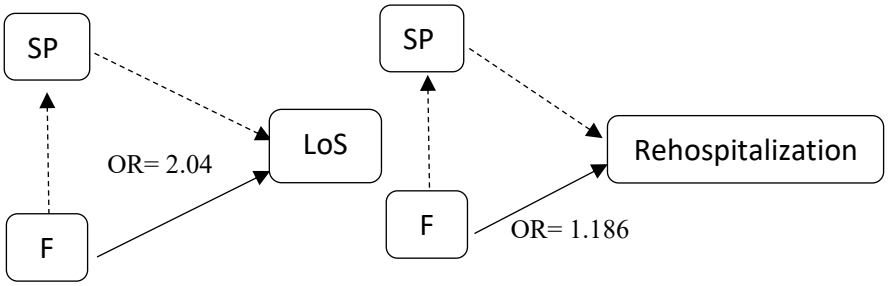
1. Kamiya, 2017



Model 5B–Fig.1

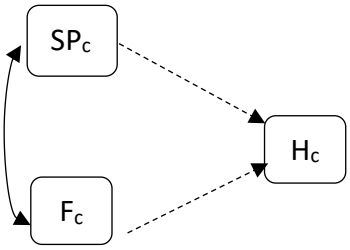
2. Dent, 2014





- Longitudinal study (Model 5C–Fig.1)

3.Li, 2015

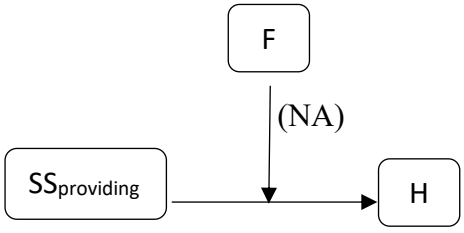


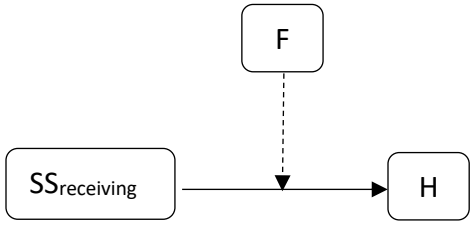
4.4 Moderation

(Model 7A–Fig.1)

Longitudinal study

1. Liao, 2018

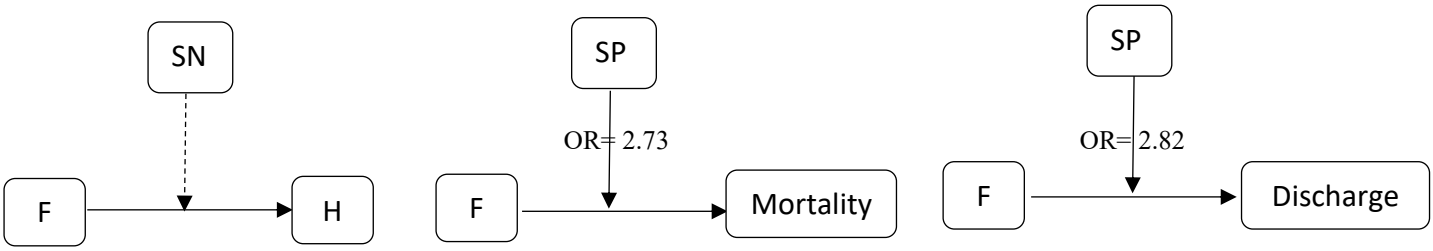


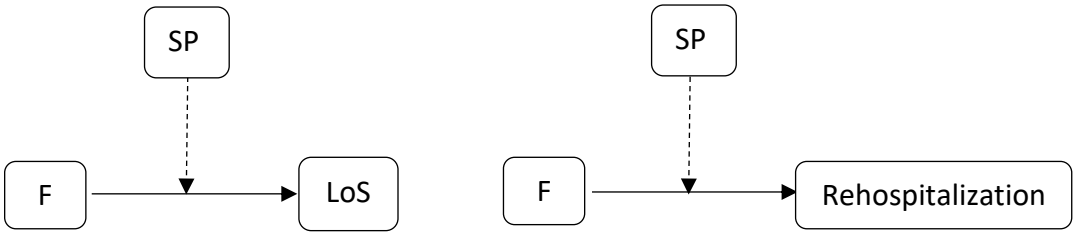


(Model 7B–Fig.1)

Cross-sectional studies

2. Dent, 2014





3.Mulasso, 2016

4. Mulasso, 2016

5. Ni Mhaolain, 2012

Longitudinal study

6. Hoogendijik, 2014

Legends: ADL: Activities of Daily Livig, IADL: Instrumental Activities of Daily Living, b: Standardized coefficient, F: Frailty, F_c: Frailty change, H: Health, H_c: Health change, LoS: Length of Stay, L: Loneliness, NA: Not Available, OR: Odd Ratio, PR: Participation Restriction, PF: Physical Functioning, RRR: Relative Risk Ratio, SN: Social Networks, SS: Social Support, SS_c: Social Support change, SP: Social Participation, SI: Social Isolation, SI_c: Social Isolation change

Moderation (Figures 4.4)

Based on Model 7A in Figure 1, Liao et al. (2018) investigated the interaction effect of social support and frailty on mortality (Fig. 4.4.1). The results showed a lower risk of mortality among non-frail and pre-frail male older adults who more often provided support to their family members; however, there was no evidence of an association between receiving family support and mortality over time. According to Model 7B in Figure 1, four studies (Dent & Hoogendijk, 2014; Hoogendijk et al., 2014; Mulasso et al., 2016; Ní Mhaoláin et al., 2012) looked at the interaction effects of frailty and social isolation on health. Dent and Hoogendijk (2014) found that frail people with a low level of social activity had an increased likelihood of mortality and discharge to a higher level of care than frail people with good psychosocial resources. However, social networks didn't modify the outcomes of frailty (Fig. 4.4.2). A cross-sectional study in Italy (Mulasso et al., 2016) found a significant interaction effect of psychosocial factors, including depression, social isolation and loneliness with frailty status on disability (Fig. 4.4.3—Fig. 4.4.4). The results indicated that isolated and lonely frail older adults had a higher level of disability compared to frail older adults with lower levels of isolation and loneliness. However, another cross-sectional study (Ní Mhaoláin et al., 2012) found no association between loneliness and fear of falling in groups of Irelander's older adults transitioning to frailty (Fig. 4.4.5). Similarly, a longitudinal study from the Netherlands Hoogendijk et al. (2014) examined the interaction effects between frailty and emotional and instrumental support on functional decline and three-year mortality (Fig. 4.4.6). The findings illustrated that social support did not appear to buffer against functional decline and mortality in Dutch frail older adults.

4.5 Discussion

We identified and reported the nature and extent of existing research evidence on the relationship between social isolation, loneliness, and frailty and on the effects of social isolation, loneliness, and frailty on health outcomes as well as the moderation and mediation effects in these relationships among community-dwelling older adults.

This review highlights that social isolation and frailty among older populations are becoming a global research topic with a growing prevalence of publications emanating from European countries, East Asia, Australia, the USA, and South America. Yet, there is still little evidence in the literature regarding the effect of loneliness on frailty. According to Models 1A and 1B in Figure 1, 65% of results (22/34) reported an association between social isolation, loneliness, and frailty. As such, evidence in the retained literature demonstrated that loneliness had the most significant association with frailty (5/5), followed by social participation (5/6), social support (6/9), social isolation (1/5) and lastly, social networks (5/9) (Figure 5A). The majority of longitudinal studies (9/13) illustrated that social isolation and loneliness were related to frailty compared with 62% from cross-sectional studies (13/21). However, the direction of the effect of social isolation and loneliness on frailty is unclear due to the nature of cross-sectional studies. Only one longitudinal study reported the bidirectional effects of loneliness on frailty (Models 1A-B, Fig.1) (Gale et al., 2018). Two longitudinal studies investigated the indirect effects of social factors on frailty through stressors, chronic diseases, and allostatic load (Models 2A-3A, Fig.1) but none found evidence of either mediation or moderation effects (Ding et al., 2017; Peek et al., 2012). According to Model 4A, we identified one study (Ding et al., 2017) on the conditional process model which revealed that the indirect effect of social support on chronic disease and allostatic load was moderated by social isolation. Relatedly, we found no study that looked at the possible moderator or mediator on the pathway from frailty to social isolation and loneliness (Models 2B-3B, Fig.1).

This scoping review shows that the evidence related to the effects of social isolation and loneliness on frailty and health outcomes is still at an early stage of understanding (Models 5A—C, Fig 1). Further research is needed to develop this theme, notably, concerning the effect of loneliness on frailty and health. The majority of the retrieved studies (16/19) demonstrated that frailty is a predictor of poor health outcomes (Figure 5B), whilst the effect of social isolation on frailty and health outcomes remains an intriguing and understudied area. Most of the retrieved studies noticeably focused on the effects of social isolation on frailty and health outcomes (Model 5C, Fig.1), whilst little research investigated the causal relationship between frailty and social isolation (Models 5A-B, Fig.1). Surprisingly, none of the retrieved studies found an association between social isolation and frailty or vice versa (Models 5A-B, Fig.1). In contrast to the Berkman theory, there is sparse evidence (3/19) supporting the causal effect of social isolation on poor health

outcomes (Model 5C, Fig.1). Specifically, these studies illustrated the association between social support and health outcomes while social networks and social participation were not linked to health (Figure 5B). It is thus possible that social isolation alters the development of frailty among older adults and makes them even more vulnerable to poor health outcomes. It means that social isolation may play a mediator role in the causal pathway between frailty and health given the well-established link of frailty and health. Nevertheless, this was not investigated in any of the retrieved studies (Model 6B, Fig.1). We identified eleven studies regarding the interaction effect of frailty and social isolation on health (Models 7A-B) though they mostly reported no evidence of interaction (6/11). Among these studies, two (Mulasso et al., 2016; Ní Mhaoláin et al., 2012) examined the interaction effect of loneliness and frailty on health, highlighting a paucity of research in this area. Furthermore, no study investigated a mediator role of frailty on the pathway from social isolation to health (Model 6A, Fig. 1).

When we compare the effects of social isolation and loneliness on frailty, overall, our findings have shown that loneliness (5/5) was a strong predictor of frailty compared to social isolation (17/29) (Fig. 6.1–Fig. 6.2). The evidence on the relationships between social isolation and frailty with health outcomes is mixed. Some studies found evidence pertaining to the relationship between social isolation and health; frailty was mostly linked to adverse outcomes (Fig. 6.3). Relatedly, almost half of the studies (4/9) found a moderation effect of social isolation on frailty and health outcomes (Fig. 6.4). Half of the studies (1/2) found that loneliness might alter the adverse outcomes of frailty (Fig. 6.5). Of note, our evidence suggests that both loneliness and social isolation might potentially have a moderator role on the pathway from frailty to health.

Figure 8A (Study 1. Figure 5A) The relationships between social isolation and loneliness with frailty

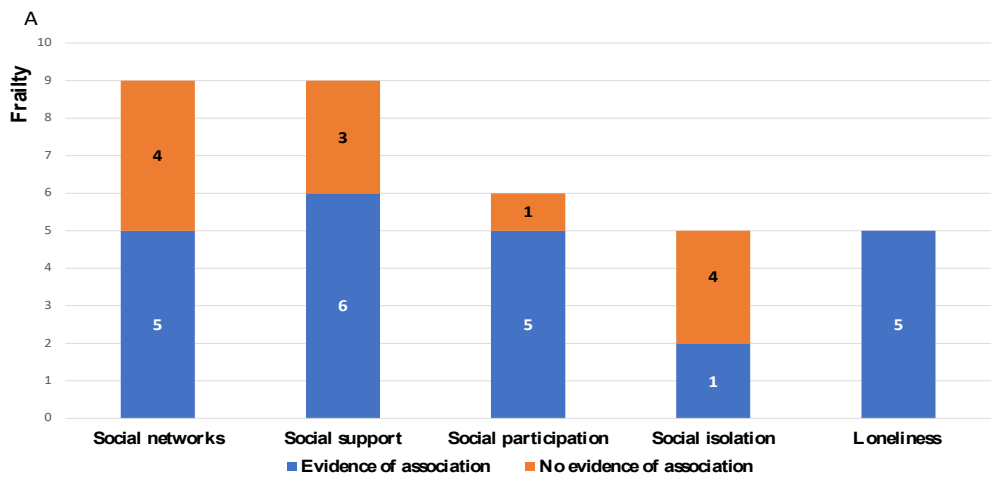
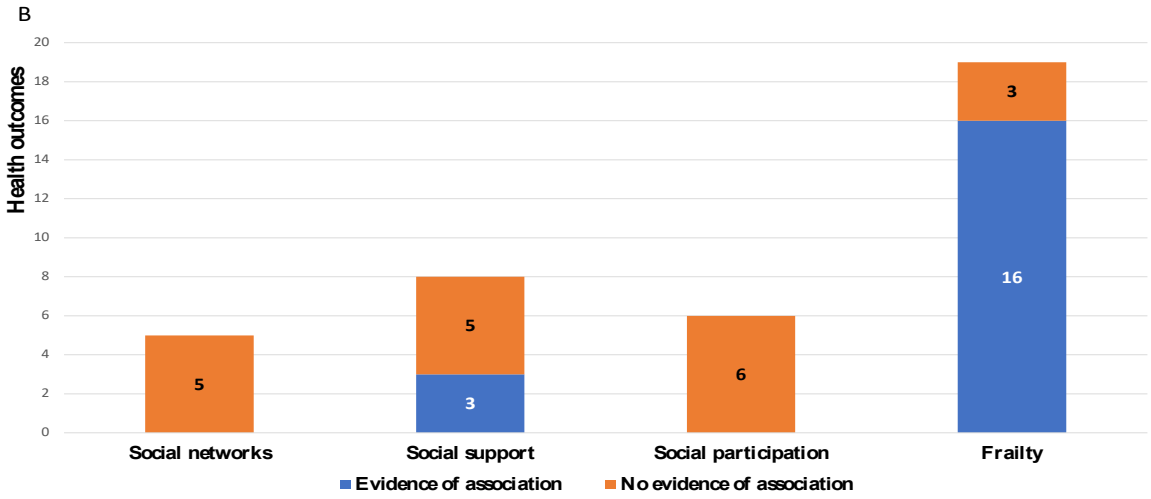


Figure 8B (Study1. Figure 5B) The relationships between social isolation and frailty with health outcomes

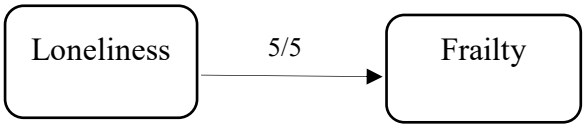


The gaps in the retained literature point to the lack of studies that are large and longitudinal in design. More longitudinal research with long-term follow-up and repeated measures is pivotal to untangle the direction of the effect of social isolation and loneliness on frailty and health and their change over time. Notably, such research can contribute to better understanding the pathway from social isolation and loneliness to frailty and health by distinguishing different types of trajectories and their potential risk factors (Hoogendijk et al., 2019). Correspondingly, much more research is

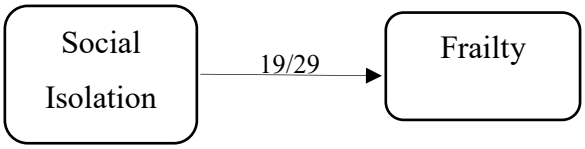
required to investigate the long-term effects of social isolation and loneliness on frailty or vice versa, particularly examining mediation and moderation effects.

Figure 9 (Study 1. Figure 6**)** The comparison of the relationships between social isolation, loneliness, and frailty with health

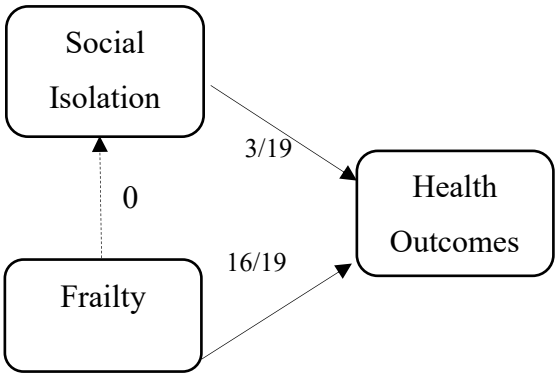
6.1 Loneliness and frailty



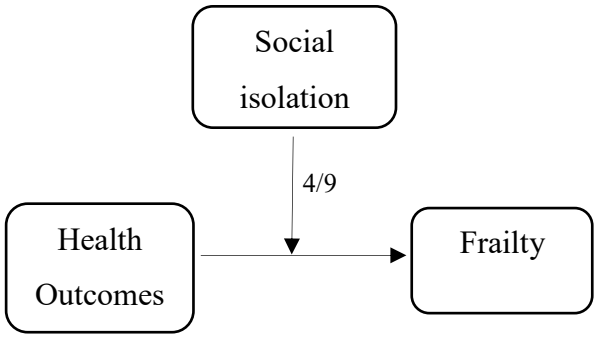
6.2 Social isolation and frailty



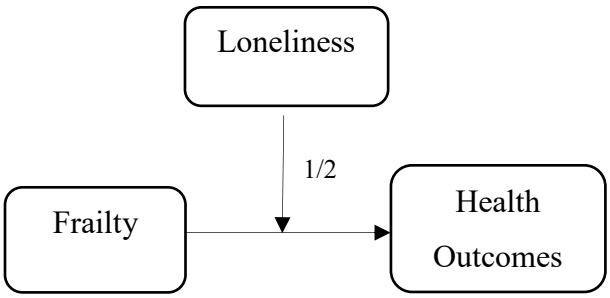
6.3 Social isoaltion, frialty, and health



6.4 moderation model (social isoaltion)



Moderation model (loneliness)



Legends: *Numerator: Number of statistically significant coefficients, **Denominator: Number of tests in the retained literature

There is a shortage of research evidence about social isolation intervention and its effect on frailty and health among community-dwelling older populations. We identified only one social support intervention, targeting frail community-dwelling older adults. Indeed, interventions that address one component of social isolation might not be effective in reducing risk across other components such as loneliness or the quality of the relationships (Holt-Lunstad et al., 2017). Further intervention in RCTs, establishing mediators and moderators of intervention responses, are required to gain a more comprehensive understanding of how an older adult could tackle social isolation and loneliness, prevent, or postpone frailty and potentially reduce the health burden of frailty. It is also important to note that effective public health interventions need to be applied across societal and population-based levels, targeting socially isolated and lonely frail older persons to promote social connectedness and well-being among older adults.

Another weakness of existing studies is the absence of mental health outcomes. Adverse health outcomes are limited to falls, cognitive decline, disability, hospitalization, and mortality. No study focused on comorbidity or mental health outcomes. Much more research in this area is required to reduce disease burden in older adults given that frailty and social isolation predict adverse outcomes and high rates of comorbid chronic diseases, depression, and dementia (Bergman et al., 2004; Fried et al., 2001; Wang et al., 2018).

Another important point that must not be overlooked is that few studies considered the effects of different types of social networks such as friends, children, extended family, and neighbors on frailty. Some studies measured kinship ties as well as non-kin ties, such as the Lubben social network scale (Lubben & Gironda, 2004); however, they did not provide any results regarding these social ties. The results of one retrieved study (Chon et al., 2018) illustrated the effects of social contact with friends on frailty in Korea. However, no study investigated the role of different social ties on both frailty and health outcomes. The beneficial effect of social contact with friends on health has also been highlighted in previous studies in China and Canada (Bélanger et al., 2016; Wang et al., 2015), though, children had more salient social roles on the health of older adults in Spain and Latin America (Bélanger et al., 2016; Zunzunegui et al., 2009). These nuances suggest

the possibility of different impacts of social network types on frailty and health, highlighting the need for further studies to examine the effects of different network types on frailty and health outcomes.

The important feature missing in many of the studies presented here is that the findings assessing the impact of social isolation on frailty or the effect of these factors on health outcomes potentially vary depending on how these variables are assessed. Several studies failed to provide detail about social networks and social support scales, their sources and the reliability and validity of these scales. Social factors tend to be considered alongside or assessed by other types of measurements such as comprehensive geriatric assessment or quality of life scale (Dent & Hoogendijk, 2014; Zhang et al., 2018). The terminology used is inconsistent and social networks and social participation are not often differentiated or separately assessed, precluding a meaningful effect on frailty and health outcomes. Further, the majority of the retrieved studies focused on the phenotype of frailty proposed by Fried et al. (2001) or its modified version, omitting one or more of the original five criteria components (i.e. exclusion of physical activity or modification of shrinking criteria). This modification of the original criteria might greatly affect results as differences in frailty measurement might impact the estimation of prevalence and health-related outcomes (Wallace et al., 2018). In addition, frailty values cannot be directly compared with previous studies using the original Fried phenotype.

Furthermore, the nature of this effect varied based on gender, ethnicity, social context, lifestyle, and the design of the study. In particular, Berkman (Berkman, 2007) argued the necessity to focus on the social and cultural contexts which might influence and shape the structure of networks and the types of social support provided. It is quite plausible that the potential risk factors such as health behaviors and lifestyle risk factors have an effect on social isolation, loneliness and frailty in older adults. As such, research suggests the association of social isolation, loneliness and frailty with harmful health behaviors such as smoking (Shankar et al., 2011), alcohol consumption (Chen et al., 2015), sleeping problems (Cacioppo et al., 2002) and dietary patterns.

Most of the retrieved studies were conducted in high-income countries while an increase of the global impact and burden of frailty in low-and middle-income countries is expected due to the rapid growth in population aging (Hoogendijk et al., 2019). Therefore, much more research and RCTs

are needed on the impact of social isolation and loneliness on frailty and health in these countries to prevent frailty and isolation in community-dwelling older adults.

Although our evidence indicates the strong relationship between loneliness and frailty, no clear pattern emerged to gauge whether the feeling of loneliness or more objective characteristics such as lack of social contacts and engagement in social activities or perceptions of social support might have deleterious effects on frailty and health outcomes. Despite the fact that studying a subset of these social features has important implications, the evidence suggests that the incorporation of both social isolation and loneliness can yield a better understanding of older adults' social world and possible health outcomes and might provide a more accurate measure to assess social isolation than a single measurement (Erin York Cornwell & Linda J. Waite, 2009; Gale et al., 2012; Newall & Menec, 2017). Ultimately, this scoping review highlights the need for studies that are specifically designed to target both loneliness and social isolation, comprising social networks, social participation, and social support in order to investigate their effects on frailty and adverse outcomes.

Strengths and limitations

To the best of our knowledge to date, this is the first review of the evidence on the relationships between social isolation, loneliness, frailty, and health outcomes. 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 the phenomenon of social isolation and loneliness among older populations; 2) exploring a wide range of literature databases; 3) including all designs across all countries worldwide in the health research literature; 4) focusing on both social isolation and loneliness, and lastly 5) this scoping review is based upon the theoretical framework on social isolation and health proposed by Berkman and Krishna (Berkman, 2014) as well as the conceptual framework of frailty developed by Bergman et al. (Bergman et al., 2004). However, our findings should be interpreted with caution. We conducted a scoping review, an approach that does not involve assessing the quality of the reported research. In addition, we did not include "grey literature" or doctoral theses. Likely, the largest limitation of this review is the dearth of existing research evidence particularly on the effects of social isolation and loneliness on frailty and health-related outcomes.

4.6 Implications for public health policies and practices

Social isolation and loneliness along with frailty are emerging public health epidemics. To date, several national campaigns across the world have raised awareness of strengthening social connectedness among older adults and notably, the United Kingdom has appointed a minister of loneliness to tackle this growing problem. In spite of these laudable efforts, social isolation and loneliness remain remarkably missing from global strategies and action plans on aging and health led by the World Health Organization and European Union (EU), including Age-Friendly cities and the EU's "healthy aging" policies and initiatives. At this juncture, the existing scientific evidence of this review calls health policymakers, researchers, healthcare providers, public health professionals and officials to broaden the scope of action plans and research to primary prevention, elevating social isolation and loneliness as a public health priority (Holt-Lunstad et al., 2017; Valtorta et al., 2018).

Our evidence that loneliness predicts frailty suggests that public health professionals ought to take into account social isolation and loneliness when designing public health interventions. Such strategies might include social isolation and loneliness measurements along with frailty screening and assessments to detect those who may not be considered at risk of loneliness or frailty according to traditional factors (Dent et al., 2019; Nicholson, 2012; Valtorta et al., 2018). Foremost, public health professionals should ask about different types of social ties such as family, intimate partner, friends and neighbors, community social activity, perceived supportive relationships or feeling of loneliness which could contribute to the development of prevention and population-based intervention strategies (Dent et al., 2019; Nicholson, 2012; Valtorta & Hanratty, 2012). From a public health perspective, identification of lonely and socially isolated older adults might prevent frailty, and consequently, a wide array of adverse outcomes and risk of premature mortality, and thereupon, reduce healthcare service costs (Holt-Lunstad et al., 2017; Nicholson, 2012). Given that the incidence of frailty, social isolation and loneliness differ by gender, social, economic, and environmental conditions, there might likewise need interventions to target at-risk groups. Of importance, public health and health policy officials should pay special attention to those who are socioeconomically deprived, addressing social determinants of health to reduce inequality (Hoogendijk et al., 2019).

At present, our findings do not allow us to make any translation from research into clinical practice because most of the included studies were population-based research. We found only one RCT intervention that reported the effectiveness of social support intervention among frail older adults. More RCT interventions focusing on social isolation and loneliness are a high priority for the frailty research agenda to improve health policy, and ultimately, older adults' wellbeing and quality of life.

4.7 Conclusion

From the standpoint of public health, our findings address one of the vital public health issues that has been widely reported in the media and urged by politicians and policymakers alike, that lonely and socially isolated frail older adults are at greater risk for poor health outcomes and death. In particular, this scoping review highlights an emerging theme in research on social gerontology: the transition from the view of social isolation as a unidimensional approach to a multidimensional phenomenon, combining both social isolation and loneliness. Nonetheless, our findings reveal the dearth of evidence in this area, especially the paucity of research on the effect of loneliness on frailty and health-related outcomes. Due to the fact that the lack of clarity in the relationships between social isolation, loneliness, frailty and their health outcomes is clearly apparent, further research is paramount in moving this research area and related public health policies further to improve prevention of social isolation, loneliness and frailty among community-dwelling older populations.

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4.8 References

Arksey, H., & O'Malley, L. (2005). Scoping studies: towards a methodological framework. International journal of social research methodology, 8(1), 19-32.

Auyeung, T. W., Lee, J., Kwok, T., & Woo, J. (2011). Physical frailty predicts future cognitive decline—a four-year prospective study in 2737 cognitively normal older adults. The journal of nutrition, health & aging, 15(8), 690-694.

Barnes, J. A. (1954). Class and committees in a Norwegian island parish. Human relations, 7(1), 39-58.

Bélanger, E., Ahmed, T., Vafaei, A., Curcio, C. L., Phillips, S. P., & Zunzunegui, M. V. (2016). Sources of social support associated with health and quality of life: a cross-sectional study among Canadian and Latin American older adults. BMJ open, 6(6), e011503.

Bergman, H., Béland, F., Karunananthan, S., Hummel, S., Hogan, D., & Wolfson, C. (2004). Developing a Working Framework for Understanding Frailty Howard Bergman, MD. Gérontologie et société, 109, 15-29.

Berkman, L. (2007). Social networks and social isolation.

Berkman, L. F., & Glass, T. (2000). Social integration, social networks, social support, and health. Social epidemiology, 1, 137-173.

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. Social Science & Medicine, 51(6), 843-857.

Berkman, L. F., & Krishna, A. (2014). Social Network Epidemiology. In L. F. Berkman, I. Kawachi, & M. M. Glymour (Eds.), Social epidemiology (2 ed., pp. 234-289). Oxford University Press.

Bott, E. (1957). Family and Social Network, 1957. Tavistock Publications, Limited, London W, 1, 218.

Bowlby, J. (1969). Attachment and Loss: Attachment.-1969.-(RUidnr.: M102591232). Basic books.

Buttery, A. K., Busch, M. A., Gaertner, B., Scheidt-Nave, C., & Fuchs, J. (2015). Prevalence and correlates of frailty among older adults: findings from the German health interview and examination survey. BMC geriatrics, 15(1), 22.

Cacioppo, J. T., Hawkley, L. C., Berntson, G. G., Ernst, J. M., Gibbs, A. C., Stickgold, R., & Hobson, J. A. (2002). Do lonely days invade the nights? Potential social modulation of sleep efficiency. Psychological Science, 13(4), 384-387.

Chen, L.-J., Chen, C.-Y., Lue, B.-H., Tseng, M.-Y., & Wu, S.-C. (2014). Prevalence and associated factors of frailty among elderly people in Taiwan. International Journal of Gerontology, 8(3), 114-119.

Chen, S., Honda, T., Chen, T., Narazaki, K., Haeuchi, Y., Supartini, A., & Kumagai, S. (2015). Screening for frailty phenotype with objectively-measured physical activity in a west Japanese suburban community: evidence from the Sasaguri Genkimon Study. BMC geriatrics, 15(1), 36.

Chon, D., Lee, Y., Kim, J., & Lee, K.-e. (2018). The Association between Frequency of Social Contact and Frailty in Older People: Korean Frailty and Aging Cohort Study (KFACS). Journal of Korean medical science, 33(51).

Clausen, T., Wilson, A. O., Molebatsi, R. M., & Holmboe-Ottesen, G. (2007). Diminished mental- and physical function and lack of social support are associated with shorter survival in community dwelling older persons of Botswana. BMC public health, 7(1), 144.

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. The Lancet, 381(9868), 752-762.

Cohen, S. (1988). Psychosocial models of the role of social support in the etiology of physical disease. Health Psychology, 7(3), 269.

Collard, R. M., Boter, H., Schoevers, R. A., & Voshaar, R. C. O. (2012). Prevalence of frailty in community-dwelling older persons: a systematic review. Journal of the American Geriatrics Society, 60(8), 1487-1492.

Cornwell, E. Y., & Waite, L. J. (2009). Social disconnectedness, perceived isolation, and health among older adults. Journal of Health and Social Behavior, 50(1), 31-48. https://doi.org/10.1177/002214650905000103

Courtin, E., & Knapp, M. (2017). Social isolation, loneliness and health in old age: a scoping review. Health & social care in the community, 25(3), 799-812.

Cummings, S. M. (2002). Predictors of psychological well-being among assisted-living residents. Health & social work, 27(4), 293-302. https://doi.org/10.1093/hsw/27.4.293

Dent, E., & Hoogendijk, E. O. (2014). Psychosocial factors modify the association of frailty with adverse outcomes: a prospective study of hospitalised older people. BMC geriatrics, 14(1), 108.

Dent, E., Martin, F. C., Bergman, H., Woo, J., Romero-Ortuno, R., & Walston, J. D. (2019). Management of frailty: opportunities, challenges, and future directions. The lancet, 394(10206), 1376-1386.

Ding, Y. Y., Kuha, J., & Murphy, M. (2017). Multidimensional predictors of physical frailty in older people: identifying how and for whom they exert their effects. Biogerontology, 18(2), 237-252.

Dröes, R., Chattat, R., Diaz, A., Gove, D., Graff, M., Murphy, K., Verbeek, H., Vernooij-Dassen, M., Clare, L., & Johannessen, A. (2017). Social health and dementia: a European consensus on the operationalization of the concept and directions for research and practice. Aging & mental health, 21(1), 4-17.

Durkheim, E. (1973). Emile Durkheim on morality and society. University of Chicago Press.

Etman, A., Kamphuis, C. B., Van der Cammen, T. J., Burdorf, A., & Van Lenthe, F. J. (2014). Do lifestyle, health and social participation mediate educational inequalities in frailty worsening? The European Journal of Public Health, 25(2), 345-350.

Fitzpatrick, T. R., Gitelson, R. J., Andereck, K. L., & Sue Mesbur, E. (2005). Social support factors and health among a senior center population in southern Ontario, Canada. Social work in health care, 40(3), 15-37.

Fokkema, T., De Jong Gierveld, J., & Dykstra, P. A. (2012). Cross-national differences in older adult loneliness. The Journal of psychology, 146(1-2), 201-228.

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 59(3), M255-M263.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., & Burke, G. (2001). Frailty in older adults: evidence for a phenotype. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 56(3), M146-M157.

Gale, C., Westbury, L., & Cooper, C. (2018). Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. Age and ageing, 47(3), 392-397.

Gale, C. R., Syddall, H. E., Bergman, H., Brunner, E. J., Cooper, C., & Sayer, A. A. (2012). Close relationships and risk of frailty: The Hertfordshire Cohort Study. Journal of the American Geriatrics Society, 60(2), 390-392.

Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, M. T., & Schols, J. M. (2010). In search of an integral conceptual definition of frailty: opinions of experts. Journal of the American Medical Directors Association, 11(5), 338-343.

Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, M. T., & Schols, J. M. (2010). Toward a conceptual definition of frail community dwelling older people. Nursing outlook, 58(2), 76-86.

Grenade, L., & Boldy, D. (2008). Social isolation and loneliness among older people: issues and future challenges in community and residential settings. Australian Health Review, 32(3), 468-478.

Hawton, A., Green, C., Dickens, A. P., Richards, S. H., Taylor, R. S., Edwards, R., Greaves, C. J., & Campbell, J. L. (2011). The impact of social isolation on the health status and health-related quality of life of older people. Quality of Life Research, 20(1), 57-67.

Hayes, A. F. (2017). Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. Guilford Publications.

Hermsen, L. A., Leone, S. S., Smalbrugge, M., Dekker, J., & van der Horst, H. E. (2014). Frequency, severity and determinants of functional limitations in older adults with joint pain and comorbidity: Results of a cross-sectional study. Archives of gerontology and geriatrics, 59(1), 98-106.

Herrera-Badilla, A., Navarrete-Reyes, A. P., Amieva, H., & Avila-Funes, J. A. (2015). Loneliness is associated with frailty in community-dwelling elderly adults. Journal of the American Geriatrics Society, 63(3), 607-609.

het Veld, L. P. O., van Rossum, E., Kempen, G. I., de Vet, H. C., Hajema, K., & Beurskens, A. J. (2015). Fried phenotype of frailty: cross-sectional comparison of three frailty stages on various health domains. BMC geriatrics, 15(1), 77.

Holt-Lunstad, J., Robles, T. F., & Sbarra, D. A. (2017). Advancing social connection as a public health priority in the United States. American Psychologist, 72(6), 517.

Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T., & Stephenson, D. (2015). Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspectives on Psychological Science, 10(2), 227-237.

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. PLoS medicine, 7(7), e1000316.

Hoogendijk, E. O., Afilalo, J., Ensrud, K. E., Kowal, P., Onder, G., & Fried, L. P. (2019). Frailty: implications for clinical practice and public health. The Lancet, 394(10206), 1365-1375.

Hoogendijk, E. O., van Hout, H. P., van der Horst, H. E., Frijters, D. H., Dent, E., Deeg, D. J., & Huisman, M. (2014). Do psychosocial resources modify the effects of frailty on functional decline and mortality? Journal of psychosomatic research, 77(6), 547-551.

Hsu, H.-C., & Chang, W.-C. (2015). Trajectories of frailty and related factors of the older people in Taiwan. Experimental aging research, 41(1), 104-114.

Janke, M. C., Payne, L. L., & Van Puymbroeck, M. (2008). The role of informal and formal leisure activities in the disablement process. The International Journal of Aging and Human Development, 67(3), 231-257.

Jürschik, P., Nunin, C., Botigué, T., Escobar, M. A., Lavedán, A., & Viladrosa, M. (2012). Prevalence of frailty and factors associated with frailty in the elderly population of Lleida, Spain: the FRALLE survey. Archives of gerontology and geriatrics, 55(3), 625-631.

Kamiya, Y., & Kenny, R. A. (2017). Does Social Engagement Predict Frailty and Mortality in the Older Population? In M. N. Hoque, B. Pecotte, & M. A. McGehee (Eds.), Applied Demography and Public Health in the 21st Century (pp. 69-79). Springer International Publishing. https://doi.org/10.1007/978-3-319-43688-3_5

Keller, B. K., Magnuson, T. M., Cernin, P. A., Stoner, J. A., & Potter, J. F. (2003). The significance of social network in a geriatric assessment population. Aging clinical and experimental research, 15(6), 512-517.

Kelley-Moore, J. A., Schumacher, J. G., Kahana, E., & Kahana, B. (2006). When do older adults become "disabled"? Social and health antecedents of perceived disability in a panel study of the oldest old. Journal of health and social behavior, 47(2), 126-141.

Kelly, M. E., Duff, H., Kelly, S., Power, J. E. M., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. Systematic reviews, 6(1), 259.

Kim, D., Arai, H., & Kim, S. (2017). Social activities are associated with cognitive decline in older Koreans. Geriatrics & gerontology international, 17(8), 1191-1196.

Kuiper, J. S., Zuidersma, M., Voshaar, R. C. O., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: a systematic review and meta-analysis of longitudinal cohort studies. Ageing research reviews, 22, 39-57.

Kulmala, J., Nykänen, I., Mänty, M., & Hartikainen, S. (2014). Association between frailty and dementia: a population-based study. Gerontology, 60(1), 16-21.

Kwan, R. Y., Cheung, D. S., Lo, S. K., Ho, L. Y., Katigbak, C., Chao, Y.-Y., & Liu, J. Y. (2019). Frailty and its association with the Mediterranean diet, life-space, and social participation in community-dwelling older people. Geriatric Nursing, 40(3), 320-326.

Landeiro, F., Barrows, P., Musson, E. N., Gray, A. M., & Leal, J. (2017). Reducing social isolation and loneliness in older people: a systematic review protocol. BMJ open, 7(5), e013778.

Li, C.-L., & Hsu, H.-C. (2015). Cognitive function and associated factors among older people in Taiwan: Age and sex differences. Archives of gerontology and geriatrics, 60(1), 196-200.

Li, T., & Zhang, Y. (2015). Social network types and the health of older adults: Exploring reciprocal associations. Social Science & Medicine, 130, 59-68.

Liao, M.-Y., Yeh, C.-J., Liao, C.-C., Lee, S.-H., Yang, S.-F., & Lee, M.-C. (2018). Effects of receiving and providing family support on mortality in non-frail, pre-frail and frail older adults in Taiwan: a 12-year follow-up longitudinal study. European Geriatric Medicine, 9(5), 679-685.

Lubben, J., & Gironda, M. (2004). Measuring social networks and assessing their benefits. Social networks and social exclusion: Sociological and policy perspectives, 20-34.

Luger, E., Dorner, T. E., Haider, S., Kapan, A., Lackinger, C., & Schindler, K. (2016). Effects of a home-based and volunteer-administered physical training, nutritional, and social support program on malnutrition and frailty in older persons: a randomized controlled trial. Journal of the American Medical Directors Association, 17(7), 671. e679-671. e616.

Malini, F. M., Lourenço, R. A., & Lopes, C. S. (2016). Prevalence of fear of falling in older adults, and its associations with clinical, functional and psychosocial factors: The Frailty in Brazilian Older People-Rio de Janeiro Study. Geriatrics & gerontology international, 16(3), 336-344.

Merz, E.-M., & Huxhold, O. (2010). Wellbeing depends on social relationship characteristics: Comparing different types and providers of support to older adults. Ageing & Society, 30(5), 843-857.

Mezuk, B., Edwards, L., Lohman, M., Choi, M., & Lapane, K. (2012). Depression and frailty in later life: a synthetic review. International journal of geriatric psychiatry, 27(9), 879-892.

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. The Scientific World Journal, 1, 323-336.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., & Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews, 4(1), 1.

Mulasso, A., Roppolo, M., Giannotta, F., & Rabaglietti, E. (2016). Associations of frailty and psychosocial factors with autonomy in daily activities: a cross-sectional study in Italian community-dwelling older adults. Clinical interventions in aging, 11, 37.

Nascimento, P. P. P., Batistoni, S. S. T., & Neri, A. L. (2016). Frailty and depressive symptoms in older adults: data from the FIBRA study-UNICAMP. Psicologia: Reflexão e Crítica, 29(1), 16.

Newall, N. E., & Menec, V. H. (2017). Loneliness and social isolation of older adults: Why it is important to examine these social aspects together. Journal of Social and Personal Relationships, 0265407517749045.

Ní Mhaoláin, A. M., Fan, C. W., Romero-Ortuno, R., Cogan, L., Cunningham, C., Lawlor, B., & Kenny, R. A. (2012). Depression: a modifiable factor in fearful older fallers transitioning to frailty? International journal of geriatric psychiatry, 27(7), 727-733.

Nicholson, N. R. (2012). A review of social isolation: an important but underassessed condition in older adults. The journal of primary prevention, 33(2-3), 137-152.

Okura, M., Ogita, M., Yamamoto, M., Nakai, T., Numata, T., & Arai, H. (2017). The relationship of community activities with cognitive impairment and depressive mood independent of mobility disorder in Japanese older adults. Archives of gerontology and geriatrics, 70, 54-61.

Peek, M. K., Howrey, B. T., Ternent, R. S., Ray, L. A., & Ottenbacher, K. J. (2012). Social support, stressors, and frailty among older Mexican American adults. Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 67(6), 755-764.

Pham, M. T., Rajić, A., Greig, J. D., Sargeant, J. M., Papadopoulos, A., & McEwen, S. A. (2014). A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Research synthesis methods, 5(4), 371-385.

Provencher, V., Béland, F., Demers, L., Desrosiers, J., Bier, N., Ávila-Funes, J. A., Galand, C., Julien, D., Fletcher, J. D., & Trottier, L. (2017). Are frailty components associated with disability in specific activities of daily living in community-dwelling older adults? A multicenter Canadian study. Archives of gerontology and geriatrics, 73, 187-194.

Romero-Ortuno, R., Fouweather, T., & Jagger, C. (2013). Cross-national disparities in sex differences in life expectancy with and without frailty. Age and ageing, 43(2), 222-228.

Romero-Ortuno, R., Walsh, C. D., Lawlor, B. A., & Kenny, R. A. (2010). A frailty instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). BMC geriatrics, 10(1), 57.

Santini, Z. I., Fiori, K. L., Feeney, J., Tyrovolas, S., Haro, J. M., & Koyanagi, A. (2016). Social relationships, loneliness, and mental health among older men and women in Ireland: A prospective community-based study. Journal of affective disorders, 204, 59-69.

Schnittger, R. I., Walsh, C. D., Casey, A.-M., Wherton, J. P., McHugh, J. E., & Lawlor, B. A. (2012). Psychological distress as a key component of psychosocial functioning in community-dwelling older people. Aging & mental health, 16(2), 199-207.

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. Health Psychology, 30(4), 377.

Sherman, A. M. (2003). Social relations and depressive symptoms in older adults with knee osteoarthritis. Social Science & Medicine, 56(2), 247-257.

Teguo, M. T., Simo-Tabue, N., Stoykova, R., Meillon, C., Cogne, M., Amiéva, H., & Dartigues, J.-F. (2016). Feelings of loneliness and living alone as predictors of mortality in the elderly: the PAQUID study. Psychosomatic medicine, 78(8), 904-909.

Vaingankar, J. A., Chong, S. A., Abdin, E., Picco, L., Chua, B. Y., Shafie, S., Ong, H. L., Chang, S., Seow, E., & Heng, D. (2017). Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatrics & gerontology international, 17(10), 1444-1454.

Valtorta, N., & Hanratty, B. (2012). Loneliness, isolation and the health of older adults: do we need a new research agenda? Journal of the Royal Society of Medicine, 105(12), 518-522.

Valtorta, N. K., Kanaan, M., Gilbody, S., & Hanratty, B. (2016). Loneliness, social isolation and social relationships: what are we measuring? A novel framework for classifying and comparing tools. BMJ open, 6(4), e010799.

Valtorta, N. K., Kanaan, M., Gilbody, S., & Hanratty, B. (2018). Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. European journal of preventive cardiology, 25(13), 1387-1396.

Valtorta, N. K., Moore, D. C., Barron, L., Stow, D., & Hanratty, B. (2018). Older adults' social relationships and health care utilization: A systematic review. American journal of public health, 108(4), e1-e10.

Vozikaki, M., Linardakis, M., Micheli, K., & Philalithis, A. (2017). Activity participation and well-being among European adults aged 65 years and older. Social Indicators Research, 131(2), 769-795.

Wallace, L., Theou, O., Rockwood, K., & Andrew, M. K. (2018). Relationship between frailty and Alzheimer's disease biomarkers: a scoping review. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 10, 394-401.

Wang, B., He, P., & Dong, B. (2015). Associations between social networks, social contacts, and cognitive function among Chinese nonagenarians/centenarians. Archives of gerontology and geriatrics, 60(3), 522-527.

Wang, J., Mann, F., Lloyd-Evans, B., Ma, R., & Johnson, S. (2018). Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review. BMC psychiatry, 18(1), 156.

Weiss, R. S. (1973). Loneliness: The experience of emotional and social isolation.

Zhang, X., Sun, M., Liu, S., Leung, C. H., Pang, L., Popat, U. R., Champlin, R., Holmes, H. M., Valero, V., & Dinney, C. P. (2018). Risk factors for falls in older patients with cancer. BMJ supportive & palliative care, 8(1), 34-37.

Zunzunegui, M.-V., Béland, F., Sanchez, M.-T., & Otero, A. (2009). Longevity and relationships with children: the importance of the parental role. BMC public health, 9(1), 351.

Appendix A Database-specific search strategies

MEDLINE	EMBASE	CINAHL	PsycINFO	Web of Science
social support or Social network* or Psychosocial Support System* or Social connectedness or Social disconnectedness or Perceived isolation or Social tie* or Social connection* or Social relation* or Social link* or Social interaction* or Social engagement* or Social participation* or Social activit* or Social integration* or Social attachment* or Social role* or Loneliness or Live alone or lonely* or Social Isolation* or Emotional isolation or Solitude*	social support or Social network* or Psychosocial Support System* or Social connectedness or Social disconnectedness or Perceived isolation or Social tie* or Social connection* or Social relation* or Social link* or Social interaction* or Social engagement* or Social participation* or Social activit* or Social integration* or Social attachment* or Social role* or Loneliness or Live alone or lonely* or Social Isolation* or Emotional isolation or Solitude*	"Social Isolation" OR (MH "Social Participation" OR "Loneliness" OR "Support, Psychosocial" OR "Social Behavior" OR "Social Adjustment" OR "Social Inclusion" OR Interpersonal Relations OR "Social Environment"	"Social support" OR "Social network*" OR "Social connectedness"OR "Social disconnectedness" OR "Perceived isolation" OR "Social tie*"OR "Social connection*" OR "Social relation*" OR "Social link*" OR "Social interaction*" OR "Social engagement*" OR "Social participation*" OR "Social activit*" OR "Social integration*" OR "Social attachment*" OR "Social role*" OR "Loneliness" OR "Live alone" OR "lonely*"OR "Social Isolation*" OR "Emotional isolation" OR "Solitude*"	"social support" or "Social network*" or "Psychosocial Support System*" or "Social connectedness" or "Social disconnectedness" or "Perceived isolation" or "Social tie*" or "Social connection*" or "Social relation*" or "Social link*" or "Social interaction*" or "Social engagement*" or "Social participation*" or "Social activit*" or "Social integration*" or "Social attachment*" or "Social role*" or "Loneliness" or "Live alone" or "lonely*" or "Social Isolation*" or "Emotional isolation" or "Solitude*"
AND	AND	AND	AND	AND
Elder* or Older people or Old age or Old people or Old* adults or Aging or Ageing or Aged or Senior* or geriatric* or older person*or gerontolog* or older patient*	lder* or Older people or Old age or Old people or Old* adults or Aging or Ageing or Aged or Senior* or geriatric* or older person*or gerontolog* or older patient*	"Aged" OR "Aged, 80 and Over"OR "Geriatrics" OR "Aging" OR "Cognitive Aging	"Elder*"OR "Older people"OR "Old age" OR "Old people" OR "Old* adults" OR "Aging" OR "Ageing" OR "Aged" OR "Senior*" OR "geriatric*" OR "older person*" OR "gerontolog*" OR "older patient*"	Elder* or "Older people" or "Old age" or "Old people" or "Old* adult*" or Aging or Ageing or Aged or Senior* or geriatric* or "older person*" or gerontolog* or "older patient*"
AND	AND	AND	AND	AND
"frail*"	"frail*"	frail*	frail*	frail*
limit to (yr="2001 -Current" and (english or french))	limit to (yr="2001 -Current" and (english or french))			Refined By: PUBLICATION YEARS: (2018 OR 2010 OR 2002 OR 2017 OR 2009 OR 2001 OR 2016 OR 2008 OR 2015 OR 2007 OR 2014 OR 2006 OR 2013 OR 2005 OR 2012 OR 2004 OR 2011 OR 2003) AND LANGUAGES: (ENGLISH OR FRENCH)

Appendix B PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4, Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 2; Figures 3-4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 2, Appendix A
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7 –8 &Table2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8–11, Figures 3-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11–14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix C The excluded studies based on full text

Excluded studies (based on full-text)	
Reference	**Reason for exclusion**
1. Shinkai S, Yoshida H, Taniguchi Y, Murayama H, Nishi M, Amano H, et al. Public health approach to preventing frailty in the community and its effect on healthy aging in Japan. Geriatrics and Gerontology International. 2016;16(Supplement 1):87-97.	Social aspects were included in the frailty scale.
2. Abbott KH, Stoller EP, Rose JH. The structure and function of frail male veterans' informal networks. Journal of Aging and Health. 2007;19(5):757-77.	The Frailty scale is mainly based on the presence of disability variables.
3. Abu-Bader SH, Rogers A, Barusch AS. Predictors of life satisfaction in frail elderly. Journal of Gerontological Social Work. 2002;38(3):3-17.	The Frailty scale is mainly based on the presence of disability variables (ADLs).
4. Ahmad R, Bath PA. Identification of risk factors for 15-year mortality among community-dwelling older people using Cox regression and a genetic algorithm. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2005;60(8):1052-8.	No results for social engagement
5. Çakmur H. Frailty among elderly adults in a rural area of Turkey. Medical science monitor: international medical journal of experimental and clinical research. 2015;21:1232.	Disability was one of the components of frailty.
6. Escourrou E, Cesari M, Chicoulaa B, Fougère B, Vellas B, Andrieu S, et al. How Older Persons Perceive the Loss of Independence: The Need of a Holistic Approach to Frailty. The Journal of frailty & aging. 2017;6(2):107-12.	Frailty was measured through the 'Gerontopole Frailty Screening Tool' and Disability was one of the criteria for frailty
7. Andrew MK, Fisk JD, Rockwood K, Andrew MK, Fisk JD, Rockwood K. Social vulnerability and prefrontal cortical function in elderly people: a report from the Canadian Study of Health and Aging. International Psychogeriatrics. 2011;23:450-458.	Frailty was measured by frailty index
8. Anzaldi LJ, Davison A, Boyd CM, Leff B, Kharrazi H. Comparing clinician descriptions of frailty and geriatric syndromes using electronic health records: a retrospective cohort study. BMC geriatrics. 2017;17:248.	No measurement for frailty
9. Barrett P. A case for examining the social context of frailty in later life. Australasian Journal on Ageing. 2006;25:114-118.	A review article
10. Bilotta C, Case A, Nicolini P, Mauri S, Castelli M, Vergani C. Social vulnerability, mental health and correlates of frailty in older outpatients living alone in the community in Italy. Aging & mental health. 2010;14:1024-1036.	No results about social factors
11. Canedo AC, Lopes CS, Lourenco RA. Prevalence of and factors associated with successful aging in Brazilian older adults: Frailty in Brazilian older people Study (FIBRA RJ). Geriatrics and	No measurement for frailty

Excluded studies (based on full-text)	
Reference	**Reason for exclusion**
Gerontology International. 2018.	
12. Chang WC, Lu FP, Lan TY, Wu SC. Multidimensional health-transition patterns among a middle-aged and older population. Geriatrics and Gerontology International. 2013;13:571-579.	No result about the association between frailty and social engagement
13. Cramm JM, Nieboer AP. Relationships between frailty, neighborhood security, social cohesion and sense of belonging among community-dwelling older people. Geriatrics and Gerontology International. 2013;13:759-763.	The Tilburg Frailty Indicator (TFI) described by Gobbens et al was used for measuring frailty.
14. Craven E, Conroy S. Hospital readmissions in frail older people. Reviews in Clinical Gerontology. 2015;25:107-116.	No results about social support.
15. Fairhall N, Sherrington C, Kurrle SE, Lord SR, Cameron ID. ICF participation restriction is common in frail, community-dwelling older people: An observational cross-sectional study. Physiotherapy. 2011;97:26-32.	Social activity was one of the components of the ICF which measures disability.
16. Fletcher PC, Hirdes JP. Restriction in activity associated with fear of falling among community-based seniors using home care services. Age and Ageing. 2004;33:273-279.	The Frailty scale is mainly based on the presence of disability variables (ADLs).
17. Frost R, Kharicha K, Jovicic A, Liljas AEM, Iliffe S, Manthorpe J, Gardner B, Avgerinou C, Goodman C, Drennan VM, Walters K. Identifying acceptable components for home-based health promotion services for older people with mild frailty: A qualitative study. Health & Social Care in the Community. 2018;26:393-403.	Frailty was measured by frailty index.
18. Fushiki Y, Ohnishi H, Sakauchi F, Oura A, Mori M. Relationship of Hobby Activities With Mortality and Frailty Among Community-Dwelling Elderly Adults: Results of a Follow-up Study in Japan. Journal of Epidemiology. 2012;22:340-347.	Frailty was defined as being newly institutionalized or bedridden at home because of physical disability or severe cognitive impairment.
19. Garcia-Garcia FJ, Avila GG, Alfaro-Acha A, Andres MSA, Lanza MDD, Aparicio MVE, Aparicio SH, Zugasti JLL, Reus MGS, Rodriguez-Artalejo F, Rodriguez-Manas L, Toledo Study G. The prevalence of frailty syndrome in an older population from Spain. The Toledo study for healthy aging. J Nutr Health Aging. 2011;15:852-856.	No results about social support.
20. Gonzalez-Moneo MJ, Sanchez-Benavides G, Verdu-Rotellar JM, Cladellas M, Bruguera J, Quinones-Ubeda S, Enjuanes C, Pena-Casanova J, Comin-Colet J. Ischemic aetiology, self-reported frailty, and gender with respect to cognitive impairment in chronic heart failure patients. BMC Cardiovascular Disorders. 2016;16 (1) (no pagination).	The Frailty scale is mainly based on the presence of disability variables (ADLs).
21. Guillet A, Robert D, Leymonie CG, Hennion C, Duboeuf L, Siriex M, et al. Intérêt de la prise en compte de la fragilité en HAD: étude prospective de 210 patients. NPG Neurologie-Psychiatrie-Gériatrie. 2017;17(101):331-9.	Frailty was defined by the multidimensional frailty.

Excluded studies (based on full-text)	
Reference	**Reason for exclusion**
22. Johannesen A, Petersen J, Avlund K. Satisfaction in everyday life for frail 85-year-old adults: A Danish population study. Scandinavian Journal of Occupational Therapy. 2004;11:3-11.	The Frailty scale is mainly based on the presence of disability variables.
23. Larsson H, Ramgard M, Bolmsjo I. Older persons' existential loneliness, as interpreted by their significant others - an interview study. BMC geriatrics. 2017;17:138.	Physical impairment was included in frailty measurement
24. Learmonth E, Taket A, Hanna L. Ways in which 'community' benefits frail older women's well-being: 'we are much happier when we feel we belong'. Australasian Journal on Ageing. 2012;31:60-63.	No measurement for frailty and social support.
25. Matz-Costa C, Carr DC, McNamara TK, James JB. Physical, Cognitive, Social, and Emotional Mediators of Activity Involvement and Health in Later Life. Research on aging. 2016;38:791-815.	Disability was one of the components of frailty.
26. Nicholson C, Meyer J, Flatley M, Holman C, Lowton K. Living on the margin: Understanding the experience of living and dying with frailty in old age. Social Science and Medicine. 2012;75:1426-1432.	Disability was one of the components of frailty.
27. Parke A, Griffiths M, Pattinson J, Keatley D. Age-related physical and psychological vulnerability as pathways to problem gambling in older adults. Journal of Behavioral Addictions. 2018;7:137-145.	They used the Clinical Frailty Scale which included items such as comorbidity, cognitive impairment, and disability.
28. Ruiz-Arregui L, Avila-Funes JA, Amieva H, Borges-Yanez SA, Villa-Romero A, Aguilar-Navarro S, Perez-Zepeda MU, Gutierrez-Robledo LM, Castrejon-Perez RC. The Coyoacan Cohort Study: Design, Methodology, and Participants' Characteristics of a Mexican Study on Nutritional and Psychosocial Markers of Frailty. The Journal of Frailty & Aging. 2013;2:68-76.	No measurement and results about social networks.
29. Serra-Prat M, Papiol M, Vico J, Palomera E, Sist X, Cabre M. Factors associated with frailty in community-dwelling elderly population. A cross-sectional study. European Geriatric Medicine. 2016;7:531-537.	No measurement for loneliness or social support.
30. Shear K, Ginsberg DL, Roose SP, Lenze EJ, Alexopoulos GS, Hollander E. Depression in the elderly - The unique features related to diagnosis and treatment. Cns Spectrums. 2005;10:A1-A13.	An expert panel review
31. Simone PM, Haas AL. Frailty, Leisure Activity and Functional Status in Older Adults: Relationship With Subjective Well Being. Clinical Gerontologist. 2013;36:275-293.	The Groningen Frailty Indicator was used for measuring frailty.
32. St. John PD, Tyas SL, Montgomery PR. Depressive symptoms and frailty. International Journal of Geriatric Psychiatry. 2013;28:607-614.	Frailty was measured by frailty index.
33. Yang F, Pang JS. Socioeconomic status, frailty, and subjective	Frailty was measured by

Excluded studies (based on full-text)	
Reference	**Reason for exclusion**
well-being: A moderated mediation analysis in elderly Chinese. Journal of Health Psychology. 2018;23:961-970.	health deficits.
34. Berglund H, Hasson H, Wilhelmson K, Dunér A, Dahlin-Ivanoff S: The impact of socioeconomic conditions, social networks, and health on frail older people's life satisfaction: a cross-sectional study. *Health psychology research* 2016, 4(1).	No findings about frailty
35. Poveda V, Filgueiras M, Miranda V, Santos-Silva A, Paúl C, Costa E: Frailty in end-stage renal disease patients under dialysis and its association with clinical and biochemical markers. *J Frailty Aging* 2017, 6:103-106.	Frailty was measured by the FRAIL questionnaire in which illness is included as one of the frailty criteria.

Chapter 5 – Cross-sectional study

Study 2. Frailty as a Moderator of the Relationship between Social Isolation and Health Outcomes in Community-Dwelling Older Adults

Fereshteh Mehrabi, François Béland

International Journal of Environmental Research and Public Health 2021, 18(4), 1675

Section: Health Behavior, Chronic Disease, and Health Promotion

Special Issue: Prevention and Management of Frailty

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Both authors have read and approved the final draft. All authors have read and agreed to the published version of the manuscript.

5.1 Abstract

This research investigated the effects of social isolation on frailty and health outcomes and tested whether these associations varied across different levels of frailty. We performed a multivariate analysis of the first wave of Frailty: A longitudinal study of its expressions (FRéLE) among 1643 Canadian older adults aged 65 years and over. We assessed social isolation using social participation, social networks, and support from various social ties, namely, friends, children, extended family, and partner. Frailty was associated with disability, comorbidity, depression, and cognitive decline. Less social participation was associated with limitations in instrumental activities of daily living (IADLs), depression, and cognitive decline. The absence of friends was associated with depression and cognitive impairment. Less social support from children and partner was related to comorbidity, depression, and cognitive decline. Overall, social isolation is linked to mental health rather than physical health. The associations of having no siblings, receiving less support from friends, and participating less in social activities with ADL limitations, depression, and cognitive decline were higher among frail than prefrail and robust older adults. This study corroborates the pivotal role of social connectedness, particularly the quality of relationships, on the mental health of older adults. Public health policies on social relationships are paramount to ameliorate the health status of frail older adults.

Keywords: frailty; social isolation; social networks; social support; social participation; aging

5.2 Introduction

The effect of social isolation on health among older adults has recently garnered increasing attention from the media and policymakers alike, recognizing it as an emerging public health priority (Holt-Lunstad et al., 2017; Mehrabi & Béland, 2020). Worldwide, roughly 50% of older

adults are at risk of social isolation, and about one-third of those aged 60 years and over experience loneliness in later life (Landeiro et al., 2017). In Canada, one in five older adults feels socially isolated (Gilmour, 2012). Social isolation is a known risk factor for a wide array of adverse health outcomes among older adults, including disability (Janke et al., 2008), cognitive decline (Li & Hsu, 2015; Okura et al., 2017), depression (Santini et al., 2020), and mortality (Holt-Lunstad et al., 2015). Holt-Lunstad et al. (2010) posited that the influence of social isolation on health is comparable with that of well-established risk factors, including smoking and obesity.

In recognition of the importance of older adults' social relationships, Berkman and Krishna (Berkman, 2014) have developed a comprehensive conceptual model of how social networks impact health, linking social networks, social participation, and social support to health outcomes. Social networks pertain to social interactions and frequency of contact with social ties (i.e., friends, children, extended family, and partner). Emotional social support refers to the amount of love and caring provided by confident or intimate ties (Berkman, 2014). According to this underpinning theoretical perspective, we use a broad definition of social isolation that encompasses structural and functional aspects. The structural aspect includes social networks and social participation. The functional aspect refers to the quality of relationships or emotional social support. The impact of social isolation on health among older adults may be influenced by other factors associated with increasing age, such as frailty.

Frailty reflects the state of increased vulnerability, deriving from cumulative declines in several physiological systems (Clegg et al., 2013; Fried et al., 2001). In a landmark study, Fried et al. (2001) proposed the "Frailty Phenotype Approach" in which frailty leads to adverse health outcomes, including disability, comorbidity, falls, depression, cognitive impairment, and premature death (Clegg et al., 2013; Fried et al., 2001). Prior research has portrayed the link between frequent social contacts and higher social support with a lower level of frailty among older adults (Mehrabi & Béland, 2020; Peek et al., 2012; Vaingankar et al., 2017). Researchers have suggested that frequent contact with friends (Berglund et al., 2016; Chon et al., 2018; Schnittger et al., 2012) and neighbors (Schnittger et al., 2012) is more protective against frailty than contact with children. The results of a recent scoping review (Mehrabi & Béland, 2020) have highlighted the link between social isolation and frailty; however, discrepancies in research results appeared when examining the effect of social isolation on adverse health outcomes. These discrepancies have led

us to the assumption that frailty might moderate the association between social isolation and health outcomes, and therefore, impact this relationship differently based on the frailty status, determining which older adults are most vulnerable to poor health outcomes. Two recent studies (Hayashi et al., 2020; Hoogendijk, Smit, et al., 2020) have investigated the combined effect of social isolation and frailty on health outcomes. The results have shown that frail and isolated older adults have a higher level of falls and mortality compared to older adults without one of these conditions or those with neither of these conditions. Nevertheless, it remains unclear whether or not frailty worsens the effect of social isolation on health. To date, a paucity of research has incorporated three dimensions of social isolation, including social participation, social networks, and social support across different types of social network ties, and little is known about the moderating role of frailty on the pathway from social isolation to health (Mehrabi & Béland, 2020). Hence, the present paper aims to investigate the effects of social isolation on frailty and adverse health outcomes and to explore how this relationship varies according to different levels of frailty. Based on the Berkman theoretical model and prior studies, this research study focuses on the following relationships:

1. Social participation, social networks, and social support across different types of social ties are associated with frailty and adverse health outcomes.
2. Frailty partially moderates the effects of social isolation on poor health outcomes.

From which, we derive the two following hypotheses:

H1. Older adults who have more contact with social ties, receive more social support, and participate more in social activities will be less frail and in better health.

H2. Frail and socially isolated older adults – with fewer social contacts, less social support, and lower participation in social activities –will experience higher levels of disability, cognitive decline, comorbidity, and depression than non-frail isolated older adults. This difference will be reduced among pre-frail older adults and will not occur among robust older adults.

5.3 Materials and methods

Data source and study population

For this cross-sectional study, we employed data from the first wave of the FRéLE study (Fragilité, une étude longitudinale de ses expressions/Frailty: A longitudinal study of its expressions), a population-based study of 1,643 community-dwelling men and women aged 65 years and over. Participants were recruited from a random sample of the Québec Medicare database in 2010, including a subset of three regions in the province of Québec, Canada, as follows: a metropolitan area (Montréal), a mid-sized city (Sherbrooke), and a small town (Victoriaville). The study population was stratified by gender, age groups, and study regions. Further details regarding the study sample and data collection procedures have been described in detail elsewhere (Béland et al., 2018; Provencher et al., 2017). Ethical approval for the FRéLE study was provided by the Research Ethics Committee of the Jewish General Hospital (12 January 2010). The Research Ethics Committee of the Integrated Health and Social Services University Network for West-Central Montréal (#CODIM-MBM-17-146-10 October 2020) and the Health Research Ethics Board of the Université de Montréal (#17-162-CERES-D-19-08-2020) approved the research protocol of the present study.

Measures

Independent variables

Social isolation: Based upon the Berkman theoretical model (Berkman, 2014), we measured social isolation through participation in social activities, social networks, and receiving social support from different types of social ties, including friends, children, extended family, and an intimate partner/spouse.

Social participation was measured by 12 items, including membership in community organizations, participating in religious activities, being a volunteer, playing music, painting, visiting family members or friends, attending a community center, going to restaurants, libraries, shopping malls, cultural and sportive centers, and events (Statistics Canada, 2010). Participants indicated their response on a five-point Likert scale, ranging from 1 (almost every day) to 5

(never). Scores were summed, with greater scores indicating lower social participation. The Cronbach's alpha for this scale was 0.69.

Social networks were assessed based on the longitudinal International Mobility in Aging Study's (IMIAS) social network scale, which is a validated scale among older populations (Ahmed et al., 2018).We measured social networks using the following four items: a) the numbers of friends, living children, and extended family (i.e., grandchildren and siblings); b) the numbers of those social ties that they see at least once a month; c) that they have a close relationship with; and d) that they speak to by phone at least once a month (Ahmed et al., 2018). The examples of questions are as follows: How many friends do you have? How many friends do you see at least once a month? How many friends do you have a very close relationship with? How many of them do you speak to by phone at least once a month? Social network questions were not asked about partners as they usually had daily contacts. Response options were "never" (code 1), "rarely" (code 2), "sometimes" (code 3), "frequently" (code 4), and "always" (code 5). The items related to each social tie were summed to give a social contact score, with higher scores indicating higher levels of social networks. The Cronbach's alpha internal consistency estimates for friends, children, siblings, and grandchildren were 0.70, 0.87, 0.75, and 0.74, respectively.

Social support was measured by the following five items of the IMIAS's social support scale: whether participants felt helpful, loved, listened to, important to, and useful to their social ties, including friends, children, extended family, and partner (Ahmed et al., 2018). The examples of questions are as follows: Do you help your friends from time to time? Do you feel that you are loved and appreciated by friends? Do your friends listen to you when you need to talk about your problems or preoccupations? Do you feel that you play an important role in your friends' lives? Do you feel useful to your friends? The scores ranged from 1 (never) to 5 (always), with a higher score indicating a higher level of social support. The Cronbach's alpha internal consistency estimates for friends, children, extended family, and partner were 0.72, 0.72, 0.70, and 0.73, respectively.

The absence of social ties: We created a binary variable for social ties to indicate the absence of friends, children, grandchildren, siblings, and partner (Béland et al., 2005; McDonough & Walters, 2001). Accordingly, we dichotomized participants' responses to the presence or absence of social ties into two categories: a) participants with social ties (score 0) (i.e., having friends) and b) participants without social ties (score 1) (i.e., having no friends).

Moderator variable

Frailty: Physical frailty was assessed based on Fried's criteria (2001), including weight loss, weakness, exhaustion, slowness, and low physical activity levels. Participants were categorized as physically frail in the presence of three or more of these criteria, as pre-frail in the presence of one or two of these criteria, and as robust if none of these characteristics were observed. The detailed measurement methods for each component of frailty in the FRéLE study are provided elsewhere (Béland et al., 2020). Frailty is described as a syndrome in the Fried phenotype of frailty. Based on the construct validity measured in the FRéLE study, frailty is a marker and determinant of health outcomes (Béland et al., 2020).

Dependent variables – health outcomes

- Cognitive function was measured by the Montreal Cognitive Assessment (MoCA) which has high test-retest reliability and internal consistency. The total MoCA scores ranged from 0 to 30 points, with higher scores indicating better cognitive function (≥ 25) (Nasreddine et al., 2005). In the FRéLE study, 66 respondents had a lower cognitive status and were excluded from taking the MoCA. We censored them to the left in our analysis (Béland et al., 2018).
- Comorbidity was evaluated by the Functional Comorbidity Index (FCI), a validated scale that predicts older adults' physical function (Groll et al., 2005). Diagnoses include arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, coronary artery disease, heart failure, myocardial infarction, neurological diseases, stroke, peripheral vascular disease, diabetes, gastroduodenal pathology, depression, anxiety or panic disorders, visual impairment, hearing impairment, degenerative disc disease, obesity, and cancer. In this study, cancer was added which was one of the comorbidities in the Cardiovascular Health Study conducted by Fried (2001). The presence of each of these conditions gave one point, with the score ranging from 1 to 19 points, with a high FCI score meaning greater comorbidity. The information on the presence of specific disease was ascertained by physician assessment.
- Disability was measured by the Katz (1992) Index of Independence in Activities of Daily Living (ADLs) and the Lawton (1969) Instrumental Activities of Daily Living (IADLs)

index. ADLs include difficulty in nine self-care activities: bathing, grooming, dressing, eating, toileting, walking, getting out of bed, getting up from a chair, and cutting toenails. IADLs comprise difficulty in the nine following activities: using the telephone, using transportation, shopping, doing errands, cooking, light housekeeping, heavy housekeeping, taking medications, and managing finances. We categorized ADLs or IADLs into two groups: 1) able to perform the activity without help (score 0), and 2) unable to perform the activity (score 1). Participants who reported that they were unable to perform any of the activities were considered to have difficulty in performing ADLs or IADLs.

- Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS-15) (Yesavage & Sheikh, 1986). The scores ranged from 0 to 15, with greater scores suggesting greater depressive symptoms. The Cronbach alpha reliability estimate for the GDS was 0.75.

Covariates

Covariates included demographic and socioeconomic characteristics (i.e., age, sex, education, and annual income), and life habits (i.e., smoking, alcohol consumption, and sleeping disturbance).

Statistical analysis

Descriptive statistics were performed to describe the sample including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. One-Way Analysis of Variance (ANOVA) and chi-square tests were applied to evaluate differences between frailty groups. According to the Hayes's multi-categorical moderation model (2017), we estimated frailty, a multi-categorical moderator, in the regression models by using a system of coding based on g–1 variables, representing the g categories of frailty (g=3). We thus categorized participants into frail (w1) and pre-frail (w2) with reference to the non-frail group. We subsequently conducted a "slope difference test" in the moderation model to examine whether the effects of social isolation on health depended on frailty. This can be described as a test of the difference between two conditional effects of social isolation on health for two different values of frailty, including frail (w1) and pre-frail (w2). As suggested by McDonough and Walters (2001) and Béland et al. (2005), we added a binary variable for the absence of children, friends,

grandchildren, siblings, and partner to all equations, considering for having or not having social ties. We performed a series of multivariate regression models to examine the effects of social isolation on frailty and health outcomes and to test whether frailty moderated the effects of social isolation on health, using Mplus version 8 (Muthén & Muthén, 2018). We added simultaneously all dependent variables into the regression equations. In the first step, we examined our first hypothesis by testing the effects of social isolation on frailty and on adverse health outcomes, including disability, chronic diseases, depression, and cognitive decline. We then investigated our second hypothesis via examination of the interaction effects of social isolation and frailty on health outcomes. We assessed whether frailty improved model fit when added to the final model, using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), adjusted BIC, and chi-square tests. All multivariate regression models were controlled for covariates, and 5,000 bootstrapped samples / Monte Carlo integration were performed to calculate 95% confidence intervals. The statistical significance was set at $p \leq 0.05$.

5.4 Results

Participants' characteristics

The mean (SD) age of participants was 78.7 (7.9) years, and 50.2 % of respondents were women. Almost 12.6% of participants were classified as being frail, with 38.2% pre-frail, and 49.2% robust. The level of frailty increased significantly with age. There was no gender difference between frailty groups. Frail older adults had higher levels of chronic diseases, disability, depressive symptoms, and cognitive impairment than robust ones. They had lower levels of participation in social activities, fewer social networks, and received less support from social ties. They were less educated, less likely to drink alcohol, and to have sleep disturbances. The percentage of participants who had no friends, children, grandchildren, siblings, and partner were 14.8, 14.7, 22.2, 13, and 45.5, respectively (Table 1).

Social isolation, frailty, and health outcomes

Table 2 presents the results of the logistic regression of the association between social isolation and frailty. Older adults who engaged less in social activities (β: 0.595; 95% CI: 0.394, 0.789) and

received less social support from children (β: −0.393; 95% CI: −0.622, −0.155) and an intimate partner (β: −0.831, 95% CI: −1.507, −0.099) were more likely to be frail. The absence of siblings (β: 0.651, 95% CI: 0.149, 1.149) was significantly associated with a higher level of frailty. However, older adults with an intimate partner (β: −1.617, 95% CI: −3.072, 0.048) and children (β: −1.297; 95% CI: −2.265, −0.245) were more likely to be frail. Our results revealed that social contacts with friends, receiving social support from friends, and having friends were not associated with frailty. Only the lack of social contact with siblings was significantly related to prefrailty (β: −0.125, 95% CI: −0.208, −0.042).

Table 4 (Study 2. Table 1) Characteristics of the participants by frailty status

Variables	Total (*N* = 1643)	Frail (*n* = 207)	Prefrail (*n* = 628)	Robust (*n* = 808)	*P* value*
Age, mean (SD)	1643	84.7 (6.7)	80.4 (7.5)	75.6 (7.2)	<0.001
Age groups (%)					<0.001
65–74	536	7.7	23.2	46.3	
75–84	555	27.1	34.4	35	
85^{+}	552	65.2	42.4	18.7	
Gender, (%)					0.451
Male	818	46.9	48.9	51.2	
Female	825	53.1	51.1	48.8	
Education, mean (SD)	1643	4.4 (2.7)	5.2 (2.8)	5.7 (2.8)	<0.001
Income, mean (SD)	1643	4.1 (1.7)	4.1 (1.6)	4.2 (2.7)	0.664
Smoking (%)					0.148
Current smoker	122	6.8	8.8	6.6	
Former smoker	797	44.4	46.3	51.2	
Non-smoker	724	48.8	44.9	42.2	
Alcohol (%)					<0.001
Yes	1166	48.3	67	79.8	
No	477	51.7	33	20.2	
Sleeping disturbance (%)					0.005
Yes	677	50.7	41.9	38.2	
No	966	49.3	58.1	61.8	
ADL (%)					<0.001
No difficulty	1223	32.9	69.7	88.7	
Have difficulty	420	67.1	30.3	11.3	
IADL (%)					<0.001
No difficulty	913	6.8	44.6	76.6	
Have difficulty	730	93.2	55.4	23.4	
Depression, mean (SD)	1635	5.7 (2.9)	3.4 (2.6)	1.8 (1.7)	<0.001
Comorbidity, mean (SD)	1642	4.3 (1.9)	3.6 (1.9)	2.5 (1.7)	<0.001
Cognitive function, mean (SD)	1643	19.1 (8.1)	21.9 (6.9)	24.6 (4.2)	<0.001
Social participation, mean (SD)	1643	12.6 (18.8)	17.3 (20.8)	20.7 (20.2)	<0.001
Friends					
Social network, mean (SD)	1643	12.5 (18.7)	17.3 (20.8)	20.7 (20.2)	<0.001
Social support, mean (SD)	1643	11.7 (10.5)	14.7 (9.3)	16.8 (8.2)	<0.001
No friends (%)	243	26.1	16.4	10.6	<0.001
Children					
Social network, mean (SD)	1643	10.3 (10.4)	9.4 (8.4)	8.4 (7.6)	0.005
Social support, mean (SD)	1643	14.5 (10)	16.9 (9.4)	17.3 (9.7)	<0.001
No children (%)	242	18.4	13.9	14.5	0.273
Extended family					
Social network, grandchildren, mean (SD)	1643	12.2 (14.6)	11.1 (12.8)	9.8 (11.9)	0.031
No grandchildren (%)	365	22.7	23.4	22.2	0.429
Social network, siblings, mean (SD)	1643	5.2 (7.9)	7 (7.4)	9.5 (8.4)	<0.001
No siblings (%)	214	25.1	14	9.2	<0.001
Social support family, mean (SD)	1643	15.3 (5.3)	16.9 (4.9)	17.5 (4.8)	<0.001
Partner					
Social support, mean (SD)	1643	5.3 (12.8)	9 (13.5)	11.2 (13.5)	<0.001
No partner (%)	748	59.9	47.3	40.5	<0.001

* $p < 0.05$.

Table 5 (Study 2. Table 2) Logistic regression of social isolation on frailty

Social isolation variables	Frailty					
	Frail			Pre-Frail		
	Coefficient	CI<0.95	CI>0.95	Coefficient	CI<0.95	CI>0.95
Intercept	**11.111**	**7.922**	**14.156**	**3.077**	**1.210**	**4.979**
Social participation	**0.595**	**0.394**	**0.789**	0.079	-0.022	0.177
Friends						
Social Network	--	--	--	--	--	--
Social Support	--	--	--	--	--	--
No Friends	--	--	--	--	--	--
Children						
Social Network	--	--	--	--	--	--
Social Support	**-0.393**	**-0.622**	**-0.155**	0.043	-0.126	0.218
No children	**-1.279**	**-2.265**	**-0.245**	0.013	-0.725	0.777
Extended family						
Social Network–Grandchildren	--	--	--	--	--	--
No Grandchildren	--	--	--	--	--	--
Social Network–Siblings	0.028	-0.140	0.180	**-0.125**	**-0.208**	**-0.042**
No siblings	**0.651**	**0.149**	**1.149**	-0.285	-0.625	0.045
Social Support–Family	--	--	--	--	--	--
Partner						
Social Support	**-0.831**	**-1.507**	**-0.099**	-0.437	-0.936	0.051
No partner	**-1.617**	**-3.072**	**0.048**	-1.013	-2.120	0.060

Notes. Statistically significant associations are highlighted in Bold. Non-statistically significant associations are indicated by two hyphens [--]. Coefficient values in plain numbers are the non-statistically significant coefficient of the categories of statistically significant independent variables. All entries are unstandardized regression coefficients. CI = confidence interval.

Table 3 displays the results of the association between social isolation and frailty with adverse health outcomes. It is evident from this table that frailty was a strong predictor of all poor health outcomes, including disability, depression, comorbidity, and cognitive function. Less participation in social activities was notably associated with IADLs, depression, and cognitive decline, but not with ADLs and comorbidity. Less social support from children was significantly associated with comorbidity and depression. Likewise, those who received less support from extended family were

at greater risk for depression. The absence of friends was associated with depression symptoms and cognitive decline. However, perceived social support from friends and social contact with friends were not linked to poor health outcomes. The presence or absence of siblings and grandchildren was unrelated to adverse health outcomes, while the presence of children was linked to depressive symptoms. Although higher levels of contact with grandchildren were related to better cognitive function; social contacts with children, siblings, and friends were not associated with older adults' health. Further, it appears that older adults who had more social contact with their grandchildren experienced a higher level of functional dependence in ADLs. Lastly, older adults who perceived less social support from a partner and had an intimate partner were more likely to be depressed or cognitively impaired.

The moderating effect of frailty on social isolation and health outcomes

Table 4 presents the findings for the final model with interaction terms. Compared to the results of Table 3, when we added the interaction models to the previous model, the first-order coefficients for the absence of friends and the presence of a partner were no longer associated with cognitive function. The other first order associations remained significant. The inclusion of the interaction terms improved the overall multivariate goodness of fit, according to the reduction in the AIC (from 21,811.26 to 21,794.66), and the significance of the chi-square at the 0.05 level ($\chi 2$=32.59). Nonetheless, the BIC and adjusted BIC values increased (from 22,259.81 to 22,286.45 and from 21,996.13 to 21,997.36, respectively), indicating that our moderation models may provide little or no extra information.

Table 6 (Study 2. Table 3) Regression of social isolation and frailty on health outcomes

	ADL			IADL			Chronic Diseases			Depression			Cognitive function		
Variables	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95
Intercept	**8.143**	**6.238**	**10.049**	**10.054**	**7.923**	**12.184**	**3.132**	**1.895**	**4.170**	**7.293**	**5.310**	**9.275**	**7.312**	**6.351**	**8.274**
Frailty															
Frail	**1.828**	**1.419**	**2.236**	**2.385**	**1.763**	**3.007**	**1.453**	**1.148**	**1.759**	**2.570**	**2.180**	**2.959**	**-0.567**	**-0.766**	**-0.368**
Pre-Frail	**0.627**	**0.321**	**0.932**	**0.653**	**0.383**	**0.923**	**0.995**	**0.796**	**1.193**	**1.045**	**0.804**	**1.285**	**-0.312**	**-0.440**	**-0.183**
Social participation	--	--	--	**0.249**	**0.122**	**0.376**	--	--	--	**0.320**	**0.217**	**0.422**	**-0.075**	**-0.131**	**-0.019**
Friends															
Social Network	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Social Support	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
No Friends	--	--	--	--	--	--	--	--	--	**0.434**	**0.135**	**0.733**	**-0.274**	**-0.436**	**-0.113**
Children															
Social Network	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Social Support	--	--	--	--	--	--	**-0.155**	**-0.287**	**-0.024**	**-0.363**	**-0.535**	**-0.191**	--	--	--
No Children*	--	--	--	--	--	--	-0.475	-1.071	0.122	**-1.423**	**-2.174**	**-0.672**	--	--	--
Extended Family															
Social Network	**0.171**	**0.050**	**0.292**	--	--	--	--	--	--	--	--	--	**0.057**	**0.001**	**0.113**
Grandchildren															
No Grandchildren*	0.050	-0.326	0.426	--	--	--	--	--	--	--	--	--	0.028	-0.131	0.186
Social Network	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Siblings															
No siblings	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Social Support-Family	--	--	--	--	--	--	--	--	--	**-0.207**	**-0.328**	**-0.086**	--	--	--
Partner															
Social Support	--	--	--	--	--	--	--	--	--	**-0.983**	**-1.453**	**-0.513**	**0.275**	**0.028**	**0.522**
No Partner	--	--	--	--	--	--	--	--	--	**-2.007**	**-3.049**	**-0.965**	**0.592**	**0.042**	**1.141**

Notes. Statistically significant associations are highlighted in bold. Non-statistically significant associations are indicated by two hyphens [--]. *These variables should always enter the equations for considering participants without social tiesADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living.

Table 7 (Study 2. Table 4) Social isolation and frailty on health outcomes with interactions

	ADL			IADL			Chronic Diseases			Depression			Cognitive function		
Variables	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95
Intercept	**8.151**	**6.224**	**10.077**	**10.053**	**7.923**	**12.184**	**3.131**	**1.895**	**4.368**	**8.337**	**6.221**	**10.453**	**7.713**	**6.627**	**8.800**
Frailty															
Frail	**1.507**	**1.059**	**1.954**	**2.385**	**1.763**	**3.007**	**1.453**	**1.148**	**1.759**	**2.566**	**2.121**	**3.011**	**-0.702**	**-0.945**	**-0.459**
Pre-Frail	**0.602**	**0.281**	**0.924**	**0.653**	**0.383**	**0.923**	**0.995**	**0.796**	**1.193**	**1.074**	**0.833**	**1.316**	**-0.361**	**-0.533**	**-0.190**
Social participation	--	--	--	**0.249**	**0.122**	**0.376**	--	--	--	**0.194**	**0.057**	**0.331**	**-0.072**	**-0.129**	**-0.016**
Friends															
Social Network	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Social Support	--	--	--	--	--	--	--	--	--	--	--	--	-0.097	-0.221	0.026
No Friends	--	--	--	--	--	--	--	--	--	**0.415**	**0.117**	**0.714**	-0.489	-1.026	0.048
Children															
Social Network	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Social Support	--	--	--	--	--	--	**-0.155**	**-0.287**	**-0.024**	**-0.361**	**-0.533**	**-0.189**	--	--	--
No Children	--	--	--	--	--	--	-0.474	-1.071	0.122	**-1.408**	**-2.157**	**-0.658**	--	--	--
Extended Family															
Social Network	**0.169**	**0.048**	**0.291**	--	--	--	--	--	--	--	--	--	**0.061**	**0.005**	**0.117**
Grandchildren															
No Grandchildren	0.051	-0.329	0.431	--	--	--	--	--	--	--	--	--	0.032	-0.126	0.190
Social Network	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

	ADL			IADL			Chronic Diseases			Depression			Cognitive function		
Variables	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95
sibling															
No siblings	-0.516	-1.354	0.322	--	--	--	--	--	--	--	--	--	--	--	--
Social Support-Family	--	--	--	--	--	--	--	--	--	**-0.207**	**-0.328**	**-0.087**	--	--	--
Partner															
Social Support	--	--	--	--	--	--	--	--	--	**-0.998**	**-1.468**	**-0.529**	**0.252**	**0.003**	**0.501**
No Partner	--	--	--	--	--	--	--	--	--	**-2.030**	**-3.071**	**-0.990**	0.545	-0.009	1.100
Interactions															
Social Participation															
×Frail	--	--	--	--	--	--	--	--	--	0.209	-0.102	0.520	--	--	--
×Pre-Frail	--	--	--	--	--	--	--	--	--	**0.270**	**0.071**	**0.469**	--	--	--
No Siblings															
×Frail	**1.758**	**0.566**	**2.950**	--	--	--	--	--	--	--	--	--	--	--	--
×Pre-Frail	0.305	-0.677	1.287	--	--	--	--	--	--	--	--	--	--	--	--
Social Support – Friends															
×Frail	--	--	--	--	--	--	--	--	--	--	--	--	**0.420**	**0.166**	**0.674**
×Pre-Frail	--	--	--	--	--	--	--	--	--	--	--	--	0.138	-0.042	0.317
No Friends															
×Frail	--	--	--	--	--	--	--	--	--	--	--	--	**1.293**	**0.281**	**2.305**
×Pre-Frail	--	--	--	--	--	--	--	--	--	--	--	--	0.239	-0.527	1.006

	ADL			IADL			Chronic Diseases			Depression			Cognitive function		
Variables	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95
Summary of Model fits															
	LL			**Parameters**			**AIC**			**BIC**			**Adjusted BIC**		
Model without interaction (LLh0)	-10822.63			83			21811.26			22259.81			21996.13		
Model with interaction (LLh1)	-10806.33			91			21794.66			22286.45			21997.36		
-2* (LLh0 - LLh1)	32.59			8			16.6			-26.64			-1.23		

Notes. Statistically significant associations are highlighted in bold. Non-statistically significant associations are indicated by two hyphens [--]. Coefficient values in plain numbers are the non-statistically significant coefficient of the categories of statistically significant independent variables. LL: log likelihood; AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion.

Table 8 (Study 2. Table 5) Conditional effects of social isolation on health outcomes at different values of frailty

		ADL			**Depression**			**Cognitive function**		
Social isolation indicators	Moderator levels	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95	Coef.	CI<0.95	CI>0.95
Social Participation	Frail	--	--	--	**0.404**	**0.119**	**0.689**	--	--	--
	Pre-Frail	--	--	--	**0.464**	**0.308**	**0.621**	--	--	--
	Robust	--	--	--	**0.194**	**0.057**	**0.331**	--	--	--
Social support-Friends	Frail	--	--	--	--	--	--	**0.323**	**0.098**	**0.547**
	Pre-Frail	--	--	--	--	--	--	0.040	-0.095	0.176
	Robust	--	--	--	--	--	--	-0.097	-0.221	0.026
No Friends	Frail	--	--	--	--	--	--	0.804	-0.059	1.666
	Pre-Frail	--	--	--	--	--	--	-0.250	-0.803	0.303
	Robust	--	--	--	--	--	--	-0.489	-1.026	0.048
No Siblings	Frail	**1.242**	**0.390**	**2.094**	--	--	--	--	--	--
	Pre-Frail	-0.211	-0.733	0.311	--	--	--	--	--	--
	Robust	-0.516	-1.354	0.322	--	--	--	--	--	--

Notes. Statistically significant associations are highlighted in bold. Non-statistically significant associations are indicated by two hyphens [--]. Coefficient values in plain numbers are the non-statistically significant coefficient of the categories of statistically significant independent variables.

The moderation regression models in Table 4 demonstrated that the following interactions with frailty were statistically significant: social participation (β: 0.270, 95% CI: 0.071, 0.469), social support from friends (β: 0.420, 95% CI: 0.166, 0.674), having no friends (β: 1.293, 95% CI: 0.281, 2.305) and no siblings (β: 1.758, 95% CI: 0.566, 2.950). Based on the Hayes moderation model, we conducted a "slope difference test" to compare whether the effect of social isolation on health outcomes varied in different values of frailty. As presented in Table 5, the conditional effect tests showed that the negative effect of having no siblings on ADL limitations was significant for frail older adults (β: 1.242, 95% CI: 0.390, 2.094). As predicted, this effect was not apparent for prefrail and robust older adults. The subsequent conditional effects revealed that the effect of non-participation in social activities on depression was stronger for frail (β: 0.404; 95% CI:0.119, 0.689) and pre-frail (β: 0.464; 95% CI:0.308, 0.621) older adults compared to robust ones (β: 0.194; 95% CI:0.057, 0.331). Of importance, this effect was significantly diminished for robust older adults. Additionally, higher levels of perceived social support from friends were protective against cognitive decline for frail older adults (β =0.323; 95% CI:0.098,0.547), but this benefit was significantly attenuated for prefrail and non-frail older adults. Lastly, frail older adults without friends had higher levels of cognitive decline compared to pre-frail and non-frail older adults (β =0.804; 95% CI: -0.059,1.666). In sum, we observed that associations of having no siblings, receiving less social support from friends, and participating less in social activities with ADL limitations, cognitive decline, and depression were higher for frail older adults than for pre-frail and robust ones.

5.5 Discussion

Drawing on the Berkman theoretical model of social relationships, we examined the interplay between social isolation, frailty, and health outcomes. Our results partially support our first hypothesis that older adults who engage in leisure activities, have social contacts with siblings, and perceive support from children and an intimate partner are less frail. The current study confirms the prior evidence that frailty is a strong predictor of adverse health outcomes (Mehrabi & Béland, 2020). Apart from frailty, our results indicate that actively engaging in social activities may alleviate the impact of IADL limitations, depressive symptoms, and cognitive decline among older adults. This result is consistent with evidence from previous longitudinal research (Béland et al.,

2005; Wang et al., 2020) and also, is in line with the World Health Organization (WHO) framework on healthy aging (2017), emphasizing the importance of social participation in later life, which may, in turn, reinforce the health of older adults.

We found that older adults who perceived a shortfall in social support from children and an intimate partner were at greater risk of depression, comorbidity, and cognitive decline. The presence of an intimate partner and children and a relative lack of friends resulted in a higher likelihood of cognitive decline and depression. In this vein, our findings shed further light on the impact of intimate and kin relations on health. This interpretation is in line with previous research that emphasizes children have salient roles on the health status of Spanish and Latin American older adults (Bélanger et al., 2016; Zunzunegui et al., 2009). Evidence in China and Canada yields the beneficial impact of social interactions with friends on the health of older adults (Bélanger et al., 2016; Wang et al., 2015). Relatedly, the findings on the importance of strong social ties for health in older age are in accord with the Berkman theory, illustrating that social ties provide essential emotional and instrumental support at times of illness (Berkman et al., 2000).

Concerning social connections with different types of social ties, our results revealed that only social contacts with grandchildren were related to health outcomes. In this view, social connection with grandchildren was positively linked to better cognitive function. Contrary to expectations, our results showed that more contacts with grandchildren (a continuous variable) were associated with higher levels of independence in ADLs. As suggested by Seeman et al. (1996), we created a binary variable, comparing those who had 0-2 grandchildren with those who had three or more grandchildren to examine whether the extreme values or gender differences were the cause of this inverse association. We ran a separate univariate analysis for males and females, entering the foregoing binary variable. The results revealed that men who had more contact with grandchildren were less likely to have ADL dependency (β = -0.453; 95% CI: 0.417, 0.969), albeit this relationship was not significant among women. This association is explained by the fact that male older adults had less functional limitations and more contact with grandchildren compared to female older adults in our sample. This binary variable was no longer significant after adjustment for covariates. The continuous variable remained significant in both univariate and multivariate analyses with a stronger association between social networks and less risk of limitations in ADL in men than in women. The results of the Survey of Health, Aging and Retirement in Europe

(SHARE) study (Scheel-Hincke et al., 2020) lend support to the sex difference in ADL among older adults in Northern, Eastern, and Western Europe, indicating that female older adults have a higher risk of ADL dependence than male older adults. This relationship needs further investigation in other datasets.

Taken together, our findings suggest that social isolation is linked to depression symptoms and cognitive decline rather than other adverse health outcomes in community-dwelling older adults. This result coheres with a population-based intervention in England (Iliffe et al., 2007), indicating that social isolation risk is related to depression and memory decline but not multiple chronic diseases and difficulties in performing ADLs and IADLs. Another longitudinal study from England (Shankar et al., 2017) reached the conclusion that neither structural nor functional aspect of social relationship is associated with ADL limitations over six years. Evidence from several reviews on social isolation and health demonstrated that the most researched outcomes in physical health are mortality and cardiovascular diseases (Courtin & Knapp, 2017; Holt-Lunstad et al., 2017; Leigh-Hunt et al., 2017). In this regard, a rapid review of 40 systematic reviews (Leigh-Hunt et al., 2017) found strong and consistent evidence for the association between social isolation and cardiovascular disease and depression, albeit evidence is less strong for other physical health conditions. Interventions and research studies on depression and cardiovascular diseases highlighted the absence of social support as an important risk factor for poor health outcomes, emphasizing the pivotal role of the quality of relationships (Courtin & Knapp, 2017; Holt-Lunstad et al., 2017).

Overall, the weak or moderate association between social isolation, frailty, and poor health outcomes is consistent with the available literature, including a scoping review of 26 studies (Mehrabi & Béland, 2020) where each social relation promotes health through different mechanisms. According to this review, few studies support the impacts of both social isolation and frailty on adverse health outcomes.

Our second hypothesis pertains to the potential moderating role of frailty on the pathway from social isolation and health. Importantly, our results confirm our hypothesis that the impact of social isolation on adverse health outcomes differs depending on the frailty status. More specifically, our results revealed that the associations of receiving less support from friends and participating less

in social activities with mental and cognitive impairment were stronger in frail than in prefrail and robust older adults. Hence, social isolation does not seem to promote the functional and mental health status of robust older adults but may reduce health decline in frail and pre-frail older adults. To the best of our knowledge, only one longitudinal study (Liao et al., 2018) has investigated the interaction effect of receiving and providing social support and frailty on mortality. The results revealed a lower risk of mortality among robust and pre-frail older adults who provided social support to their family ties, but not among those who received family support.

This study was cross-sectional which limits our understanding of causative relationships between social isolation, frailty, and health outcomes. Future studies with longitudinal methods are warranted to capture developmental changes in social isolation and frailty and their effects on health outcomes over time. In particular, more research is needed to further explore the direction of the association between contact with family members and the likelihood of ADL limitations. Despite these limitations, the present study extends the social isolation domain, focusing on frailty. The notable strengths of the study include the large and population-based sample; the multicenter nature of the study; and the use of validated scales for social isolation, frailty, and health outcomes. To our knowledge, this is the first attempt to focus on frailty as a moderator on the pathway from social isolation to physical and mental health, incorporating the multidimensional measure of social isolation across different types of social ties.

From a public health standpoint, the results of our study elucidate the pivotal role of kin and intimate relationships in older age, and particularly their impacts on mental and cognitive health. In this respect, several public health policies and programs implicitly incorporate social connectedness as mechanisms for enhancing older population health and well-being across the globe. As such, social participation is one of the eight domains of the Global Network of Age-Friendly Cities and Communities (AFCCs) led by the WHO in 2007. The WHO decade of Healthy Aging (2020-2030) is another initiative to promote health and well-being in later life. Several models have been developed in the United States, Canada, and Europe based on the political priorities and needs of older adults. For example, the village models of Age-Friendly communities (Scharlach et al., 2014) in the US foster neighborhood social ties. In Québec, Age-Friendly cities (Garon et al., 2014) focus mainly on the social participation of older adults in communities, addressing social determinants of health. Despite these laudable efforts on enhancing social

interrelatedness in the communities, there is scant evidence on the effectiveness of these actions and their impacts on the physical or mental health of older adults. Additionally, the current Age-Friendly policies focus on the physical environment but not so far on the social or mental environment (Duppen et al., 2020). At this juncture, our results underscore that social isolation influences older adults' mental and cognitive health, though its association with physical health is notably non-statistically significant except in some limited instances. Therefore, health care policies and public health initiatives could benefit from considering explicitly these results in efforts aimed at reducing mental health problems and cognitive decline among vulnerable older populations. In particular, the results of our study are highly relevant for health policymakers in the context of the current coronavirus disease 2019 (COVID-19) pandemic in which frail older adults are mostly affected by restriction measures imposed by governments all over the world. Ultimately, strategies to prevent or lessen the long-term effect of social isolation on older adults' mental health are of paramount importance in post-pandemically.

5.6 Conclusions

In conclusion, this study is a novel contribution to the empirical literature on social gerontology by highlighting the key roles of social ties, perceived support, and engagement in social activities on promoting mental health in later life, particularly among frail older adults.

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Informed consent statement: Written Informed consent was obtained from all participants involved in the FRéLE study.

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5.7 References

1. Holt-Lunstad, J.; Robles, T.F.; Sbarra, D.A. Advancing social connection as a public health priority in the United States. Am. Psychol. 2017, 72, 517–530, doi:10.1037/amp0000103.

2. Mehrabi, F.; Béland, F. Effects of social isolation, loneliness and frailty on health outcomes and their possible mediators and moderators in community-dwelling older adults: A scoping review. Arch. Gerontol. Geriatr. 2020, 90, 104119, doi:10.1016/j.archger.2020.104119.

3. Landeiro, F.; Barrows, P.; Musson, E.N.; Gray, A.M.; Leal, J. Reducing social isolation and loneliness in older people: A sys-tematic review protocol. BMJ Open 2017, 7, e013778, doi:10.1136/bmjopen-2016-013778.

4. Gilmour, H. Social participation and the health and well-being of Canadian seniors. Health Rep. 2012, 23, 23–32.

5. Janke, M.C.; Payne, L.L.; Van Puymbroeck, M. The role of informal and formal leisure activities in the disablement process. Int. J. Aging Hum. Dev. 2008, 67, 231–257, doi:10.2190/AG.67.3.c.

6. Okura, M.; Ogita, M.; Yamamoto, M.; Nakai, T.; Numata, T.; Arai, H. The relationship of community activities with cognitive impairment and depressive mood independent of mobility disorder in Japanese older adults. Arch. Gerontol. Geriatr. 2017, 70, 54–61.

7. Li, C.-L.; Hsu, H.-C. Cognitive function and associated factors among older people in Taiwan: Age and sex differences. Arch. Gerontol. Geriatr. 2015, 60, 196–200, doi:10.1016/j.archger.2014.10.007.

8. Santini, Z.I.; Jose, P.E.; Cornwell, E.Y.; Koyanagi, A.; Nielsen, L.; Hinrichsen, C.; Meilstrup, C.; Madsen, K.R.; Koushede, V. Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): A longitudinal mediation analysis. Lancet Public Health 2020, 5, e62–e70, doi:10.1016/s2468-2667(19)30230-0.

9. Holt-Lunstad, J.; Smith, T.B.; Baker, M.; Harris, T.; Stephenson, D. Loneliness and social isolation as risk factors for mortali-ty: A meta-analytic review. Perspect. Psychol. Sci. 2015, 10, 227–237.

10. Holt-Lunstad, J.; Smith, T.B.; Layton, J.B. Social relationships and mortality risk: A Meta-analytic review. PLoS Med. 2010, 7, e1000316, doi:10.1371/journal.pmed.1000316.

11. Berkman, L.F.; Krishna, A. Social network epidemiology. In Social Epidemiology, 2nd ed.; Berkman, L.F., Kawachi, I., Glymour, M.M., Eds.; Oxford University Press: New York, United States of America, 2014; pp. 234–289.

12. Clegg, A.; Young, J.; Iliffe, S.; Rikkert, M.O.; Rockwood, K. Frailty in elderly people. Lancet 2013, 381, 752–762, doi:10.1016/s0140-6736(12)62167-9.

13. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in older adults: Evidence for a phenotype. J. Gerontol. Ser. A 2001, 56, M146–M156, doi:10.1093/gerona/56.3.m146.

14. Peek, M.K.; Howrey, B.T.; Ternent, R.S.; Ray, L.A.; Ottenbacher, K.J. Social support, stressors, and frailty among older Mexi-can American adults. Journals Gerontol. Ser. B 2012, 67, 755–764, doi:10.1093/geronb/gbs081.

15. Vaingankar, J.A.; Chong, S.A.; Abdin, E.; Picco, L.; Chua, B.Y.; Shafie, S.; Ong, H.L.; Chang, S.; Seow, E.; Heng, D. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatr. Gerontol. Int. 2017, 17, 1444–1454.

16. Chon, D.; Lee, Y.; Kim, J.; Lee, K.-E. The association between frequency of social contact and frailty in older people: Korean Frailty and Aging Cohort Study (KFACS). J. Korean Med. Sci. 2018, 33, e332, doi:10.3346/jkms.2018.33.e332.

17. Berglund, H.; Hasson, H.; Wilhelmson, K.; Dunér, A.; Dahlin-Ivanoff, S. The impact of socioeconomic conditions, social net-works, and health on frail older people's life satisfaction: A cross-sectional study. Health Psychol. Res. 2016, 4, 5578, doi:10.4081/hpr.2016.5578.

18. Schnittger, R.I.; Walsh, C.; Casey, A.-M.; Wherton, J.; McHugh, J.E.; Lawlor, B. Psychological distress as a key component of psychosocial functioning in community-dwelling older people. Aging Ment. Health 2012, 16, 199–207, doi:10.1080/13607863.2011.604024.

19. Hayashi, T.; Umegaki, H.; Makino, T.; Huang, C.; Inoue, A.; Shimada, H.; Kuzuya, M. Combined impact of physical frailty and social isolation on rate of falls in older adults. J. Nutr. Health Aging 2020, 24, 312–318, doi:10.1007/s12603-020-1316-5.

20. Hoogendijk, E.O.; Smit, A.P.; Van Dam, C.; Schuster, N.A.; De Breij, S.; Holwerda, T.J.; Huisman, M.; Dent, E.; Andrew, M.K. Frailty combined with loneliness or social isolation: An elevated risk for mortality in later life. J. Am. Geriatr. Soc. 2020, 68, 2587–2593, doi:10.1111/jgs.16716.

21. Béland, F.; Julien, D.; Bier, N.; Desrosiers, J.; Kergoat, M.-J.; Demers, L. Association between cognitive function and life-space mobility in older adults: Results from the FRéLE longitudinal study. BMC Geriatr. 2018, 18, 227, doi:10.1186/s12877-018-0908-y.

22. Provencher, V.; Béland, F.; Demers, L.; Desrosiers, J.; Bier, N.; Ávila-Funes, J.A.; Galand, C.; Julien, D.; Fletcher, J.D.; Trottier, L.; et al. Are frailty components associated with disability in specific activities of daily living in community-dwelling older adults? A multicenter Canadian study. Arch. Gerontol. Geriatr. 2017, 73, 187–194, doi:10.1016/j.archger.2017.07.027.

23. Statistics Canada, Canadian Community Health Survey (CCHS)- Healthy Aging questionnaire (2008–2009); Statistics Canada, Ottawa, Canada, 2010; pp.117–120.

24. Ahmed, T.; IMIAS Research Group; Belanger, E.; Vafaei, A.; Koné, G.K.; Alvarado, B.; Beland, F.; Zunzunegui, M.V. Valida-tion of a social networks and support measurement tool for use in international aging research: The International Mobility in Aging Study. J. Cross-Cult. Gerontol. 2018, 33, 101–120, doi:10.1007/s10823-018-9344-x.

25. Béland, F.; Zunzunegui, M.-V.; Alvarado, B.; Otero, A.; Del Ser, T. Trajectories of cognitive decline and social relations. J. Gerontol. Ser. B 2005, 60, P320–P330, doi:10.1093/geronb/60.6.p320.

26. McDonough, P.; Walters, V. Gender and health: Reassessing patterns and explanations. Soc. Sci. Med. 2001, 52, 547–559, doi:10.1016/s0277-9536(00)00159-3.

27. Béland, F.; Julien, D.; Wolfson, C.; Bergman, H.; Gaudreau, P.; Galand, C.; Fletcher, J.; Zunzunegui, M.-V.; Shatenstein, B.; Ker-goat, M.-J.; et al. Revisiting the hypothesis of syndromic frailty: A cross-sectional study of the structural validity of the frailty phenotype. BMC Geriatr. 2020, 20, 1–13, doi:10.1186/s12877-020-01839-7.

28. Nasreddine, Z.S.; Phillips, N.A.; Bedirian, V.; Charbonneau, S.; Whitehead, V.; Collin, I.; Cummings, J.L.; Chertkow, H. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 2005, 53, 695–699, doi:10.1111/j.1532-5415.2005.53221.x.

29. Groll, D.L.; To, T.; Bombardier, C.; Wright, J.G. The development of a comorbidity index with physical function as the out-come. J. Clin. Epidemiol. 2005, 58, 595–602, doi:10.1016/j.jclinepi.2004.10.018.

30. Katz, S.; Ford, A.B.; Moskowitz, R.W.; Jackson, B.A.; Jaffe, M.W.; White, K.L. Studies of illness in the aged—The index of ADL: A standardized measure of biological and psychosocial functions. JAMA 1963, 185, 914–919. doi:10.1001/jama.1963.03060120024016.

31. Lawton, M.P.; Brody, E.M. Assessment of older people: Self-maintaining and instrumental activities of daily living. Geron-tologist 1969, 9, 179–186, doi:10.1093/geront/9.3_Part_1.179.

32. Yesavage, J.A.; Sheikh, J.I. 9/Geriatric Depression Scale (GDS)—Recent evidence and development of a shorter version. Clin. Gerontol. 1986, 5, 165–173.

33. Hayes, A.F. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach; Guilford Press: New York, NY, USA, 2017.

34. Muthén, L.; Muthén, B. Mplus User's Guide: Statistical analysis with latent variables, user's guide, Eight Edition, Los Angeles, United States, Muthén & Muthén, 2017.

35. Wang, R.; Feng, Z.; Liu, Y.; Lu, Y. Relationship between neighbourhood social participation and depression among older adults: A longitudinal study in China. Health Soc. Care Community 2019, 28, 247–259, doi:10.1111/hsc.12859.

36. World Health Organization. Global Strategy and Action Plan on Ageing and Health; WHO: Geneva, Switzerland, 2017.

37. Belanger, E.; Ahmed, T.; Vafaei, A.; Curcio, C.L.; Phillips, S.P.; Zunzunegui, M.V. Sources of social support associated with health and quality of life: A cross-sectional study among Canadian and Latin American older adults. BMJ Open 2016, 6, e011503, doi:10.1136/bmjopen-2016-011503.

38. Zunzunegui, M.-V.; Béland, F.; Sanchez, M.-T.; Otero, A. Longevity and relationships with children: The importance of the parental role. BMC Public Health 2009, 9, 351.

39. Wang, B.; He, P.; Dong, B. Associations between social networks, social contacts, and cognitive function among Chinese no-nagenarians/centenarians. Arch. Gerontol. Geriatr. 2015, 60, 522–527, doi:10.1016/j.archger.2015.01.002.

40. Berkman, L.F.; Glass, T.; Brissette, I.; Seeman, T.E. From social integration to health: Durkheim in the new millennium. Soc. Sci. Med. 2000, 51, 843–857, doi:10.1016/s0277-9536(00)00065-4.

41. Seeman, T.E.; Bruce, M.L.; McAvay, G.J. Social network characteristics and onset of adl disability: MacArthur studies of successful aging. J. Gerontol. Ser. B 1996, 51, S191–S200, doi:10.1093/geronb/51b.4.s191.

42. Scheel-Hincke, L.L.; Möller, S.; Lindahl-Jacobsen, R.; Jeune, B.; Ahrenfeldt, L.J. Cross-national comparison of sex differences in ADL and IADL in Europe: Findings from SHARE. Eur. J. Ageing 2020, 17, 69–79.

43. Iliffe, S.; Kharicha, K.; Harari, D.; Swift, C.; Gillmann, G.; Stuck, A.E. Health risk appraisal in older people 2: The implications for clinicians and commissioners of social isolation risk in older people. Br. J. Gen. Pract. 2007, 57, 277–282.

44. Shankar, A.; McMunn, A.; Demakakos, P.; Hamer, M.; Steptoe, A. Social isolation and loneliness: Prospective associations with functional status in older adults. Health Psychol. 2017, 36, 179–187, doi:10.1037/hea0000437.

45. Courtin, E.; Knapp, M. Social isolation, loneliness and health in old age: A scoping review. Health Soc. Care Community 2017, 25, 799–812, doi:10.1111/hsc.12311.

46. Leigh-Hunt, N.; Bagguley, D.; Bash, K.; Turner, V.; Turnbull, S.; Valtorta, N.; Caan, W. An overview of systematic reviews on the public health consequences of social isolation and loneliness. Public Health 2017, 152, 157–171, doi:10.1016/j.puhe.2017.07.035.

47. Liao, M.-Y.; Yeh, C.-J.; Liao, C.-C.; Lee, S.-H.; Yang, S.-F.; Lee, M.-C. Effects of receiving and providing family support on mor-tality in non-frail, pre-frail and frail older adults in Taiwan: A 12-year follow-up longitudinal study. Eur. Geriatr. Med. 2018, 9, 679–685, doi:10.1007/s41999-018-0094-7.

48. Scharlach, A.E.; Davitt, J.K.; Lehning, A.J.; Greenfield, E.A.; Graham, C. Does the village model help to foster Age-Friendly communities? J. Aging Soc. Policy 2014, 26, 181–196, doi:10.1080/08959420.2014.854664.

49. Garon, S.; Paris, M.; Beaulieu, M.; Veil, A.; Laliberté, A. Collaborative partnership in Age-Friendly cities: two case studies from Quebec, Canada. J. Aging Soc. Policy 2014, 26, 73–87, doi:10.1080/08959420.2014.854583.

50. Duppen, D.; Lambotte, D.; Dury, S.; Smetcoren, A.-S.; Pan, H.; De Donder, L.; D-SCOPE Consortium. Social participation in the daily lives of frail older adults: Types of participation and influencing factors. J. Gerontol. Ser. B 2019, 75, 2062–2071, doi:10.1093/geronb/gbz045.

Chapter 6 – Longitudinal study

Study 3. The Longitudinal Relationships between Social Relationships and Physical, Mental, and Cognitive Health: The Role of Frailty

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6.1 Abstract

Background: Socially isolated older adults incur increased risks of adverse health outcomes, though the strength of this association is unclear. We examined whether changes in physical frailty moderated the associations between changes in social relationships and changes in health outcomes among older adults.

Methods: This longitudinal study is based on three waves of the FRéLE study among 1643 Canadian community-dwelling older adults aged 65 years and older over two years. We performed latent growth curve modeling to assess changes with the assumption of missing not at random, adjusting for time-invariant covariates. Social relationships were measured by social participation, social networks, and support from social ties. Frailty was assessed using the five components of the phenotype of frailty.

Results: Our moderation results revealed that increasing changes in social participation, social support from friends and nuclear and extended family, and social contact with friends were

associated with greater changes in cognitive and mental health, but not physical health, among older adults with changes toward frailty in contrast with those with changes toward robustness.

Conclusions: This longitudinal study suggests that social support has a protective and compensatory role in enhancing mental health among frail older adults. Future studies may consider other health-related risk factors that may impact the relationships between social relationship and physical, mental, and cognitive health outcomes among older adults.

Keywords: Social Networks, Social Participation, Social Support, Moderation

6.2 Introduction

Social isolation is a global public health concern with important implications for well-being in later life (Holt-Lunstad et al., 2017). Empirical research has indicated that social isolation is linked to poor physical, mental, and cognitive health outcomes in older age (Evans et al., 2019; Holt-Lunstad et al., 2015; Santini et al., 2016), rivaling the effects of cigarette smoking and obesity (Holt-Lunstad et al., 2015). These risks are represented in an underpinning theoretical model proposed by Berkman and Krishna (2014) that links structural (social networks and social participation) and functional (social support) aspects of social isolation to adverse health outcomes.

Previous research suggests an association between social isolation and biological processes such as frailty (Holt-Lunstad & Steptoe, 2021). Physical frailty is a state of increased vulnerability to external stressors due to a decline in physiological reserves across multiple organ systems (Clegg et al., 2013; Fried et al., 2001). Frailty is associated with increased risks of disability, comorbidity (Fried et al., 2001), depression (Smith et al., 2019), cognitive impairment (Yu, Steptoe, Chen, et al., 2020), and mortality (Fan et al., 2021). Given the physiologic vulnerability inherent in physical frailty, it is plausible that the stress of isolation may result in adverse health outcomes in frail older adults compared to robust peers. The underlying mechanism is that social isolation is a stressor leading to poor health and challenges resilience, similar to the development of physical frailty due to the effect of stressors on physiological reserves (Cacioppo & Hawkley, 2003; Fried et al., 2001). Fried et al. (2001) provided support for the assumption that frail older adults are at greater risk for various deleterious outcomes due to key features of frailty such as muscle weakness, decreased endurance performance, and diminished physical activity.

A paucity of research has examined the interplay between structural and functional aspects of social isolation, frailty, and health outcomes, and the results appear inconsistent among studies. Some (Risbridger et al., 2021; Zhang et al., 2018) found that less social support and social participation were associated with frailty and falls. In a longitudinal study examining the combined effects of frailty and social isolation on health outcomes, Hoogendijk et al. (2020) illustrated that coexisting frailty and social isolation in older adults increased the risk of mortality compared to those with one or none of these conditions. However, Malini et al. (2016) reported contradictory results that neither social support nor frailty was linked to fear of falling. These discrepancies suggest that frailty might alter the relationship between social isolation and health outcomes such that frail and socially isolated older adults become more vulnerable to health-related conditions than their robust and isolated peers.

Thus far, few studies have assessed the impact of changes in structural and functional aspects of social isolation and frailty on health outcomes. None of these studies shed light on whether changes in one's social networks are more or less problematic than changes in social support and social participation. The general conclusion derived from the existing evidence is that structural and functional aspects of social isolation may differently impact frailty and health outcomes among older adults. To our knowledge and based on a recent scoping review (Mehrabi & Béland, 2020), no studies have specifically examined the longitudinal moderating effects of frailty on the relationship between multidimensional social isolation and health outcomes. To address gaps and shortcomings in the literature, the objective of this study was to explore whether the relationship between changes in social relationships and changes in health outcomes varied based on changes in frailty among older adults. We explored two alternative hypotheses that might explain the moderating role of frailty in this relationship.

H_{1a}: Increased changes in social relationships will lead to increasing changes in health outcomes in older adults with changes toward robustness compared to those with changes toward frailty.

Rationale: Older adults with changes toward robustness have sufficient physiological reserves to mobilize social relationships. In contrast, the positive impact of social relationships on health outcomes will be small for older adults with stable frailty or frailer older adults because they lack the physiological reserves to benefit from social relationships.

H_{1b}: Increased changes in social relationships will lead to positive changes in health outcomes among older adults with changes toward frailty compared to those with changes toward robustness.

Rationale: Social relationships compensate for the lack of physiologic reserves in frailer older adults. Consequently, the beneficial effect of social relationships on health outcomes will be more pronounced for frailer older adults compared to those who are more robust. However, the health of older adults with stable frailty or those who are more robust will be less impacted by changes in social relationships and they do not need social relationships to maintain or enhance their health status.

A null hypothesis is as follows:

H_0: Changes in frailty do not moderate the relationship between changes in social relationships and changes in health outcomes in older adults.

6.3 Methods

Study population

We analyzed data from three waves of the FRéLE (Frailty: A longitudinal study of its expressions) population-based longitudinal study. The study population comprised 1643 community-dwelling older adults aged 65 and over from three areas in the province of Québec in Canada, including a metropolitan city (Montréal), an urban city (Sherbrooke), and an urban-rural area (Victoriaville). The sample was stratified by age (65–74;75– 84; 85+), sex and living areas. Twelve subgroups with an equal number of respondents were obtained. Wave 1 of the study (baseline) took place in 2010, and subsequent data were collected yearly over two longitudinal waves (2011-2012). Of the 1643 participants at baseline, 84.4% participated in the first follow-up, and 88.4% of those from the first follow-up participated in the second follow-up. Losses were either due to mortality (13% over two years) or voluntary withdrawal and inability to contact (13% over two years). The full cohort profile has been described in detail elsewhere (Béland et al., 2018; Béland et al., 2020). All FRéLE participants provided signed informed consent. The Jewish General Hospital's Research Ethics Committee granted ethical approval for the FRéLE study. The Integrated Health and Social Services University Network for West-Central Montréal Research Ethics Board (#CODIM-MBM-

17-146) and the Health Research Ethics Board of the Université de Montréal approved the ethical oversight for the present study (#17-162-CERES-D).

Predictors: Social relationships

According to Berkman's (2014) theory, we measured social relationships by social participation, social networks, and social support from different social ties, namely friends, nuclear family (i.e., children and spouse), and extended family (i.e., grandchildren and siblings). The Cronbach alpha coefficients of internal consistency for social variables are provided in Supplementary Table1.

Social participation

Social participation is a 12-item measure on a five-point scale, ranging from 1 (almost every day) to 5 (never) (Statistics Canada, 2010). The components of this scale included membership in community organizations, involvement in religious, community-based, and family activities, volunteering, playing music, painting, shopping, and going to restaurants, libraries, and sports, and recreation centers. Scores were summed, and higher scores equated to lower social participation. We reversed the score so that higher values represented a higher level of participation.

Social networks

We measured social networks with the longitudinal International Mobility in Aging Study's (IMIAS) social network scale (Ahmed et al., 2018), a validated scale among older populations. Social networks comprised a series of questions asked separately about family members, friends, and children: "How many family/friends/ living children do you have?"; "How many of them do you see at least once a month?"; "How many of them do you have a very close relationship with?"; and "How many of them do you speak to by phone at least once a month?" Social contact with a spouse was not asked due to daily contact. The items for each social tie were summed to give a related social network score. The scores ranged from 1 (never) to 5 (always), with greater scores indicating higher levels of social contact.

Social support

We used the IMIAS's social support scale (Ahmed et al., 2018) to determine social support. The following questions were asked separately about one's friends and members of one's nuclear and extended family: "Do you help your family/friends/ children/ partner from time to time?"; "Do you

feel that you are loved by them?"; "Do they listen to you when you need to talk about your problems?"; " Do you feel that you play an important role in their lives?; and "Do you feel useful to them?" The scores ranged from 1 (never) to 5 (always), with greater scores suggesting higher levels of support.

The absence of social ties

Following the methodology proposed in the previous study (Béland et al., 2005), we created binary variables, indicating the absence of social ties. We assigned a score of zero to the participants with social ties (i.e., having friends) and a score of one to the participants without social ties (i.e., having no friends). The absence of social ties is a time-invariant variable as the number of participants' social ties did not change over time. In addition, we created a continuous variable for each social network and social support variable by multiplying each continuous social variable by its related-binary variable (i.e., social networks with friends × no friends). We introduced these continuous variables along with binary variables simultaneously in the equations (Béland et al., 2005).

Moderator: Frailty

In the FRéLE study, frailty was operationalized based on Fried's (2001) frailty criteria. The frailty scale consists of five components, including exhaustion, weight loss, low physical activity, slow gait, and low grip strength. Full details about the measurement methods for each criterion of frailty have been previously described (Béland et al., 2020). Frailty refers to a clinical syndrome in the Fried (2001) frailty phenotype. Unlike the frailty phenotype, we considered frailty a marker and determinant of health outcomes based on the construct validity of frailty measurement assessed in the FRéLE study (Béland et al., 2020). Accordingly, we adopted Béland and colleagues' (2020) procedures and defined frailty as a continuous latent variable. Higher scores equated to a lower level of frailty.

Health outcomes

Cognitive health

Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), which has high reliability and internal consistency (α =0.83). Scores ranged from 0 to 30, with higher scores suggesting better cognitive performance (≥25) (Nasreddine et al., 2005).

Comorbidity

Comorbidity was measured with the Functional Comorbidity Index (FCI) which is a validated scale for predicting physical function among older adults (Groll et al., 2005). Diagnoses included 19 health problems (i.e., arthritis, asthma, heart disease, stroke, diabetes, visual and hearing impairment, obesity, cancer, etc.). Scores ranged from 1 to 19, with higher scores indicating comorbid conditions. We reversed this scale so that higher scores indicated less comorbidity.

Depressive symptoms

The 15-item Geriatric Depression Scale (GDS-15) was used to assess depressive symptoms. The scores ranged from 0 to 15, with higher scores indicating higher depressive symptoms (Sheikh & Yesavage, 1986). We reversed this scale so that higher scores indicated better mental health. The Cronbach alphas for the GDS were 0.75 in T0 and 0.78 in T1and T2.

Disability

We measured functional disability by the Katz (1963) scale of the Independence in Activities of Daily Living (ADLs) and the Lawton (1969) scale of the Instrumental ADLs. ADLs consisted of bathing and showering, grooming, dressing, eating, toileting, walking across a room, getting in/out of bed, getting up from a chair, and cutting nails. IADLs were as follows: preparing hot meals, telephoning, using transportation, shopping, doing errands, and light and heavy housekeeping, taking medications, and handling finances. A scale ranged from 0 to 9, with higher scores indicating greater functional limitations. As suggested by Spector and Fleishman (1998), we combined ADLs and IADLs items into one single scale, representing a count variable.

Covariates

The time-invariant covariates comprised sociodemographic and life habit variables associated longitudinally with frailty (Gil-Salcedo et al., 2020) and health outcomes (Kobayashi & Steptoe, 2018), including age (*65–98 years*), gender (*1= female, 0= male*), education level (*range=0-30, none-master/doctorate*), annual income (*range= 2,500– >80,000*), smoking status (*0=non-smoker, 1=former smoker, 2=current smoker*), alcohol consumption (*1=yes, 0=no*), and sleeping disturbance (*1=yes, 0=no*).

Analytic strategy

We employed a series of latent growth curve models (LGMs) in Mplus (Muthén & Muthén, 2017) to assess changes, adjusting for time-invariant covariates. The LGMs estimated two indicators for each time-variant variable, including the initial status at baseline (intercept) and the growth change (slope). We estimated the interactions in LGMs using the latent moderated structural equations (LMS) approach under the normality assumption (Wen et al., 2014). This approach minimizes the convergent problems and provides less biased estimates for coefficients and standard errors (Wen et al., 2014). In this study, the distributions of all change scores were almost normal (See Figures 1–3). As the central aim of this study was to examine longitudinal associations, the interactions of slopes (indicating change over time) of social relationships and frailty on slopes of health outcomes were of primary interest. Model building occurred in four steps. First, we regressed the slopes of changes in health outcomes on the interactions between slopes of change in frailty and that of social relationships. Second, we regressed the slope of changes in health outcomes on the interactions between the intercepts of binary indicators of social isolation and the slope of change in frailty. Third, we regressed the slopes of changes in health outcomes on the interactions between the intercepts of binary indicators of social isolation and frailty. Fourth, we regressed the intercepts of health outcomes on the interactions between the intercepts of social isolation (continuous and binary) and frailty. Of note, the interactions involving intercepts in the third and fourth steps were not the subject of our moderation hypotheses and were added as control variables. Among predicted variables, the growth rate for disability was low and unstable. Therefore, we examined the intercept of disability, not the slope.

Estimation procedures for the interaction models are prone to convergence problems (Kim et al., 2018). To minimize convergence problems, we estimated sets of starting values for residual variances and other terms from a collection of sub-models that were together approaching a saturated model (Kim et al., 2018). In addition, convergence problems increased with an increasing number of interaction terms. Accordingly, we first estimated LGMs separately for friends, nuclear family, extended family, and social participation, simultaneously entering all health outcomes into the models. Second, including both binary and continuous indicators of social isolation caused recurrent convergence problems in models involving changes. We thus considered only binary indicators of social isolation for testing the intercepts of the interaction terms except for social

participation which had no related binary indicator. We performed simple slope analyses (Bauer & Curran, 2005) for significant interactions that depict the association between changes in social isolation and health outcomes at one standard deviation (SD) below, one SD above, and at the mean value of changes in frailty. All continuous predictors and moderators were mean-centered. To test the significance of the interaction terms, we calculated p-values of the likelihood-ratio tests and compared models without and with interactions. We also used the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC), and an adjusted BIC.

We compared the log-likelihood, number of parameters, and BIC values in all LGMs. The lower the BIC value, the better the model (Muthén & Asparouhov, 2008). We estimated LGMs using the maximum likelihood estimator. The Poisson regression models were used for disability. The bootstrap procedure could not be applied in moderation analyses due to tedious computations. The estimations of interactions for social contacts with children and siblings were unstable, perhaps due to the small residual variances which were close to zero. Therefore, the findings were not reported. We handled missing data through a pattern mixture approach with the assumption of missing not at random (Muthén et al., 2011). The statistical significance level was defined at $p < .05$.

6.4 Results

Participants' Characteristics

Among 1643 participants at baseline, the average age was 78.7 years (SD= 7.9), and at least half were women (50.2%). Most of the participants were either former smokers (49%) or non-smokers (44%) and consumed alcohol (71%). More than half of the participants had no sleeping problems (58%). The averages for education and income levels ranged from (10.6 ± 4.7, 4.1 ± 1.7) at baseline to time-point 2 (10.8 ± 4.6, 4.3 ± 1.7), respectively (Supplementary Table 2). We compared participants who completed the study with those with missing values at follow-up. Those who dropped out were more likely to be women, frail, consume alcohol, and have chronic conditions and cognitive decline than those who remained in the study.

Estimates of changes

Table 1 presents descriptive statistics on estimates of the average initial status and the average growth rate of variables of interest at the population (fixed) and individual levels (random) (Muthén

& Khoo, 1998). At the population level, a variable may vary at baseline, but growth rates may or may not differ between individuals. At the individual level, baseline averages and growth rates may head toward similar or different trends. As such, high averages at baseline may be associated with downward rates of growth and low averages with upward rates of growth. At the population level, all variables varied significantly at baseline as shown by the fixed averages and standard deviations (initial status). Growth rates were positive and significant for chronic conditions and disability, indicating a selective effect, such that respondents remaining in the sample were in better physical health than those who dropped out and the deceased. However, growth rates were not significant for depressive symptoms, cognitive function, and frailty. Nonetheless, their random terms were significant, indicating changes at the individual level. Individual growth rates did not vary significantly for disability. At the population level, average growth rates for all social relationships were negative and significant except for social contact with grandchildren (positive and significant), indicating an increase in social contact with grandchildren over time. At the individual level, only growth rates for social support from friends and spouse and social contact with grandchildren were significant.

Moderating effects of changes in frailty on changes in social relationships and health

Multivariate LGMs revealed significant interactions between changes in social participation, contacts with friends, and support from different social ties and changes in frailty on changes in cognitive and mental health. No other moderation effects were observed. Visualizing these interactions, Figures 1–3 illustrate the simple slope analyses of the conditional effects of changes in social relationships on changes in mental and cognitive health across three levels of change in frailty (average changes in frailty ± 1 SD). To contextualize these changes, one standard deviation (SD) above the average change in frailty refers to older adults who experienced changes toward robustness (positive), whereas one SD below the average change in frailty refers to those with changes toward frailty (negative).

Overall, 6 out of 24 interaction terms were significant after adjustment for covariates. The results of the simple slopes analyses demonstrated that greater changes in social participation, support from friends and nuclear and extended family members, and contacts with friends were consistently and positively related to greater changes in mental and cognitive health among older adults with

negative changes in frailty (1 SD below average) compared to those with average and positive (1 SD above average) changes in frailty (See Figures 1-3). However, the slope linking changes in social relationships to changes in mental and cognitive health was almost flat or negative among older adults with positive changes in frailty. For example, as depicted in Figure 3-Panel A, changes in support from friends were positively associated with greater changes in cognitive function among individuals with negative changes in frailty (β=2.406, 95% CI: 1.894, 2.917). However, this association was not significant for older adults with gradual and positive changes in frailty (β=0.109, 95% CI: -0.343, 0.561). Another example can be seen in Figure 3-Panel B, where changes in support from children were positively associated with increasing changes in cognitive function among those with negative changes in frailty (β=2.957, 95% CI: 1.932, 3.982). However, contrary to our hypotheses, greater changes in support from children were associated with decreasing changes in cognitive function among older adults with positive changes in frailty (β= -1.322, 95% CI: -2.215, -0.429). Of note, cases with decreasing change scores on frailty had lower scores on the frailty scales at baseline than cases with increasing change scores.

The gray bars in Figures 1-3 show the distributions of cases according to changes in social relationships. The distributions are almost normal with medians located at no change and the number of cases is decreasing with greater changes. The conditional effects of changes in social relationships on changes in cognitive and mental health across changes in frailty appeared to be clustered among participants with decreasing loss of social relationships. In most cases, the interactions between changes in social relationships and frailty were significant in the extreme quartiles, indicating that the interaction effects were apparent for a few older adults. In particular, the effect size between changes in family support and changes in frailty was small.

Moderating effects of frailty on baseline social relationships

We found no interaction effects of baseline frailty and binary indicators of social relationships on baseline health outcomes, suggesting that the initial status of binary social variables was not part of the moderation terms with frailty. We found only two significant interactions involving continuous indicators of social relationships. Concordant with the second hypothesis (H_{1b}), social participation at baseline was associated with increasing changes in mental health among older adults with decreasing changes in frailty (β= 0.059, 95% CI: 0.003, 0.116). However, contrary to

our hypotheses and similar to Figure 3-Panel B, baseline social participation was associated with declining changes in mental health among older adults with increasing changes in frailty (β= -0.056, 95% CI: -0.107, -0.004) (Supplementary Figure 1). In line with the second hypothesis (H_{1b}), support from children was related to less functional limitations among frail older adults at baseline.

6.5 Discussion

The link between social relationships and health is well-established, as demonstrated through Berkman and Krishna's (2014) theory and prior studies (Holt-Lunstad et al., 2017; Holt-Lunstad et al., 2015). However, the biological explanatory mechanisms by which social relationships connect to health, such as frailty, remain unknown. Our findings extend the research on the interplay between social relationships, frailty, and health in later life in three ways. First and foremost, in line with our second hypothesis (H_{1b}), changes in frailty moderated the associations between changes in social participation, contacts with friends, and support from different social ties with changes in cognitive and mental health among older adults. The underlying assumption is that robust older adults have sufficient physiological reserves and capacity to cope with challenges related to aging, respond to health stressors, and recover or maintain health status without support from others (Whitson et al., 2016). Therefore, social connectedness provides fewer benefits for health status among robust older adults than frail peers. In this vein, the concept of physiological reserves buffers the positive impact of social relationships on health for robust older adults. However, social relationships compensate for age-related challenges among frail older adults who have low physiological reserves to overcome stressors.

Second, we examined the distinct associations between multiple aspects of social relationships with physical, mental, and cognitive health outcomes. This examination provided insight into the impacts of social relationships on various health outcomes and whether the effects of multidimensional social relationships on health differ based on frailty. The moderation results further corroborate two key points. First, changes in frailty moderated the longitudinal relationship between social relationships and mental and cognitive health, but not physical health, among older adults. Prior studies (Erin York Cornwell & Linda J. Waite, 2009; Fiordelli et al., 2020) lend support to this assumption, reporting that perceived social relationships were linked to mental health rather than physical health in later life. Second, the moderation results elucidate the

substantial role of social support from all types of social ties rather than social networks on the mental health of frail older adults. It is not thus simply the absence of social ties or frequency of social contacts – but the quality of those interactions – that has an important bearing on a person's mental health (Uchino et al., 2016). The underlying mechanism is that social support is a protective and compensatory factor against life stressors which may ameliorate vulnerability and lead to better health status among older adults with changes toward frailty, and a fundamental feature of frailty is physiological vulnerability to stressors (Peek et al., 2012). According to Berkman and Krishna's (2014) theory, such social ties may provide essential emotional or instrumental support and companionship during illness by helping a person to better cope and compensate for psychological stress and recover more quickly from an illness.

Third, the moderation findings corroborate that higher levels of social activities at baseline and increasing changes in social participation compensated for a decline in mental health among older adults with changes toward frailty over two years. This result reflects findings from a previous longitudinal study (Min et al., 2016), indicating that social gathering at baseline predicted changes in mental health among older adults over four years. This result is concerning for age-friendly initiatives that focus predominantly on healthy individuals and leave behind people with health conditions and high-risk groups such as frail older populations (Buffel et al., 2019).

This study has some limitations. We could not estimate changes in disability. We faced estimation problems for social contacts with children and siblings that limited our ability to estimate changes in these variables. We were also unable to simultaneously incorporate all social isolation variables in one model due to convergence issues. Accordingly, further analysis over a longer period would be valuable to capture changes and unveil how differently these variables could be influenced by changes in frailty. Additionally, this study cannot rule out the possibility of reverse causation. The observational design of the study precludes any inference on causality, although time-varying variables were used. Future intervention research targeting contact with family members is necessary to clarify the directionality of our findings. Attrition is another limitation in the present study, resulting in a dropout rate of 26% and more healthy individuals remaining in the sample. Despite these limitations, this study has several notable strengths. In addition to examining structural and functional aspects of social isolation, we considered whether different sources of social ties showed different patterns of association with multiple health outcomes in older age.

Another strength of this study is the population-based longitudinal follow-up design with a relatively large sample size. Additionally, we employed comprehensive and validated measurements of social relationships, frailty, and health outcomes to capture different dimensions of social relationships and health status.

In conclusion, this longitudinal study addresses one of the main components of healthy aging (World Health Organization, 2015), underlining that the beneficial impact of social support and social participation on mental health mainly appeared among frailer older adults over time. However, social connectedness has limited benefits on the health status of robust older adults. Future studies may consider other health-related risk factors (i.e., sedentary behaviors) that may impact the relationships between social relationships and physical, mental, and cognitive health outcomes among older adults. Fundamental questions remain about how public health policies may foster social programs to enhance social support and activity, targeting frail older people.

Figure 10 (Study 3. Figure 1) Relationship between changes in social participation (A) and friends' networks (B) and change in depressive symptoms as a function of change in frailty (average frailty ± 1 SD).

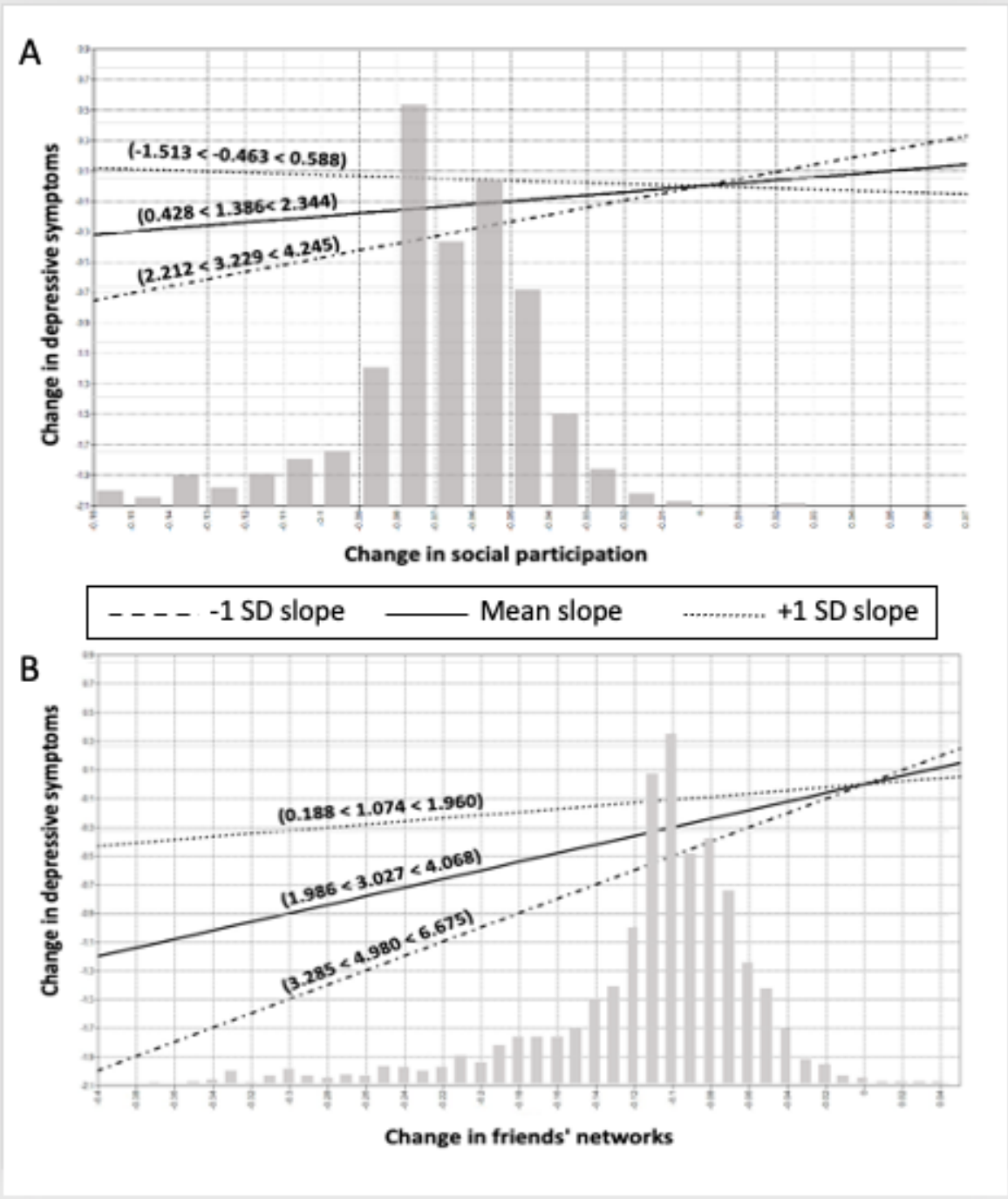
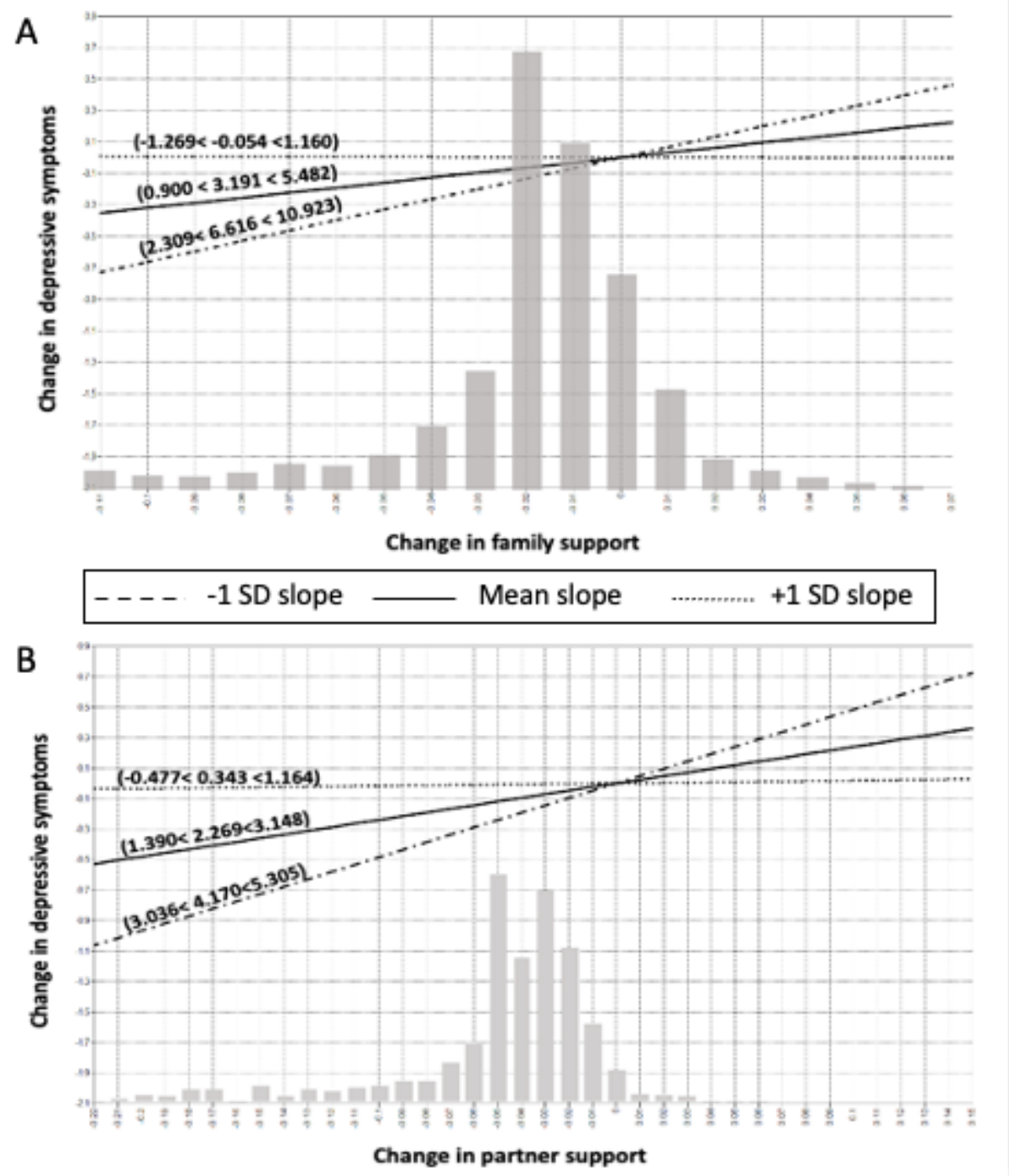


Figure 11 (Study 3. Figure 2) Relationship between changes in family (A) and partner (B) support and change in depressive symptoms as a function of change in frailty (average frailty ± 1 SD).



Note: For simplicity, random terms and covariates are not shown.

Figure 12 (Study 3. Figure 3) Relationship between changes in friends (A) and children (B) support and change in cognitive function as a function of change in frailty (average frailty ± 1 SD).

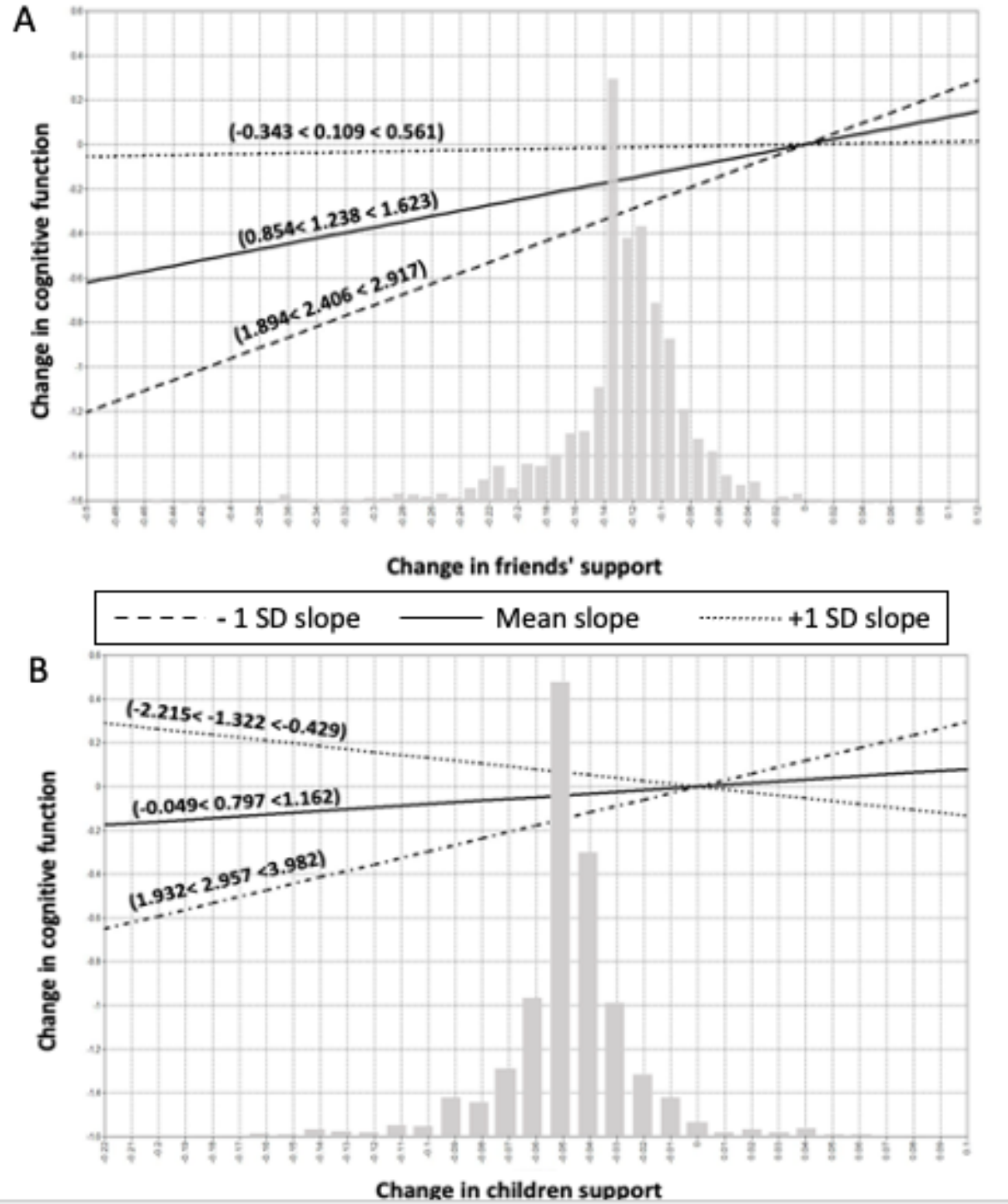


Table 9 (Study 3. Table 1) Parameters estimates from latent growth curve models

		Fixed			Random		
Health outcomes		**Coef.**	**CI<0.95**	**CI>0.95**	**Coef.**	**CI<0.95**	**CI>0.95**
Cognitive function	Average (i)	4.822***	4.773	4.867	0.669***	0.591	0.762
	Growth rate (s)	0.001	-0.016	0.019	0.033*	0.002	0.070
	i WITH s				0.054**	0.017	0.090
Depressive symptoms	Average (i)	-1.330***	-1.402	-1.264	1.408***	1.229	1.600
	Growth rate (s)	0.002	-0.027	0.031	0.171***	0.100	0.238
	i WITH s				-0.110*	-0.194	-0.032
Chronic conditions	Average (i)	-1.584***	-1.641	-1.528	0.879***	0.796	0.965
	Growth rate (s)	-0.076***	-0.096	-0.054	0.110***	0.070	0.149
	i WITH s				-0.008	-0.047	0.031
Disability	Average (i)	-0.967***	-1.107	-0.828	2.730***	2.384	3.076
	Growth rate (s)	0.226 ***	0.156	0.297	0.001	-0.002	0.004
	i WITH s				-0.045	-0.131	0.041
Moderator/mediator							
Frailty	Average (i)	0.225***	0.148	0.300	1.791***	1.657	1.910
	Growth rate (s)	0.001	-0.026	0.028	0.162***	0.106	0.208
	i WITH s				-0.005	-0.070	0.056
Predictors							
Social Participation	Average (i)	-7.022***	-7.073	-6.971	0.669***	0.607	0.737
	Growth rate (s)	-0.059***	-0.078	-0.040	0.014	-0.014	0.041
	i WITH s				-0.011	-0.042	0.019
Social Networks- Friends	Average (i)	0.921***	0.875	0.968	0.445***	0.373	0.517
	Growth rate (s)	-0.094***	-0.114	-0.073	0.010	-0.024	0.045
	i WITH s				-0.036	-0.080	0.007
Social Support- Friends	Average (i)	3.316***	3.233	3.396	2.004***	1.826	2.187
	Growth rate (s)	-0.116***	-0.147	-0.088	0.100**	0.039	0.163
	i WITH s				-0.031	-0.109	0.025
Social Networks-Children	Average (i)	1.905***	1.822	1.987	2.149***	1.962	2.373
	Growth rate (s)	-0.028***	-0.041	-0.016	0.022	-0.018	0.065
	i WITH s				-0.083***	-0.142	-0.033
Social Support-Children	Average (i)	3.566 ***	3.473	3.649	2.402***	2.215	2.617
	Growth rate (s)	-0.037***	-0.054	-0.022	0.000	-0.029	0.028
	i WITH s				-0.005	-0.036	0.026
Social Support-Partner	Average (i)	1.211***	1.148	1.274	1.212***	1.179	1.245
	Growth rate (s)	-0.040***	-0.053	-0.030	0.035***	0.019	0.049
	i WITH s				-0.036***	-0.055	-0.019
Social Networks-Grandchildren	Average (i)	1.139***	1.1077	1.201	1.115***	1.007	1.223
	Growth rate (s)	0.018**	0.005	0.032	0.037***	0.024	0.049
	i WITH s				0.029*	0.000	0.058
Social Networks-Siblings	Average (i)	1.816***	1.731	1.899	1.953***	1.782	2.144
	Growth rate (s)	-0.066***	-0.084	-0.048	0.024	-0.029	0.074
	i WITH s				-0.052	-0.111	0.006
Social Support-Family	Average (i)	3.453***	3.403	3.503	0.600***	0.506	0.701
	Growth rate (s)	-0.030**	-0.052	-0.007	0.017	-0.021	0.054
	i WITH s				-0.015	-0.058	0.027

Notes: Coef: coefficient, (i): intercept, (s): slope, "WITH" indicates covariance between intercept and slope, Number of Bootstrap Samples=5000, * p≤0.05, ** p≤0.01, *** p≤0.001, †p≤0.20. The models were unadjusted for covariates.

Table 10 (Study3. Table 2) The effects of frailty on the association between social relationships and health outcomes

	Chronic conditions slope	Cognitive function slope	Depressive symptoms slope
Interaction effects	**β [95%CI]**	**β [95%CI]**	**β [95%CI]**
Social participation (T0) × Frailty (slope)	--	--	-0.347 [-0.027, -0.112]
Social participation (slope) × Frailty (slope)	--	--	-17.577 [-21.282, -13.873]
Social networks-friends (slope) × Frailty (slope)	--	--	-15.022 [-21.666, -8.379]
Social support-friends (slope) × Frailty (slope)	--	-8.833 [-11.070, -6.596]	--
Social support-children (slope) × Frailty (slope)	--	-15.847 [-19.225, -12.469]	--
Social support-partner (slope) × Frailty (slope)	--	--	-16.639 [-20.621, -12.657]
Social support-family (slope) × Frailty (slope)	--	--	-25.657[-42.045, -9.270]

Notes: Significant associations are solely presented. Two hyphens (--) represent not-significant associations. All models were adjusted for covariates (age, gender, life habits, income, and education levels).

6.6 References

Ahmed, T., Belanger, E., Vafaei, A., Koné, G. K., Alvarado, B., Béland, F., Zunzunegui, M. V., & Group, I. R. (2018). Validation of a social networks and support measurement tool for use in international aging research: The International Mobility in Aging Study. *Journal of cross-cultural gerontology*, *33*(1), 101-120.

Bauer, D. J., & Curran, P. J. (2005). Probing interactions in fixed and multilevel regression: Inferential and graphical techniques. *Multivariate behavioral research*, *40*(3), 373-400.

Béland, F., Julien, D., Bier, N., Desrosiers, J., Kergoat, M.-J., & Demers, L. (2018). Association between cognitive function and life-space mobility in older adults: results from the FRéLE longitudinal study. *BMC geriatrics*, *18*(1), 1-15.

Béland, F., Julien, D., Wolfson, C., Bergman, H., Gaudreau, P., Galand, C., Fletcher, J., Zunzunegui, M.-V., Shatenstein, B., & Kergoat, M.-J. (2020). Revisiting the hypothesis of syndromic frailty: a cross-sectional study of the structural validity of the frailty phenotype. *BMC geriatrics*, *20*(1), 1-13.

Béland, F., Zunzunegui, M.-V., Alvarado, B., Otero, A., & Del Ser, T. (2005). Trajectories of cognitive decline and social relations. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *60*(6), P320-P330.

Berkman, L. F., & Krishna, A. . (2014). Social Network Epidemiology. In L. F. K. Berkman, I. & Glymour, M. M. (Ed.), *Social Epidemiology (2 ed.)* (pp. 234-289). Oxford University Press.

Buffel, T., Phillipson, C., & Rémillard-Boilard, S. (2019). Age-Friendly cities and communities: New directions for research and policy. *Encyclopedia of Gerontology and Population Aging; Gu, D., Dupre, ME, Eds*, 1-11.

Cacioppo, J. T., & Hawkley, L. C. (2003). Social isolation and health, with an emphasis on underlying mechanisms. *Perspectives in biology and medicine*, *46*(3), S39-S52.

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *The Lancet*, *381*(9868), 752-762.

Cornwell, E. Y., & Waite, L. J. (2009). Social disconnectedness, perceived isolation, and health among older adults. *Journal of health and social behavior*, *50*(1), 31-48.

Evans, I. E., Martyr, A., Collins, R., Brayne, C., & Clare, L. (2019). Social isolation and cognitive function in later life: A systematic review and meta-analysis. *Journal of Alzheimer's disease*, *70*(s1), S119-S144.

Fan, L., Wang, S., Xue, H., Ding, Y., Wang, J., Tian, Y., & Du, W. (2021). Social Support and Mortality in Community-Dwelling Chinese Older Adults: The Mediating Role of Frailty. *Risk Management and Healthcare Policy*, *14*, 1583.

Fiordelli, M., Sak, G., Guggiari, B., Schulz, P. J., & Petrocchi, S. (2020). Differentiating objective and subjective dimensions of social isolation and apprasing their relations with physical and mental health in italian older adults. *BMC geriatrics*, *20*(1), 1-13.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., & Burke, G. (2001). Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(3), M146-M157.

Gil-Salcedo, A., Dugravot, A., Fayosse, A., Dumurgier, J., Bouillon, K., Schnitzler, A., Kivimäki, M., Singh-Manoux, A., & Sabia, S. (2020). Healthy behaviors at age 50 years and frailty at older ages in a 20-year follow-up of the UK Whitehall II cohort: A longitudinal study. *PLoS medicine*, *17*(7), e1003147.

Groll, D. L., To, T., Bombardier, C., & Wright, J. G. (2005). The development of a comorbidity index with physical function as the outcome. *Journal of clinical epidemiology*, *58*(6), 595-602.

Holt-Lunstad, J., Robles, T. F., & Sbarra, D. A. (2017). Advancing social connection as a public health priority in the United States. *American Psychologist*, *72*(6), 517.

Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T., & Stephenson, D. (2015). Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspectives on psychological science*, *10*(2), 227-237.

Holt-Lunstad, J., & Steptoe, A. (2021). Social Isolation: An Underappreciated Determinant of Physical Health. *Current Opinion in Psychology*.

Hoogendijk, E. O., Smit, A. P., van Dam, C., Schuster, N. A., de Breij, S., Holwerda, T. J., Huisman, M., Dent, E., & Andrew, M. K. (2020). Frailty combined with loneliness or social isolation: an elevated risk for mortality in later life. *Journal of the American Geriatrics Society*, *68*(11), 2587-2593.

Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *Jama*, *185*(12), 914-919.

Kim, M., Hsu, H.-Y., Kwok, O.-m., & Seo, S. (2018). The optimal starting model to search for the accurate growth trajectory in Latent Growth Models. *Frontiers in psychology*, *9*, 349.

Kobayashi, L. C., & Steptoe, A. (2018). Social isolation, loneliness, and health behaviors at older ages: longitudinal cohort study. *Annals of Behavioral Medicine*, *52*(7), 582-593.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *The gerontologist*, *9*(3_Part_1), 179-186.

Malini, F. M., Lourenço, R. A., & Lopes, C. S. (2016). Prevalence of fear of falling in older adults, and its associations with clinical, functional and psychosocial factors: The Frailty in Brazilian Older People-Rio de Janeiro Study. *Geriatrics & gerontology international*, *16*(3), 336-344.

Mehrabi, F., & Béland, F. (2020). Effects of social isolation, loneliness and frailty on health outcomes and their possible mediators and moderators in community-dwelling older adults: A scoping review. *Archives of Gerontology and Geriatrics*, 104119. https://doi.org/10.1016/j.archger.2020.104119

Min, J., Ailshire, J., & Crimmins, E. M. (2016). Social engagement and depressive symptoms: do baseline depression status and type of social activities make a difference? *Age and Ageing*, *45*(6), 838-843.

Muthén, B., & Asparouhov, T. (2008). Growth mixture modeling: Analysis with non-Gaussian random effects. *Longitudinal data analysis*, *143165*.

Muthén, B., Asparouhov, T., Hunter, A. M., & Leuchter, A. F. (2011). Growth modeling with nonignorable dropout: alternative analyses of the STAR* D antidepressant trial. *Psychological methods*, *16*(1), 17.

Muthén, B. O., & Khoo, S.-T. (1998). Longitudinal studies of achievement growth using latent variable modeling. *Learning and individual differences*, *10*(2), 73-101.

Muthén, L. K., & Muthén, B. (2017). *Mplus user's guide: Statistical analysis with latent variables, user's guide*. Muthén & Muthén.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699.

Peek, M. K., Howrey, B. T., Ternent, R. S., Ray, L. A., & Ottenbacher, K. J. (2012). Social support, stressors, and frailty among older Mexican American adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *67*(6), 755-764.

Rafnsson, S. B., Maharani, A., & Tampubolon, G. (2022). Social contact mode and 15-year episodic memory trajectories in older adults with and without hearing loss: findings from the English longitudinal study of ageing. *The Journals of Gerontology: Series B*, *77*(1), 10-17.

Risbridger, S., Walker, R., Gray, W., Kamaruzzaman, S., Ai-Vyrn, C., Hairi, N., Khoo, P., & Pin, T. (2021). Social Participation's Association with Falls and Frailty in Malaysia: A Cross-Sectional Study. *The Journal of frailty & aging*, 1-7.

Santini, Z. I., Fiori, K. L., Feeney, J., Tyrovolas, S., Haro, J. M., & Koyanagi, A. (2016). Social relationships, loneliness, and mental health among older men and women in Ireland: A prospective community-based study. *Journal of affective disorders*, *204*, 59-69.

Sharifian, N., Kraal, A. Z., Zaheed, A. B., Sol, K., & Zahodne, L. B. (2020). Longitudinal associations between contact frequency with friends and with family, activity engagement, and cognitive functioning. *Journal of the International Neuropsychological Society*, *26*(8), 815-824.

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*.

Smith, L., Firth, J., Grabovac, I., Koyanagi, A., Veronese, N., Stubbs, B., Soysal, P., Yang, L., & Jackson, S. E. (2019). The association of grip strength with depressive symptoms and cortisol in hair: A cross-sectional study of older adults. *Scandinavian journal of medicine & science in sports*, *29*(10), 1604-1609.

Spector, W. D., & Fleishman, J. A. (1998). Combining activities of daily living with instrumental activities of daily living to measure functional disability. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *53*(1), S46-S57.

Statistics Canada. (2010). Canadian Community Health Survey (CCHS)-Healthy Aging questionnaire (2008-2009). 117-120. (Statistics Canada)

Uchino, B., Ong, A., Queen, T., & Kent de Grey, R. (2016). Theories of social support in health and aging. *Handbook of theories of aging (3rd. ed.). New York, NY: Springer*.

Wen, Z., Marsh, H. W., Hau, K.-T., Wu, Y., Liu, H., & Morin, A. J. (2014). Interaction effects in latent growth models: Evaluation of alternative estimation approaches. *Structural Equation Modeling: A Multidisciplinary Journal*, *21*(3), 361-374.

Whitson, H. E., Duan-Porter, W., Schmader, K. E., Morey, M. C., Cohen, H. J., & Colón-Emeric, C. S. (2016). Physical resilience in older adults: systematic review and development of an emerging construct. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *71*(4), 489-495.

World Health Organization. (2015). *World report on ageing and health* (9241565047).

Wu, A. D., & Zumbo, B. D. (2008). Understanding and using mediators and moderators. *Social Indicators Research*, *87*(3), 367-392.

Yu, B., Steptoe, A., Chen, Y., & Jia, X. (2020). Social isolation, rather than loneliness, is associated with cognitive decline in older adults: the China Health and Retirement Longitudinal Study. *Psychological medicine*, 1-8.

Zhang, X., Sun, M., Liu, S., Leung, C. H., Pang, L., Popat, U. R., Champlin, R., Holmes, H. M., Valero, V., & Dinney, C. P. (2018). Risk factors for falls in older patients with cancer. *BMJ supportive & palliative care*, *8*(1), 34-37.

6.7 Supplementary files

Table 1. Cronbach alpha internal consistency estimates for social variables in three waves

Variables	T0	T1	T2
Social participation	0.69	0.67	0.66
Social networks			
Friends	0.70	0.80	0.75
Children	0.87	0.90	0.88
Siblings	0.75	0.79	0.79
Grandchildren	0.74	0.71	0.71
Social support			
Friends	0.72	0.67	0.65
Children	0.72	0.71	0.72
Family	0.70	0.73	0.72
Partner /Spouse	0.73	0.74	0.74

Table 2. Characteristics of the participants in three waves

Variables	Baseline (n=1643)	Time-point 1 (n=1386)	Time-point 2 (n=1224)
Covariates			
Age (years), mean ± SD	78.7 ±7.9	78.1±7.8	77.6±7.6
Gender (%)			
Male	49.8	49.1	48.1
Female	50.2	50.9	51.9
Income, mean ± SD	4.1 ± 1.7	4.2±1.7	4.3±1.7
Education (years), mean ± SD	10.6 ±4.7	10.7 ±4.7	10.8 ±4.6
Smoking status (%)			
Current smoker	7.4	6.9	6.5
Former smoker	48.5	49.6	49.4
Non-smoker	44.1	43.5	44.1
Alcohol consumption (%)			
Yes	71	71.1	71.8
No	29	28.9	28.2
Sleeping disturbance (%)			
Yes	41	40.6	41.4
No	58.8	59.4	58.6
Predictors			
Social participation, mean ± SD	42.8 ± 5.7	42.8±5.5	42.8±5.4
Friends			
Social Network, mean ± SD	18 ± 16.6	15.6±15	15.2±15.3
Social Support, mean ± SD	16.1 ± 7.5	15.3±8.1	15.5±8.1
No friends (%)	14.8	14.1	14.1
Nuclear family			
Social Network-children, mean ± SD	9.6 ± 7.4	9.3±7.1	9.2±6.8
Social Support-children, mean ± SD	17.5 ± 8	17.3±8	17.5±7.9
Social Support-partner, mean ± SD	11.9 ± 11.1	11.5±11	11.2±11
No children (%)	14.7	14.6	14
No partner (%)	45.5	46.2	46.7
Extended family			
Social Network-Grandchildren, mean ± SD	11.3 ± 11	12±12.1	11.7±11.5
Social Network- siblings, mean ± SD	8.5 ±7.4	8.5±7.2	8.3±7.1
Social support -family, mean ± SD	17.1 ± 4.7	16.9±4.7	17±4.6
No grandchildren (%)	22.2	21.8	21.6
No siblings (%)	13	13.2	13.4
Moderator/mediator			
Frailty, mean ± SD	20±8.6	21.4±9.1	21.2±9.3
Health outcomes			
Disability, mean ± SD	1.6±6.8	1.7±7.5	1.8±8.4
Depressive symptoms, mean ± SD	2.8±2.6	2.8±2.7	2.6±2.6
Comorbidity, mean ± SD	3.1±1.9	3.3±2.3	3.4±2.3
Cognitive function, mean ± SD	23.4±4.6	23.9±4.8	24±5.1
Missing, %	0	15.6	25.5

Notes: SD = Standard deviation, n=Total number.

Table 3. Minimum and maximum values of variables in three waves

	T0		T1		T2	
Predictors	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Social participation	22	55	23	55	25	55
Friends						
Social networks	0	70	0	60	0	70
Social support	0	25	0	25	0	25
Nuclear family						
Social setworks-children	0	38	0	36	0	30
Social support-children	0	25	0	25	0	25
Social support-partner	0	25	0	25	0	25
Extended family						
Social networks-grandchildren	0	50	0	62	0	56
Social networks- siblings	0	34	0	36	0	34
Social support-family	0	25	0	25	0	25
Moderator/mediator						
Frailty	0	34	0	36	0	39
Outcomes						
Disability	0	9	0	9	0	9
Depression	0	13	0	14	0	15
Comorbidity	0	7	0	13	0	12
Cognitive function	0	30	0	30	0	30

Notes: Due to the large variances, we rescaled the scores by dividing them by a constant of such size that their variances fall between one and ten after rescaling (Muthén & Muthén, 2017). We divided each score in Mplus as follows: Social support and cognitive decline/5; frailty/6; social network-siblings and children/5; social networks-grandchildren/10; social networks-friends/20; social participation/6; depression and chronic diseases/2.

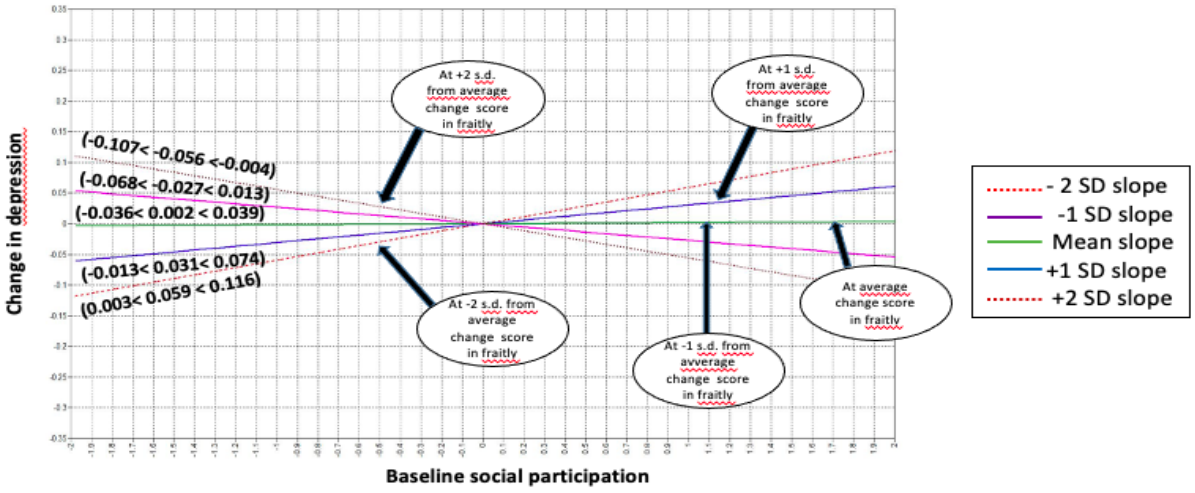


Figure 1. Relationship between baseline social participation and change in depressive symptoms as a function of change in frailty (mean slope ± 1 SD).

Chapter 7 – Discussion

"No one should be alone in old age, he thought, but it is unavoidable."

--The Old Man and the Sea, Ernest Hemingway

Globally, there are growing public health concerns about rates and health-related consequences of social isolation, which have been more salient during the coronavirus disease 2019 (COVID-19) pandemic, especially among older adults (Berg-Weger & Morley, 2020). To address this public health concern, the overall aim of this dissertation was to enhance our understanding of the role of frailty in the relationships between social isolation and health outcomes among community-dwelling older adults. To achieve this aim, we first conducted a scoping review on the interrelationships between structural and functional aspects of social isolation, physical frailty, and health outcomes and their possible moderators and mediators (Study 1- Chapter 4). To address the scientific gaps identified in this review, we explored cross-sectionally the moderating role of frailty on the relationships between social isolation and health outcomes (Study 2 - Chapter 5). For the first time, we analyzed whether frailty moderated the link between social relationships and health outcomes over time, using the three waves of the FRéLE study (Study 3 - Chapter 6). In this final chapter, I first recapitulate the main findings of each study and how these findings are related (7.1). I then present the dissertation's contributions to the research evidence supported by scientific literature from the gerontology and public health fields (7.2), followed by reflections on the study's strengths and limitations (7.3). Lastly, beyond the academic literature, I identify opportunities for building on the gaps with future recommendations for research (7.4) and conclude the chapter (7.5).

7.1 Synthesis of results

Taking each of the objectives, I summarize the key messages from each study in the three sections below.

7.1.1 Scoping review

The scoping review (Study 1) focused on the evidence examining the relationship between social isolation, frailty, and health outcomes and their possible moderators and mediators. Overall, the

evidence in the existing literature highlights several important points: First, the current evidence demonstrated that social isolation is linked to frailty in more than half of the studies. Second, the evidence on the interrelationship between social isolation, frailty, and health outcomes is at an early stage. The current evidence on this interrelationship illustrated that frailty is strongly linked to poor health outcomes; however, few studies found an association between social isolation and adverse health outcomes. Third, the evidence suggested social support (functional aspect) had a more significant association with health outcomes than social networks and social participation (structural aspect). This finding highlights the importance of the quality of relationships rather than the quantity and frequency of interactions in older age. Regarding the knowledge gaps, longitudinal studies on the interplay between social isolation, frailty, and health outcomes are particularly scarce. No research has looked at mental health outcomes and chronic diseases. Yet, their absence is striking. None of the current research studies has explicitly examined the longitudinal moderating role of frailty on the relationship between multidimensional aspects of social isolation and health outcomes. Of importance, no study has focused on different types of social ties such as friends, children, and extended family on frailty and health outcomes. This dissertation notably adds to the current knowledge by addressing these gaps in studies 2 and 3.

7.1.2 Cross-sectional study

The objectives of the cross-sectional study (Study 2) were to examine the relationships between social isolation, frailty, and health outcomes and whether the relationship between social isolation and health outcomes varied based on frailty status among community-dwelling older adults in Québec. In line with the results of the scoping review, the cross-sectional results revealed several key findings. First, frailty was a strong predictor of physical, mental, and cognitive health outcomes. Second, social support rather than social networks was associated with health outcomes. Third, frail older adults who received social support from friends, participated in social activities, and had friends and siblings were in better mental and cognitive health than robust peers. Taken together, the key message is that social isolation, particularly social support, is linked to mental and cognitive health rather than physical health among frail older adults. Furthermore, these results notably underscore the importance of intimate and kin relationships on mental and cognitive health in later life.

7.1.3 Longitudinal study

The purpose of the longitudinal study (Study 3) was to examine the moderating role of changes in frailty on the relationship between changes in social relationships and changes in health outcomes among older adults in Québec. The results revealed that changes in frailty moderated the associations between changes in social participation, contacts with friends, and support from different types of social ties with changes in cognitive and mental health but not physical health among older adults. Most importantly, the results suggest that increased changes in social relationships are related to improving mental and cognitive health among older adults experiencing changes in frailty status. In this vein, these results highlight the beneficial and compensatory role of social relationships on mental and cognitive health among this group. However, there are no such relationships for older adults who have a stable level of frailty or a lower level of frailty. In line with the scoping review and cross-sectional study, the longitudinal results highlight the key role of social support rather than social networks on mental and cognitive health among frail older adults over two years.

7.2 Contributions to gerontology and public health fields

The present dissertation addresses current knowledge gaps in the scientific literature and contributes to gerontology and public health literature by extending the limited evidence on the relationships between structural and functional aspects of social isolation, physical frailty, and physical, mental, and cognitive health outcomes. According to House (2001) and Holt-Lunstad (2010), the magnitude of risk associated with social isolation is comparable with the effects of smoking, obesity, and other important biomedical and psychosocial risk factors on health. However, our understanding of whether the impact of social isolation on health differs in certain groups of older adults remains limited. Conversely, our current understanding is limited regarding whether the protective effects of social relationships on health differ in some groups of older adults. These questions were central to the purpose of this dissertation. A question of critical importance is what are the mechanisms by which social relationships influence health outcomes in different groups of older adults? A mechanism of particular importance is the biological pathway linking social relationships to health outcomes (Berkman, 2014; Holt-Lunstad et al., 2015; National Academies of Sciences & Medicine, 2020; Uchino, 2006). Frailty as a determinant of health status

represents the clinical expression of the accumulations of biological deficits and dysfunctions that occur with the physiologic processes of aging (Fried et al., 2001). Although the scholarly literature on social relationships and health outcomes is growing, earlier studies did not examine the role of biological factors such as frailty. In an attempt to answer these questions, this research study is the first to examine the role of frailty in the association between multidimensional aspects of social isolation and health outcomes among community-dwelling older adults. A plausible hypothesis to explain this effect is that social isolation is a stressful and anxious condition that can lead to serious health outcomes and ultimately mortality. The process is similar to frailty, which refers to a state of decreased physiological reserves and resistance to stressors, causing vulnerability to poor health outcomes (Fried et al., 2001). Relatedly, the impact of social isolation on health may differ among frail older adults who have low physiological reserves compared to robust peers with a high level of physiological reserves. So far, it is unclear whether the impacts of social isolation or social relationships on health vary on measures of physiological conditions. This dissertation contributes importantly to increasing such understanding by focusing on the physiological characteristics of frailty.

7.2.1. Compensating role of social relationships

The most notable findings of this dissertation are that both cross-sectional and longitudinal results supported our moderation hypotheses (Studies 2 and 3). The results suggest the protective effects of social relationships on health remarkably appear among frail older adults compared to robust peers. In line with this idea, Brummett et al. (2001) and Putnam (2000) found that the lack of social relationships is linked to poor health; however, once the deficiency of social relationships is eliminated, additional social relationships have no substantial effect on health. This indicates that meaningful social relationships with at least one or a few other individuals might be protective against illness. Based on this view, robust older adults have sufficient physiological reserves to cope effectively with stressors, negative events, and difficulties and recover or maintain health status without social support from family members and others (Tugade & Fredrickson, 2004). However, social relationships have a compensation role for frail older adults with declined physiological reserves. With social relationships, frail older adults may compensate for their loss of functional capacity. This idea is also in line with Berkman's theory that social relationships with ties provide essential social support during illness by helping a person cope with stressful

experiences and recover from an illness (Berkman & Glass, 2000). This may be the reason why the extent of the benefit of social relationships on health is more pronounced among frail older adults than robust peers. This dissertation contributes to the current literature by highlighting the protective and compensatory role of social relationships against poor health outcomes among frail older populations, but not robust ones.

7.2.2 Social relationships and health outcomes

Another important contribution of this dissertation is that we examined the relationships between different types of social ties with mental, physical, and cognitive health outcomes. This examination is especially useful in developing our understanding of whether the impacts of social relationships on various health outcomes or the effects of different sources of social ties on health differ based on the frailty status of older adults. As such, our contribution is twofold. The first is that both cross-sectional and longitudinal moderation results suggest that social relationships, in general, are more linked to mental health rather than physical health among frail older adults. Among social variables, social participation is more related to mental health. The second is that the impact of certain types of social ties on health may vary based on frailty. Our findings suggest that friendship ties rather than other types of social ties may protect against mental and cognitive health among frail older adults (see Table 11).

The first fold of the contribution is that both cross-sectional and longitudinal moderation results suggest the link between social relationships and mental health among frail older adults. In particular, we found no moderation effects of frailty on the relationship between social relationships and chronic conditions. There is a scientific consensus that strong interpersonal social interactions are especially important for a person's mental health (Almedom & Glandon, 2008; Bassett & Moore, 2013; De Silva et al., 2005; Rohde et al., 2016; Smith & Victor, 2019).

Table 11 The cross-sectional and longitudinal interactions between social relationship and frailty on health outcomes at baseline and over time

Interactions	Disability	Chronic conditions	Depressive symptoms		Cognitive function	
	T0	T0 & slope	T0	slope	T0	Slope
Social participation						
Social participation (T0) × Frailty (T0)	--	--	✓	--	--	--
Social participation (T0) × Frailty (slope)	--	--	--	✓	--	--
Social participation (slope) × Frailty (slope)	--	--	--	✓	--	--
Friends						
Social support (T0) × Frailty (T0)	--	--	--	--	✓	--
Social support (slope) × Frailty (slope)	--	--	--	--	--	✓
Social networks (slope) × Frailty (slope)	--	--	--	✓	--	--
No Friends × Frailty (T0)	--	--	--	--	✓	--
Nuclear family						
Children						
Social network× Frailty	--	--	--	--	--	--
Social support (T0) × Frailty (T0)	✓	--	--	--	--	--
Social support (slope)× Frailty (slope)	--	--	--	--	--	✓
No children × Frailty	--	--	--	--	--	--
Partner						
Social support (slope) × Frailty (slope)	--	--	--	✓	--	--
No partner × Frailty	--	--	--	--	--	--
Extended family						
Social networks-grandchildren × Frailty	--	--	--	--	--	--
Social networks-siblings × Frailty	--	--	--		--	--
Social support-family (slope)× Frailty (slope)	--	--	--	✓	--	--
No grandchildren× Frailty	--	--	--	--	--	--
No siblings × Frailty (T0)	✓	--	--	--	--	--

Note: Tick symbol shows the significant interactions (Studies 2 and 3). Non-significant associations are indicated by two hyphens [--].

The underlying mechanism can be explained by the concept of physiological reserves that can provide a buffer against stress. Older adults with a good reserve can usually withstand illness. However, older adults with diminished physiological reserves are at greater risk of lengthier or incomplete recovery and consequently need social interactions and emotional support to overcome stressful conditions and recover or maintain their health status. In accordance with our findings, the results of a randomized clinical trial in England (Iliffe et al., 2007) demonstrated that social isolation is more linked to depressive symptoms and cognitive decline than chronic diseases and disability. Likewise, a cross-sectional study from Italy (Fiordelli et al., 2020) examined the impact of objective and subjective social isolation on physical and mental health among older adults. The results have shown that objective and subjective aspects of social isolation were not directly associated with physical health. However, there was a strong relationship between perceived social isolation and depressive symptoms. Cornwell and Waite (2009) reached a similar conclusion in

their study. Their results indicated that perceived social isolation was strongly linked to mental health rather than physical health.

The results of a systematic review of forty systematic reviews and meta-analyses illustrated that social isolation is strongly linked to mortality and cardiovascular diseases, followed by mental health. However, there is less evidence for other physical health conditions, and no systematic reviews looked at physiological mechanisms by which social isolation may influence health outcomes (Leigh-Hunt et al., 2017). This dissertation extends the prior research by examining the role of frailty on the relationships between social isolation and health outcomes. In an intriguing review, Courtin and Knapp (2017) demonstrated that 3 studies out of 121 included studies investigated the association between social isolation and depression, using a unidimensional aspect of social isolation (social networks). Only one study reported an association between social networks and depressive symptoms in old adults. This review also highlighted that few studies (5/121) looked at cognitive health as a health outcome (Courtin & Knapp, 2017). In line with our scoping review (Study 1), these systematic and scoping reviews highlight the dearth of evidence regarding the impact of social isolation on depressive symptoms and chronic conditions (Courtin & Knapp, 2017; Leigh-Hunt et al., 2017; Mehrabi & Béland, 2020). This dissertation contributes to the prior research studies by addressing this dearth in cross-sectional and longitudinal studies (Studies 2 and 3), examining both chronic conditions and depressive symptoms.

7.2.2.1 Social participation and mental health

Our moderation results further demonstrated that among social variables, social participation was more beneficial for the mental health of frail older adults. Our findings corroborate and extend previous studies by demonstrating that both baseline and greater changes in social participation were related to increased mental health at baseline and over time among frail older adults. To the best of our knowledge, no studies examined the moderating role of frailty on the linkage between social relationships/isolation and health outcomes. However, our results are consistent with expectations from studies examining both predictors (social isolation and frailty) individually (Hayes, 2017). In line with the concept of age-friendly cities (World Health Organization, 2007), several cross-sectional and longitudinal studies have shown the linkage between less participation in social activities (Chiao et al., 2011; Guo et al., 2018; Wang et al., 2020) and frailty (Collard et

al., 2015; Feng et al., 2014; Makizako et al., 2015) with depressive symptoms in older age. These results are consistent with observations in a previous longitudinal study (Min et al., 2016), indicating that higher levels of social activities at baseline were linked to increasing changes in mental health in four years among older adults. Although age-friendly initiatives aim to optimize social participation and increase the quality of life for older adults, these initiatives are mostly focused on healthy individuals, whereas the needs of underrepresented and vulnerable populations with certain health conditions such as frail older adults are often overlooked (Buffel et al., 2019; Zhang et al., 2019). There is strong evidence that social isolation is modifiable (Holt-Lunstad et al., 2017) and frailty at an early stage is reversible (Hoogendijk et al., 2019; Landi et al., 2017; Martin, 2017). Hence, our moderation results call for changes in age-friendly policies to create an inclusive society, targeting frail older populations in age-friendly initiatives.

7.2.2.2 Friendship and health

The second fold of this thesis contribution is that, as shown in Table 11, the impact of different sources of social ties on health varied based on the frailty status. Our findings suggest that some ties and the dynamic interchange between them may protect against adverse health outcomes more than other types of social ties. Among social ties, friendship ties seem to have a more compensating role for frail older adults than kin and intimate relationships. As such, the cross-sectional and longitudinal moderation results suggest that increased levels of social support from friends at baseline and over time were related to increasing cognitive functioning at baseline and in two years among frail older adults. Additionally, increasing changes in social contact with friends were linked to increasing changes in mental health among frail older adults in two years. In other words, these results point to the beneficial effect of connection with friends (structural aspect) on mental health, and the protective effect of perceived support from friends (functional aspect) on cognitive health. These results cohere with the previous studies on the linkage between friendship and cognitive performance (Ihle et al., 2018; Sharifian et al., 2020) and mental health (Fiori et al., 2006; Fiori et al., 2020). Another cross-sectional study replicated these results, concluding that having close friends was related to better cognitive performance in older age (Ihle et al., 2018). A longitudinal study reported that more social contact with friends but not with family members might promote cognitive health among older adults (Sharifian et al., 2020). A systematic review highlighted the protective effect of spousal support, followed by friends against depressive symptoms among older

adults. However, the link between social support from children and family members and mental health was less consistent and weak among studies (Gariepy et al., 2016). Previous research has also shown that frailty could lead to cognitive decline (Chou et al., 2019; Hoogendijk, Rijnhart, et al., 2020) and depressive symptoms (Han et al., 2019; Smith et al., 2019) among older adults. Likewise, the evidence of several systematic reviews, including 29 prospective studies (Chu et al., 2021) and 31 prospective studies (Vermeiren et al., 2016), has shown that frail older adults had a higher risk of poor health outcomes. According to our scoping review, there is no evidence of the relationships between different types of social ties, frailty, and health outcomes (Mehrabi & Béland, 2020). Although friendship has been examined for a century (Monroe, 1898), less attention has been paid to friendships in older adults and their relationship with health outcomes (Holt-Lunstad, 2017). Additionally, empirical evidence on the effect of friendship on frailty is sparse and inconsistent (Mehrabi & Béland, 2020). The relationship between frailty and comorbidity is also poorly investigated (Bergman et al., 2007). Of importance, this dissertation addresses notably these knowledge gaps (Studies 2 and 3) by specifying the specific nature of the relationship type, though there is still a need to further explore this relationship in future studies due to the inconsistency in research studies. Based upon Berkman's theory (2014), the discrepancies in results may be due to the social and cultural contexts. It is also plausible that the design of the studies and the type of measurements result in inconsistency across studies. Furthermore, the nature of these relationships may vary based on potential risk factors related to social isolation and frailty, including gender, ethnicity, socioeconomic status, and life habits such as smoking, dietary pattern, alcohol consumption, and sleeping patterns (Li & Hsu, 2015; Poli et al., 2017; Shankar et al., 2011). In this dissertation, we controlled for most of these risk factors; however, further research is needed in this area to determine the potential particular pathways by which friendships influence health.

7.2.3 Functional versus structural features

Social relationships—both quantity and quality—affect mental, cognitive, and physical health and mortality risk (Umberson & Karas Montez, 2010). Past work has identified a wide range of indicators of social isolation that pose health risks, including living alone, small social networks, perceived lack of social support, and infrequent participation in social activities (Cornwell et al., 2008; Erin York Cornwell & Linda J Waite, 2009; Grenade & Boldy, 2008). Multiple aspects of social isolation are rarely studied together, making it difficult to determine which aspects of social

isolation are more or less consequential for health and well-being in later life. Prior research studies that have relied on a single aspect of social isolation may have missed these conceptual distinctions and their unique consequences. Studying simultaneously structural and functional aspects of social isolation allowed us to clarify their distinct associations with health outcomes, highlighting that the perceptions of social relationships may be particularly important. This approach was an advancement in rigor utilized in this dissertation.

In accordance with our scoping review, both cross-sectional and longitudinal moderation results revealed that social support at baseline and over time, rather than social networks, was linked to better health outcomes at baseline and over time among frail older adults (see Table 11). In this view, meaningful and strong social ties rather than regular interaction with a spouse, children, relatives, and friends appear to extend health benefits (House, 2001; Seeman, 1996). This indicates that adding relationships to a social network does not increase health outcomes. What may matter is not the quantity but rather the quality of relationships (Bruhn, 2009). These results are certainly reasonable and consistent with existing evidence (Bruhn, 2009; House, 2001; Putnam, 2000) along with Berkman and Krishna's (2014) theory that the supportiveness of social relationships and the provision of various kinds of emotional and instrumental support could explain the beneficial impact of social relationships on health. There is some evidence to lend support to this assumption. Two studies, using the Baltimore Epidemiologic Catchment Area Cohort, demonstrated that social support from friends and relatives rather than social networks was associated with increased mental health (Maulik et al., 2010, 2011).

As per Berkman and Krishna's (2014) theory, social relationships, or lack thereof, may impact health outcomes by alteration in immune response. The substantial research evidence points out the importance of the quality of social relationships in influencing immune response. In particular, research has shown that social support plays an important role in physiological processes (Uchino, 2006). Poor quality of social relationships has been associated with inflammatory biomarkers and impaired immune function, factors associated with poor health outcomes and mortality. There is some evidence that among different types of support, emotional support is the strongest stress buffer (Mattie et al., 2018). Given that frailty reflects age-related physiological vulnerability to stressors, the concept of physiological processes may help to explain the link between social support from different ties and mental health. The explanation lies in the fact that social support

may enhance health outcomes among frail older adults by reducing the impact of stress. More fundamentally, supportive social ties may promote a sense of meaning and purpose in life and may trigger physiological sequelae (i.e., lowering stress hormones and blood pressure) that benefit health outcomes and enhance physiological processes. Social support may thus reduce physiological responses to internal and external stressors in frail older adults (Peek et al., 2012; Umberson & Karas Montez, 2010).

Although social ties have the potential to benefit health, health policy efforts must recognize that the link between social relationships and health may vary across social groups and different population subgroups. For example, gender, race, immigration status, disability, and age are associated with different levels and types of responsibilities, strains, and resources in social ties that consequently impact health outcomes (Caetano et al., 2013; Stewart et al., 2008; Umberson & Karas Montez, 2010). As such, this dissertation is among the rare studies that examine the link between social relationships and health among at-risk populations. Of importance, frail populations are at greater risk for illness and disease than others, and these vulnerable groups should receive higher priority in public health policy efforts.

7.3 Strengths and limitations

This dissertation has several notable strengths. The key strength of this dissertation is its grounding in systematic methods to address crucial public health issues. In this vein, we first identified knowledge gaps in the scoping review (Study 1). Based on this extensive review of the current evidence in the literature, we subsequently investigated the role of frailty in the relationship between social isolation and health cross-sectionally (Study 2) and longitudinally (Study 3). Accordingly, this research is the first longitudinal study to examine the moderating role of physical frailty on the relationship between social relationships and physical, mental, and cognitive health over time. Second, this research used the multidimensional measure of social isolation across different types of social ties. Studying social networks, social support, and social participation allowed us to clarify their distinct association with frailty and adverse health outcomes. Beyond that, we considered the impact of social relationships with different sources of social ties on health outcomes which allowed us to develop a comprehensive understanding of how relationships with different types of social ties impact frailty and multiple health outcomes in older adults. Third, this

study drew on an underpinning theoretical framework on social isolation and health proposed by Berkman and Krishna (2014) and the conceptual framework of frailty developed by Bergman et al. (2004). The fourth strength of this study is the population-based multi-center longitudinal study design with a large sample size. Fifth, we performed latent growth curve models, a core methodology in aging research, which allowed us to examine the role of changes in frailty on the relationship between changes in social relationships and multiple health outcomes. Last but not least, we employed comprehensive and validated measurements of social isolation, physical frailty, and health outcomes. This enabled us to capture different dimensions of social relationships and health status that may be differently influenced by changes in frailty and its underlying physiological mechanism.

Despite these strengths, this study has several limitations. First, this study relied on secondary data analysis that was constrained by the variables collected in the FRéLE study. The FRéLE study was not primarily aimed at investigating the association between social isolation, frailty, and health outcomes. Research evidence has identified other variables of interest as risk factors of social isolation and frailty that were not assessed in the present study. For example, variables like ethnicity, and dietary patterns might have improved the understanding of potential behavioral, contextual, and cultural factors that could impact social isolation, frailty, and health outcomes. In this regard, research has shown that the association between social isolation and health might differ across different ethnic groups (Miyawaki, 2015). Another longitudinal study points to the link between a healthy diet and physical health among community-dwelling older adults over three years (Pérez-Tasigchana et al., 2020). Several studies have also demonstrated the association between malnutrition with social isolation and frailty in later life (Boulos et al., 2016; Boulos et al., 2017). Second, another related limitation lies in the fact that we could not assess loneliness because studies 2 and 3 were based on secondary data analysis. Prior studies have shown that both social isolation and loneliness were associated with frailty and poor health outcomes, yet each might independently influence these pathways (Erin York Cornwell & Linda J Waite, 2009; Holt-Lunstad et al., 2010; Shankar et al., 2011). Third, this study focused on the phenotype of frailty, though there are other frailty measurements (Aguayo et al., 2017; Dent et al., 2016). Fourth, we could not estimate changes in disability and social contact with children and siblings in our longitudinal study. Moreover, we could not incorporate simultaneously all social isolation variables in multivariate LGMs due to the convergence problems. Accordingly, a longer longitudinal study

will provide larger estimates of changes. It is also more likely that changes would cumulate in one direction with a longer longitudinal study (Roberts et al., 2006). Fifth, attrition is a limitation in our longitudinal study. The last limitation is that the present study was a longitudinal observational study and cannot rule out the possibility of reverse causation. In this research study, we examined the nature of associations and correlations between variables of interest, not necessarily a causal pathway. The possible causal relationships for the identified moderator variable can be supported in studies with specified study designs such as quasi-experimental or RCT studies (Baron & Kenny, 1986; Goldstein et al., 2021; Hayes, 2017; Kraemer et al., 2008). It is worth noting that statistical techniques cannot substitute for random assignment and manipulation of independent variables (Goldstein et al., 2021).

7.4 Future research directions

Several research recommendations result from this dissertation. According to our scoping review (Study 1), loneliness is more related to frailty than social isolation. However, few researchers have examined social isolation and loneliness together (Holt-Lunstad et al., 2015; Mehrabi & Béland, 2020; Newall & Menec, 2017; Valtorta & Hanratty, 2012). In particular, the interrelationship between social isolation, loneliness, frailty, and health outcomes still is unknown. Future studies need to examine loneliness and social isolation simultaneously to better understand their distinct associations with frailty and health outcomes. Newall and Menec (2017) suggested a need for the incorporation of both social isolation and loneliness to better understand older adults' social world and possible health outcomes. This also opens up exciting possibilities to combine the knowledge gained from the social isolation literature with the knowledge from the loneliness literature (Lubben, 2017). Future empirical research should consider other risk factors that are more specific to various populations, such as linguistic isolation. For example, older adults who report linguistic isolation are more likely at risk of social isolation and feelings of loneliness (Coyle & Dugan, 2012). In addition, other subgroups of people may be particularly at risk for social isolation. Research has shown that older adults with low levels of education, income, and technology literacy; older women and indigenous people, older adults with sensory impairments and sedentary behaviors; and older adults who live alone, are at high risk of experiencing the negative consequences of social isolation and frailty, including adverse health outcomes (Haider et al., 2020;

Hayajneh & Rababa, 2021; Im et al., 2022; Khosravi et al., 2016; Tan et al., 2020; Theeke, 2010). Given that studies of ethnic minorities and lower socioeconomic groups are still a rarity in the field of gerontology (Hoogendijk et al., 2019), further research could explore the relationships between social isolation, frailty, and health outcomes by race and across different age subgroups (youngest-old, middle-old, and oldest-old). It is thus important to examine these subgroups in greater detail and target these populations in public health interventions. In addition, age-related sensory impairments, sedentary behaviors, and frailty are common conditions among older adults; however, existing research on their possible relationships is inconclusive (Tan et al., 2020). It is thus imperative that future public health interventions and research studies should consider sedentary behaviors and sensory impairments to prevent or reduce the development and progression of frailty and alleviate social isolation among older populations.

Longer longitudinal studies with more time points and larger sample sizes are warranted to capture developmental changes in social isolation and frailty and their effects on health outcomes over time. Further studies should consider examining the relationships between social isolation, frailty, and health outcomes with national datasets (i.e., the Canadian Longitudinal Study on Aging (CLSA), ELSA, LASA, CHARLS, SHARE, and so on) or the harmonization of different datasets. In particular, more research is needed to further explore the direction of the association between social isolation, frailty, and health outcomes. It is plausible that cognitive decline leads to higher levels of social isolation and that social isolation leads to cognitive impairment. It is also possible that the relationship between frailty and social isolation is bidirectional such that higher levels of social isolation predict frailty and that frailty leads to social isolation (Gale et al., 2018; Maltby et al., 2020). Additional analysis, including causal mediation and moderation analyses with a longer longitudinal study, would be valuable to disentangle the complex interrelationship between social isolation, frailty, and health outcomes, and track changes over longer periods. More quasi-experimental studies are needed to address reverse causality. Studies with a longer interval between the baseline assessment of social measures and the follow-up of health outcomes are more reliable for inferring the direction of causality. More randomized controlled trials that assess the effectiveness of interventions to enhance social connections in later life should be conducted to determine whether this may improve health outcomes among frail older adults. These types of studies may further help to clarify the nature of the association between social connections and health outcomes in later life. Furthermore, the cross-sectional analysis demonstrated that frequent

contact with grandchildren was associated with less likelihood of ADL limitations among older men but not women (Mehrabi & Béland, 2021). In the future, research studies should consider the effects of social isolation on frailty and health by gender. Gender analysis would be particularly important in understanding the different patterns of involvement that older women and men have in their social life. Accordingly, research has shown that the prevalence of frailty seems to increase with age and appears to be greater in women than in men (Collard et al., 2012).

Evidence has shown that several potential plausible mediators and moderators can influence the pathway from social isolation to health. Mediators could help explain the mechanisms, or plausible pathways, by which social isolation affects health outcomes. Moderator variables could help to determine whether the deleterious health effects of social isolation are stronger for some subgroups of persons than others. Moderator variables are generally important for understanding the generalizability of findings to certain subgroups (MacKinnon, 2011; National Academies of Sciences & Medicine, 2020). Relatedly, future studies may benefit from exploring whether the association between social isolation and health outcomes is moderated and mediated by other factors and from investigating this association longitudinally and in larger populations. In addition, future studies could seek to explore these relationships in greater detail by combining mediation and moderation to test moderated mediation or conditional process analysis (Hayes, 2017). We found that social isolation is linked to health outcomes among frail older adults but not robust older adults who were healthier and had fewer health issues. This observation provides support for the idea that health and wellbeing are important correlates of social isolation in older adults. It is possible that increased social relationships help frail older adults to maintain their health; however, it could also be the case that robust older adults do not experience social isolation because they do not have any health issues (Berkman & Glass, 2000). There is evidence suggesting that social isolation is a risk factor for the development of serious illness and mortality (Holt-Lunstad et al., 2015; Shankar et al., 2017; Valtorta & Hanratty, 2012). However, empirical evidence also suggests that poor health is a risk factor for the development of social isolation and loneliness in older age (Victor et al., 2005). Therefore, future studies could examine the direction of causality between maintenance of health and lack of social isolation.

We assessed frailty using the Fried criteria, one of the most commonly used and widely validated frailty instruments (Fried et al., 2001). However, other methods have been developed to assess

frailty such as the frailty index (Mitnitski et al., 2001) or the concept of intrinsic capacity proposed by the WHO (World Health Organization, 2020). It would be valuable to use different frailty screening tools to explore the relationships between social isolation, frailty, and health outcomes. This dissertation focuses on quantitative analysis. To gain further insight into how loneliness and social isolation impact an individual's daily routine or why someone might feel lonely and isolated, qualitative studies are needed to better understand the nuances and diversity of experiences and the coping mechanisms through which we could alleviate social isolation and loneliness in later life. These insights would be particularly valuable for better understanding the reasons behind reported changes in objective characteristics of social relationships and for shedding light on individual variations, both within and between individuals, in loneliness and social isolation over time. Qualitative studies could also help us better understand the role of past experiences in shaping social relationships in later life.

7.5 Conclusion

From a public health standpoint, this dissertation, by addressing key factors of healthy aging (World Health Organization, 2015), is a novel contribution to the empirical research on gerontology and public health. Notably, this dissertation adds to the current literature by outlining three key messages. First, the cross-sectional and longitudinal moderation results underscore the compensating role of social relationships on the mental health of frail older adults at baseline and over time. Second, moderation results elucidate the pivotal role of friendships and social participation in promoting mental and cognitive health among older adults over two years. Third, social support is related more than social networks to health outcomes in frail older adults. It is thus of utmost importance to identify physically frail older adults for social isolation interventions, and these populations should be a priority to target in public health policies and interventions. It is also imperative that public health policies and interventions focus on ameliorating social relationships and connectedness among physically frail older adults to enhance mental health outcomes. Now that the majority of older adults, particularly frail older adults, have experienced social isolation and loneliness due to the COVID-19 pandemic, there is a better understanding of the need to tackle and prioritize this public health issue. It means that being better prepared to alleviate social isolation and loneliness in the future and not perpetuate them in a post-pandemic world (Berg-Weger & Morley, 2020). Given the potentially preventable nature of frailty, public

health strategies are paramount in preventing the onset of frailty and reducing the risks of frailty progression (Hoogendijk et al., 2019) and its related health outcomes, and ultimately, premature mortality (Holt-Lunstad et al., 2017). Of note, it is necessary to reflect more on the current public health policies, particularly age-friendly city programs, to improve the health status of older populations. The age-friendly policies should focus on both social and physical environments aligned with social and contextual factors to enhance healthy aging among older populations, especially frail older adults (Berkman, 2014; Duppen et al., 2019). In addition, despite laudable efforts to alleviate and prevent social isolation and loneliness in these communities, there is limited evidence regarding the effectiveness of health promotion interventions and their impacts on the physical, cognitive, and mental health of older populations (Cattan et al., 2005; Duppen et al., 2019; Findlay, 2003). Our results revealed that social connectedness with kin and intimate ties is not a sufficient condition to tackle social isolation in older adults. Ultimately, public health policies should tailor interventions to prevent or lessen the long-term effects of social isolation on older adults' health so that social relationships do not exist only in their intimate social life, particularly post-pandemic. Therefore, health care policies and public health initiatives could benefit from considering explicitly our results in efforts aimed at reducing mental health problems among vulnerable older populations.

References

Aguayo, G. A., Donneau, A.-F., Vaillant, M. T., Schritz, A., Franco, O. H., Stranges, S., Malisoux, L., Guillaume, M., & Witte, D. R. (2017). Agreement between 35 published frailty scores in the general population. *American journal of epidemiology*, *186*(4), 420-434.

Ahmed, T., Belanger, E., Vafaei, A., Koné, G. K., Alvarado, B., Béland, F., Zunzunegui, M. V., & Group, I. R. (2018). Validation of a social networks and support measurement tool for use in international aging research: The International Mobility in Aging Study. *Journal of cross-cultural gerontology*, *33*(1), 101-120.

Almedom, A. M., & Glandon, D. (2008). Social capital and mental health. In *Social capital and health* (pp. 191-214). Springer.

Andrew, M. K., Mitnitski, A. B., & Rockwood, K. (2008). Social vulnerability, frailty and mortality in elderly people. *PloS one*, *3*(5), e2232.

Antonucci, T. C., Ajrouch, K. J., & Birditt, K. S. (2014). The convoy model: Explaining social relations from a multidisciplinary perspective. *The Gerontologist*, *54*(1), 82-92.

Arksey, H., & O'Malley, L. (2005). Scoping studies: towards a methodological framework. *International journal of social research methodology*, *8*(1), 19-32.

Bandeen-Roche, K., Gross, A. L., Varadhan, R., Buta, B., Carlson, M. C., Huisingh-Scheetz, M., Mcadams-Demarco, M., Piggott, D. A., Brown, T. T., & Hasan, R. K. (2020). Principles and issues for physical frailty measurement and its clinical application. *The Journals of Gerontology: Series A*, *75*(6), 1107-1112.

Bandeen-Roche, K., Xue, Q.-L., Ferrucci, L., Walston, J., Guralnik, J. M., Chaves, P., Zeger, S. L., & Fried, L. P. (2006). Phenotype of frailty: characterization in the women's health and aging studies. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *61*(3), 262-266.

Barnes, J. A. (1954). Class and committees in a Norwegian island parish. *Human relations*, *7*(1), 39-58.

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of personality and social psychology*, *51*(6), 1173.

Bassett, E., & Moore, S. (2013). *Mental health and social capital: Social capital as a promising initiative to improving the mental health of communities*. IntechOpen.

Bauer, D. J., & Curran, P. J. (2005). Probing interactions in fixed and multilevel regression: Inferential and graphical techniques. *Multivariate behavioral research*, *40*(3), 373-400.

Béland, F., Julien, D., Bier, N., Desrosiers, J., Kergoat, M.-J., & Demers, L. (2018). Association between cognitive function and life-space mobility in older adults: results from the FRéLE longitudinal study. *BMC geriatrics*, *18*(1), 227.

Béland, F., Julien, D., Wolfson, C., Bergman, H., Gaudreau, P., Galand, C., Fletcher, J., Zunzunegui, M.-V., Shatenstein, B., & Kergoat, M.-J. (2020). Revisiting the hypothesis of syndromic frailty: a cross-sectional study of the structural validity of the frailty phenotype. *BMC geriatrics*, *20*(1), 1-13.

Béland, F., Zunzunegui, M.-V., Alvarado, B., Otero, A., & Del Ser, T. (2005). Trajectories of cognitive decline and social relations. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *60*(6), P320-P330.

Bélanger, E., Ahmed, T., Vafaei, A., Curcio, C. L., Phillips, S. P., & Zunzunegui, M. V. (2016). Sources of social support associated with health and quality of life: a cross-sectional study among Canadian and Latin American older adults. *BMJ open*, *6*(6).

Berg, R. L., & Cassells, J. S. (1992). Social isolation among older individuals: The relationship to mortality and morbidity. In *The second fifty years: Promoting health and preventing disability*. National Academies Press (US).

Berg-Weger, M., & Morley, J. E. (2020). Editorial: Loneliness and Social Isolation in Older Adults during the COVID-19 Pandemic: Implications for Gerontological Social Work. *The journal of nutrition, health & aging*, *24*(5), 456–458. https://doi.org/10.1007/s12603-020-1366-8

Berglund, H., Hasson, H., Wilhelmson, K., Dunér, A., & Dahlin-Ivanoff, S. (2016). The impact of socioeconomic conditions, social networks, and health on frail older People's life satisfaction: a cross-sectional study. *Health Psychology Research*, *4*(1).

Bergman, H., Béland, F., Karunananthan, S., Hummel, S., Hogan, D., & Wolfson, C. (2004). Developing a Working Framework for Understanding Frailty Howard Bergman, MD. *Gérontologie et société*, *109*, 15-29.

Bergman, H., Ferrucci, L., Guralnik, J., Hogan, D. B., Hummel, S., Karunananthan, S., & Wolfson, C. (2007). Frailty: an emerging research and clinical paradigm—issues and controversies.

The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, *62*(7), 731-737.

Berkman, L. (2007). Social networks and social isolation.

Berkman, L. F., & Krishna, A. . (2014). Social Network Epidemiology. In L. F. K. Berkman, I. & Glymour, M. M. (Ed.), *Social Epidemiology (2 Eds)* (pp. 234-289). Oxford University Press.

Berkman, L. F., & Glass, T. (2000). Social integration, social networks, social support, and health. *Social epidemiology*, *1*, 137-173.

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. *Social Science & Medicine*, *51*(6), 843-857.

Bettmann, J. E. (2006). Using attachment theory to understand the treatment of adult depression. *Clinical Social Work Journal*, *34*(4), 531.

Bloom, I., Edwards, M., Jameson, K. A., Syddall, H. E., Dennison, E., Gale, C. R., Baird, J., Cooper, C., Aihie Sayer, A., & Robinson, S. (2017). Influences on diet quality in older age: the importance of social factors. *Age and ageing*, *46*(2), 277-283.

Bohnert, N., Chagnon, J., Coulombe, S., Dion, P., & Martel, L. (2015). *Population projections for Canada (2013 to 2063), provinces and territories (2013 to 2038): technical report on methodology and assumptions*. Statistics Canada= Statistique Canada.

Bott, E. (1957). Family and Social Network, 1957. *Tavistock Publications, Limited, London W*, *1*, 218.

Bouillon, K., Kivimaki, M., Hamer, M., Sabia, S., Fransson, E. I., Singh-Manoux, A., Gale, C. R., & Batty, G. D. (2013). Measures of frailty in population-based studies: an overview. *BMC geriatrics*, *13*(1), 1-11.

Boulos, C., Salameh, P., & Barberger-Gateau, P. (2016). Malnutrition and frailty in community dwelling older adults living in a rural setting. *Clinical nutrition*, *35*(1), 138-143.

Boulos, C., Salameh, P., & Barberger-Gateau, P. (2017). Social isolation and risk for malnutrition among older people. *Geriatrics & gerontology international*, *17*(2), 286-294.

Bowlby, J. (1969). *Attachment and Loss: Attachment.-1969.-(RUidnr.: M102591232)*. Basic books.

Bowlby, J. (1982). Attachment and loss: retrospect and prospect. *American journal of Orthopsychiatry*, *52*(4), 664.

Bruhn, J. (2009). The Significance of the Social Group. In *The Group Effect* (pp. 1-29). Springer.

Brummett, B. H., Barefoot, J. C., Siegler, I. C., Clapp-Channing, N. E., Lytle, B. L., Bosworth, H. B., Williams Jr, R. B., & Mark, D. B. (2001). Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. *Psychosomatic medicine*, *63*(2), 267-272.

Buffel, T., Phillipson, C., & Rémillard-Boilard, S. (2019). Age-friendly cities and communities: New directions for research and policy. *Encyclopedia of Gerontology and Population Aging; Gu, D., Dupre, ME, Eds*, 1-11.

Buttery, A. K., Busch, M. A., Gaertner, B., Scheidt-Nave, C., & Fuchs, J. (2015). Prevalence and correlates of frailty among older adults: findings from the German health interview and examination survey. *BMC geriatrics*, *15*(1), 22.

Cacioppo, J. T., & Hawkley, L. C. (2003). Social isolation and health, with an emphasis on underlying mechanisms. *Perspectives in biology and medicine*, *46*(3), S39-S52.

Cacioppo, J. T., Hawkley, L. C., Berntson, G. G., Ernst, J. M., Gibbs, A. C., Stickgold, R., & Hobson, J. A. (2002). Do lonely days invade the nights? Potential social modulation of sleep efficiency. *Psychological Science*, *13*(4), 384-387.

Caetano, S. C., Silva, C. M., & Vettore, M. V. (2013). Gender differences in the association of perceived social support and social network with self-rated health status among older adults: a population-based study in Brazil. *BMC geriatrics*, *13*(1), 1-14.

Carr, D. (2019). Aging Alone? International Perspectives on Social Integration and Isolation. *The Journals of Gerontology: Series B*, *74*(8), 1391-1393.

Carstensen, L. L. (2006). The influence of a sense of time on human development. *Science*, *312*(5782), 1913-1915.

Cassel, J. (1976). The contribution of the social environment to host resistance: the Fourth Wade Hampton Frost Lecture. *American journal of epidemiology*, *104*(2), 107-123.

Cattan, M., White, M., Bond, J., & Learmouth, A. (2005). Preventing social isolation and loneliness among older people: a systematic review of health promotion interventions. *Ageing & Society*, *25*(1), 41-67.

Cesari, M., Demougeot, L., Boccalon, H., Guyonnet, S., Abellan Van Kan, G., Vellas, B., & Andrieu, S. (2014). A self-reported screening tool for detecting community-dwelling older

persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire. *PloS one*, *9*(7), e101745.

Charpentier, M., & Kirouac, L. (2019). Vieillir et vivre seul-e.

Chatters, L. M., Taylor, H. O., Nicklett, E. J., & Taylor, R. J. (2018). Correlates of objective social isolation from family and friends among older adults. Healthcare,

Chen, L.-J., Chen, C.-Y., Lue, B.-H., Tseng, M.-Y., & Wu, S.-C. (2014). Prevalence and associated factors of frailty among elderly people in Taiwan. *International Journal of Gerontology*, *8*(3), 114-119.

Chen, S., Honda, T., Chen, T., Narazaki, K., Haeuchi, Y., Supartini, A., & Kumagai, S. (2015). Screening for frailty phenotype with objectively-measured physical activity in a west Japanese suburban community: evidence from the Sasaguri Genkimon Study. *BMC geriatrics*, *15*(1), 36.

Chhetri, J. K., Xue, Q.-L., Ma, L., Chan, P., & Varadhan, R. (2021). Intrinsic capacity as a determinant of physical resilience in older adults. *The journal of nutrition, health & aging*, 1-6.

Chiao, C., Weng, L.-J., & Botticello, A. L. (2011). Social participation reduces depressive symptoms among older adults: an 18-year longitudinal analysis in Taiwan. *BMC public health*, *11*(1), 1-9.

Chon, D., Lee, Y., Kim, J., & Lee, K.-e. (2018). The association between frequency of social contact and frailty in older people: Korean Frailty and Aging Cohort Study (KFACS). *Journal of Korean medical science*, *33*(51).

Chou, M.-Y., Nishita, Y., Nakagawa, T., Tange, C., Tomida, M., Shimokata, H., Otsuka, R., Chen, L.-K., & Arai, H. (2019). Role of gait speed and grip strength in predicting 10-year cognitive decline among community-dwelling older people. *BMC geriatrics*, *19*(1), 1-11.

Chu, W., Chang, S. F., & Ho, H. Y. (2021). Adverse Health Effects of Frailty: Systematic Review and Meta-Analysis of Middle-Aged and Older Adults With Implications for Evidence-Based Practice. *Worldviews on Evidence-Based Nursing*.

Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K. (2013). Frailty in elderly people. *The Lancet*, *381*(9868), 752-762.

Cobb, S. (1976). Social support as a moderator of life stress. *Psychosomatic medicine*.

Cohen, S. (1988). Psychosocial models of the role of social support in the etiology of physical disease. *Health Psychology*, *7*(3), 269.

Collard, R. M., Boter, H., Schoevers, R. A., & Oude Voshaar, R. C. (2012). Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society*, *60*(8), 1487-1492.

Collard, R. M., Comijs, H. C., Naarding, P., Penninx, B. W., Milaneschi, Y., Ferrucci, L., & Voshaar, R. C. O. (2015). Frailty as a predictor of the incidence and course of depressed mood. *Journal of the American Medical Directors Association*, *16*(6), 509-514.

Cornwell, B., Laumann, E. O., & Schumm, L. P. (2008). The social connectedness of older adults: A national profile. *American sociological review*, *73*(2), 185-203.

Cornwell, E. Y., & Waite, L. J. (2009). Measuring social isolation among older adults using multiple indicators from the NSHAP study. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *64*(suppl_1), i38-i46.

Cornwell, E. Y., & Waite, L. J. (2009). Social disconnectedness, perceived isolation, and health among older adults. *Journal of Health and Social Behavior*, *50*(1), 31-48. https://doi.org/10.1177/002214650905000103

Coté, J., Gagnon, L., Julien, M., & Généreux, S. (2012). Vieillir et vivre ensemble, chez soi, dans sa communauté, au Québec. *Québec: Ministère de la famille et des aînés*.

Council, N. S. (2015). *Report on the Social Isolation of Seniors, 2013-2014*. National Seniors Council.

Courtin, E., & Knapp, M. (2017). Social isolation, loneliness and health in old age: a scoping review. *Health & social care in the community*, *25*(3), 799-812.

Coyle, C. E., & Dugan, E. (2012). Social isolation, loneliness and health among older adults. *Journal of Aging and Health*, *24*(8), 1346-1363.

Curran, P. J., Obeidat, K., & Losardo, D. (2010). Twelve frequently asked questions about growth curve modeling. *Journal of cognition and development*, *11*(2), 121-136.

Das, A. (2013). How does race get "under the skin"?: Inflammation, weathering, and metabolic problems in late life. *Social Science & Medicine*, *77*, 75-83.

Davies, K., Maharani, A., Chandola, T., Todd, C., & Pendleton, N. (2021). The longitudinal relationship between loneliness, social isolation, and frailty in older adults in England: a prospective analysis. *The Lancet Healthy Longevity*, *2*(2), e70-e77.

de Goeij, M. C., van Diepen, M., Jager, K. J., Tripepi, G., Zoccali, C., & Dekker, F. W. (2013). Multiple imputation: dealing with missing data. *Nephrology Dialysis Transplantation*, *28*(10), 2415-2420.

De Jong Gierveld, J., Van Tilburg, T., & Dykstra, P. . (2006). Loneliness and Social Isolation. In V. D. Perlman (Ed.), *he Cambridge Handbook of Personal Relationships (Cambridge Handbooks in Psychology* (pp. 485-500). Cambridge University Press. https://doi.org/10.1017/CBO9780511606632.027

De Silva, M. J., McKenzie, K., Harpham, T., & Huttly, S. R. (2005). Social capital and mental illness: a systematic review. *Journal of epidemiology & community health*, *59*(8), 619-627.

Dent, E., & Hoogendijk, E. O. (2014). Psychosocial factors modify the association of frailty with adverse outcomes: a prospective study of hospitalised older people. *BMC geriatrics*, *14*(1), 108.

Dent, E., Kowal, P., & Hoogendijk, E. O. (2016). Frailty measurement in research and clinical practice: a review. *European journal of internal medicine*, *31*, 3-10.

Dent, E., Martin, F. C., Bergman, H., Woo, J., Romero-Ortuno, R., & Walston, J. D. (2019). Management of frailty: opportunities, challenges, and future directions. *The lancet*, *394*(10206), 1376-1386.

Dickens, A. P., Richards, S. H., Greaves, C. J., & Campbell, J. L. (2011). Interventions targeting social isolation in older people: a systematic review. *BMC public health*, *11*(1), 1-22.

Ding, Y. Y., Kuha, J., & Murphy, M. (2017). Multidimensional predictors of physical frailty in older people: identifying how and for whom they exert their effects. *Biogerontology*, *18*(2), 237-252.

Ditzen, B., & Heinrichs, M. (2014). Psychobiology of social support: the social dimension of stress buffering. *Restorative neurology and neuroscience*, *32*(1), 149-162.

Djundeva, M., Dykstra, P., & Fokkema, T. (2018). Is living alone "aging alone"? Solitary living, network types, and well-being. *Journal of Gerontology: Social Sciences*.

Domènech-Abella, J., Lara, E., Rubio-Valera, M., Olaya, B., Moneta, M. V., Rico-Uribe, L. A., Ayuso-Mateos, J. L., Mundó, J., & Haro, J. M. (2017). Loneliness and depression in the elderly: the role of social network. *Social psychiatry and psychiatric epidemiology*, *52*(4), 381-390.

Duncan, T. E., & Duncan, S. C. (2009). *The ABC's of LGM: An introductory guide to latent variable growth curve modeling* (Vol. 3).

Duppen, D., Lambotte, D., Dury, S., Smetcoren, A.-S., Pan, H., & De Donder, L. (2020). Social participation in the daily lives of frail older adults: types of participation and influencing factors. *The Journals of Gerontology: Series B*, *75*(9), 2062-2071.

Duppen, D., Machielse, A., Verté Rn, D., Dury, S., De Donder, L., & Consortium, D.-S. (2019). Meaning in life for socially frail older adults. *Journal of community health nursing*, *36*(2), 65-77.

Durkheim, E. (1973). *Emile Durkheim on morality and society*. University of Chicago Press.

Dykstra, P. A. (2015). Childless older adults. *The encyclopedia of adulthood and aging*, 1-5.

Eck, J., & Riva, P. (2016). Bridging the gap between different psychological approaches to understanding and reducing the impact of social exclusion. In *Social Exclusion* (pp. 277-289). Springer.

Etman, A., Burdorf, A., Van der Cammen, T. J., Mackenbach, J. P., & Van Lenthe, F. J. (2012). Socio-demographic determinants of worsening in frailty among community-dwelling older people in 11 European countries. *J Epidemiol Community Health*, *66*(12), 1116-1121.

Etman, A., Kamphuis, C. B., Van der Cammen, T. J., Burdorf, A., & Van Lenthe, F. J. (2014). Do lifestyle, health and social participation mediate educational inequalities in frailty worsening? *The European Journal of Public Health*, *25*(2), 345-350.

Evans, I. E., Martyr, A., Collins, R., Brayne, C., & Clare, L. (2019). Social isolation and cognitive function in later life: A systematic review and meta-analysis. *Journal of Alzheimer's disease*, *70*(s1), S119-S144.

Fan, L., Wang, S., Xue, H., Ding, Y., Wang, J., Tian, Y., & Du, W. (2021). Social Support and Mortality in Community-Dwelling Chinese Older Adults: The Mediating Role of Frailty. *Risk Management and Healthcare Policy*, *14*, 1583.

Feng, L., Nyunt, M. S. Z., Feng, L., Yap, K. B., & Ng, T. P. (2014). Frailty predicts new and persistent depressive symptoms among community-dwelling older adults: findings from Singapore longitudinal aging study. *Journal of the American Medical Directors Association*, *15*(1), 76. e77-76. e12.

Findlay, R. A. (2003). Interventions to reduce social isolation amongst older people: where is the evidence? *Ageing & Society*, *23*(5), 647-658.

Fiordelli, M., Sak, G., Guggiari, B., Schulz, P. J., & Petrocchi, S. (2020). Differentiating objective and subjective dimensions of social isolation and apprasing their relations with physical and mental health in italian older adults. *BMC geriatrics*, *20*(1), 1-13.

Fiori, K. L., Antonucci, T. C., & Cortina, K. S. (2006). Social network typologies and mental health among older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *61*(1), P25-P32.

Fiori, K. L., Windsor, T. D., & Huxhold, O. (2020). The increasing importance of friendship in late life: Understanding the role of sociohistorical context in social development. *Gerontology*, *66*(3), 286-294.

Freedman, A., & Nicolle, J. (2020). Social isolation and loneliness: The new geriatric giants: Approach for primary care. *Canadian Family Physician*, *66*(3), 176-182.

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *59*(3), M255-M263.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W. J., & Burke, G. (2001). Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(3), M146-M157.

Gale, C. R., Syddall, H. E., Cooper, C., Sayer, A. A., Bergman, H., & Brunner, E. J. (2012). Close relationships and risk of frailty: The Hertfordshire Cohort Study. *Journal of the American Geriatrics Society*, *60*(2), 390-392.

Gale, C. R., Westbury, L., & Cooper, C. (2018). Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. *Age and ageing*, *47*(3), 392-397.

Gariepy, G., Honkaniemi, H., & Quesnel-Vallee, A. (2016). Social support and protection from depression: systematic review of current findings in Western countries. *The British Journal of Psychiatry*, *209*(4), 284-293.

Garon, S., Paris, M., Beaulieu, M., Veil, A., & Laliberté, A. (2014). Collaborative partnership in age-friendly cities: Two case studies from Quebec, Canada. *Journal of aging & social policy*, *26*(1-2), 73-87.

Garon, S., Veil, A., Paris, M., & Rémillard-Boilard, S. (2016). How can a research program enhance a policy? AFC-Quebec governance and evaluation opportunities. In *Age-friendly cities and communities in international comparison* (pp. 99-120). Springer.

Gil-Salcedo, A., Dugravot, A., Fayosse, A., Dumurgier, J., Bouillon, K., Schnitzler, A., Kivimäki, M., Singh-Manoux, A., & Sabia, S. (2020). Healthy behaviors at age 50 years and frailty at older ages in a 20-year follow-up of the UK Whitehall II cohort: A longitudinal study. *PLoS medicine*, *17*(7), e1003147.

Gilmour, H. (2012). Social participation and the health and well-being of Canadian seniors. *Health reports*, *23*(4), 23-32.

Gobbens, R., Luijkx, K., Wijnen-Sponselee, M. T., & Schols, J. (2010). Towards an integral conceptual model of frailty. *The journal of nutrition, health & aging*, *14*(3), 175-181.

Gobbens, R. J., Luijkx, K. G., Wijnen-Sponselee, M. T., & Schols, J. M. (2010). In search of an integral conceptual definition of frailty: opinions of experts. *Journal of the American Medical Directors Association*, *11*(5), 338-343.

Gobbens, R. J., van Assen, M. A., Luijkx, K. G., & Schols, J. M. (2012a). The predictive validity of the Tilburg Frailty Indicator: disability, health care utilization, and quality of life in a population at risk. *The Gerontologist*, *52*(5), 619-631.

Gobbens, R. J., van Assen, M. A., Luijkx, K. G., & Schols, J. M. (2012b). Testing an integral conceptual model of frailty. *Journal of advanced nursing*, *68*(9), 2047-2060.

Gobbens, R. J., van Assen, M. A., Luijkx, K. G., Wijnen-Sponselee, M. T., & Schols, J. M. (2010). The Tilburg frailty indicator: psychometric properties. *Journal of the American Medical Directors Association*, *11*(5), 344-355.

Goldstein, B. L., Finsaas, M. C., Olino, T. M., Kotov, R., Grasso, D. J., & Klein, D. N. (2021). Three-variable systems: An integrative moderation and mediation framework for developmental psychopathology. *Development and psychopathology*, 1-12.

Gordon, E. H., & Hubbard, R. E. (2020). Differences in frailty in older men and women. *Medical Journal of Australia*, *212*(4), 183-188.

Grenade, L., & Boldy, D. (2008). Social isolation and loneliness among older people: issues and future challenges in community and residential settings. *Australian Health Review*, *32*(3), 468-478.

Grimm, K. J., & Ram, N. (2009). Nonlinear growth models in M plus and SAS. *Structural equation modeling*, *16*(4), 676-701.

Grimm, K. J., Ram, N., & Estabrook, R. (2016). *Growth modeling: Structural equation and multilevel modeling approaches*. Guilford Publications.

Groll, D. L., To, T., Bombardier, C., & Wright, J. G. (2005). The development of a comorbidity index with physical function as the outcome. *Journal of clinical epidemiology*, *58*(6), 595-602.

Guida, J. L., Holt, C. L., Dallal, C. M., He, X., Gold, R., & Liu, H. (2020). Social relationships and functional impairment in aging cancer survivors: A longitudinal social network study. *The Gerontologist*, *60*(4), 607-616.

Guo, L., An, L., Luo, F., & Yu, B. (2021). Social isolation, loneliness and functional disability in Chinese older women and men: a longitudinal study. *Age and ageing*, *50*(4), 1222-1228.

Guo, Q., Bai, X., & Feng, N. (2018). Social participation and depressive symptoms among Chinese older adults: A study on rural–urban differences. *Journal of affective disorders*, *239*, 124-130.

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., Scherr, P. A., & Wallace, R. B. (1994). A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *Journal of gerontology*, *49*(2), M85-M94.

Haider, S., Grabovac, I., Drgac, D., Mogg, C., Oberndorfer, M., & Dorner, T. E. (2020). Impact of physical activity, protein intake and social network and their combination on the development of frailty. *European journal of public health*, *30*(2), 340-346.

Hämmig, O. (2019). Health risks associated with social isolation in general and in young, middle and old age. *PloS one*, *14*(7), e0219663.

Han, K.-M., Chang, J., Yoon, H.-K., Ko, Y.-H., Ham, B.-J., Kim, Y.-K., & Han, C. (2019). Relationships between hand-grip strength, socioeconomic status, and depressive symptoms in community-dwelling older adults. *Journal of affective disorders*, *252*, 263-270.

Hayajneh, A. A., & Rababa, M. (2021). The Association of Frailty with Poverty in Older Adults: A Systematic Review. *Dementia and geriatric cognitive disorders*, 1-7.

Hayashi, T., Umegaki, H., Makino, T., Huang, C., Inoue, A., Shimada, H., & Kuzuya, M. (2020). Combined impact of physical frailty and social isolation on rate of falls in older adults. *The journal of nutrition, health & aging*, *24*(3), 312-318.

Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. Guilford publications.

Hennessy, M. B., Kaiser, S., & Sachser, N. (2009). Social buffering of the stress response: diversity, mechanisms, and functions. *Frontiers in neuroendocrinology*, *30*(4), 470-482.

Hermsen, L. A., Leone, S. S., Smalbrugge, M., Dekker, J., & van der Horst, H. E. (2014). Frequency, severity and determinants of functional limitations in older adults with joint pain and comorbidity: results of a cross-sectional study. *Archives of Gerontology and Geriatrics*, *59*(1), 98-106.

Herrera-Badilla, A., Navarrete-Reyes, A. P., Amieva, H., & Avila-Funes, J. A. (2015). Loneliness is associated with frailty in community-dwelling elderly adults. *Journal of the American Geriatrics Society*, *63*(3), 607-609.

het Veld, L. P. O., van Rossum, E., Kempen, G. I., de Vet, H. C., Hajema, K., & Beurskens, A. J. (2015). Fried phenotype of frailty: cross-sectional comparison of three frailty stages on various health domains. *BMC geriatrics*, *15*(1), 1-11.

Holt-Lunstad, J. (2017). Friendship and health. In H. A. Moyer (Ed.), *The psychology of friendship* (pp. 233-248). Oxford University Press.

Holt-Lunstad, J., Robles, T. F., & Sbarra, D. A. (2017). Advancing social connection as a public health priority in the United States. *American Psychologist*, *72*(6), 517.

Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T., & Stephenson, D. (2015). Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspectives on psychological science*, *10*(2), 227-237.

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: a meta-analytic review. *PLoS medicine*, *7*(7), e1000316.

Holt-Lunstad, J., & Steptoe, A. (2021). Social Isolation: An Underappreciated Determinant of Physical Health. *Current Opinion in Psychology*.

Hoogendijk, E. O., Afilalo, J., Ensrud, K. E., Kowal, P., Onder, G., & Fried, L. P. (2019). Frailty: implications for clinical practice and public health. *The Lancet*, *394*(10206), 1365-1375.

Hoogendijk, E. O., Rijnhart, J. J., Skoog, J., Robitaille, A., van den Hout, A., Ferrucci, L., Huisman, M., Skoog, I., Piccinin, A. M., & Hofer, S. M. (2020). Gait speed as predictor of transition into cognitive impairment: Findings from three longitudinal studies on aging. *Experimental gerontology*, *129*, 110783.

Hoogendijk, E. O., Smit, A. P., van Dam, C., Schuster, N. A., de Breij, S., Holwerda, T. J., Huisman, M., Dent, E., & Andrew, M. K. (2020). Frailty combined with loneliness or social isolation: an elevated risk for mortality in later life. *Journal of the American Geriatrics Society*, *68*(11), 2587-2593.

Hoogendijk, E. O., Suanet, B., Dent, E., Deeg, D. J., & Aartsen, M. J. (2016). Adverse effects of frailty on social functioning in older adults: Results from the Longitudinal Aging Study Amsterdam. *Maturitas*, *83*, 45-50.

Hoogendijk, E. O., van Hout, H. P., van der Horst, H. E., Frijters, D. H., Dent, E., Deeg, D. J., & Huisman, M. (2014). Do psychosocial resources modify the effects of frailty on functional decline and mortality? *Journal of psychosomatic research*, *77*(6), 547-551.

Hortulanus, R., Machielse, A., & Meeuwesen, L. (2006). *Social isolation in modern society*. Routledge.

House, J. S. (2001). Social isolation kills, but how and why? *Psychosomatic medicine*, *63*(2), 273-274.

House, J. S., Kahn, R. L., McLeod, J., & Williams, D. (1985). Measures and concepts of social support In Cohen S & Syme SL (Eds.), Social support and health (pp. 83–108). *New York: Academic*.

House, J. S., Umberson, D., & Landis, K. R. (1988). Structures and processes of social support. *Annual review of sociology*, *14*(1), 293-318.

Howlett, S. E., Rutenberg, A. D., & Rockwood, K. (2021). The degree of frailty as a translational measure of health in aging. *Nature Aging*, *1*(8), 651-665.

Hsu, H.-C., & Chang, W.-C. (2015). Trajectories of frailty and related factors of the older people in Taiwan. *Experimental aging research*, *41*(1), 104-114.

Huntley, J., Ostfeld, A. M., Taylor, J. O., Wallace, R. B., Blazer, D., Berkman, L. F., Evans, D. A., Kohout, J., Lemke, J. H., & Scherr, P. A. (1993). Established populations for epidemiologic studies of the elderly: study design and methodology. *Aging Clinical and Experimental Research*, *5*(1), 27-37.

Ihle, A., Oris, M., Baeriswyl, M., & Kliegel, M. (2018). The relation of close friends to cognitive performance in old age: The mediating role of leisure activities. *International Psychogeriatrics*, *30*(12), 1753-1758.

Iliffe, S., Kharicha, K., Harari, D., Swift, C., Gillmann, G., & Stuck, A. E. (2007). Health risk appraisal in older people 2: the implications for clinicians and commissioners of social isolation risk in older people. *British Journal of General Practice*, *57*(537), 277-282.

Im, J. H., Rodrigues, R., Anderson, K. K., Wilk, P., Stranges, S., & Nicholson, K. (2022). Examining the prevalence and correlates of multimorbidity among community-dwelling older adults: cross-sectional evidence from the Canadian Longitudinal Study on Aging (CLSA) first-follow-up data. *Age and ageing*, *51*(8), afac165.

Janke, M. C., Payne, L. L., & Van Puymbroeck, M. (2008). The role of informal and formal leisure activities in the disablement process. *The International Journal of Aging and Human Development*, *67*(3), 231-257.

Jarach, C. M., Tettamanti, M., Nobili, A., & D'avanzo, B. (2021). Social isolation and loneliness as related to progression and reversion of frailty in the Survey of Health Aging Retirement in Europe (SHARE). *Age and ageing*, *50*(1), 258-262.

Jin, Y., Si, H., Qiao, X., Tian, X., Liu, X., Xue, Q.-L., & Wang, C. (2020). Relationship between frailty and depression among community-dwelling older adults: the mediating and moderating role of social support. *The Gerontologist*, *60*(8), 1466-1475.

Jones, D. M., Song, X., & Rockwood, K. (2004). Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *Journal of the American Geriatrics Society*, *52*(11), 1929-1933.

Jones, E., Hanly, J., Mooney, R., Rand, L., Spurway, P., Eastwood, B., & Jones, J. V. (1991). Strength and function in the normal and rheumatoid hand. *The Journal of Rheumatology*, *18*(9), 1313-1318.

Jung, Y., Lyu, J., & Kim, G. (2021). Multi-Group Frailty Trajectories Among Older Koreans: Results from the Korean Longitudinal Study of Aging. *Archives of Gerontology and Geriatrics*, 104533.

Jürschik, P., Nunin, C., Botigué, T., Escobar, M. A., Lavedán, A., & Viladrosa, M. (2012). Prevalence of frailty and factors associated with frailty in the elderly population of Lleida, Spain: the FRALLE survey. *Archives of Gerontology and Geriatrics*, *55*(3), 625-631.

Kahn, R. L., & Antonucci, T. C. (1980). Convoys over the life course: Attachment, roles, and social support. *Life-span development and behavior*.

Kamiya, Y., & Kenny, R. A. (2017). Does social engagement predict frailty and mortality in the older population? In *Applied demography and public health in the 21st century* (pp. 69-79). Springer.

Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *Jama*, *185*(12), 914-919.

Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., Jaffe, M. W., & White, K. L. (1992). Studies of illness in the aged--The index of ADL: A standardized measure of biological and psychosocial functions. In *PAHO. Scientific Publication* (pp. 272-280). Pan American Health Organization.

Kawachi, I., & Berkman, L. (2000). Social cohesion, social capital, and health. *Social epidemiology*, *174*(7).

Keefe, J., Andrew, M., Fancey, P., & Hall, M. (2006). A profile of social isolation in Canada. *Report submitted to the F/P/T Working Group on Social Isolation. Province of British Columbia and Mount Saint Vincent University*.

Kehler, D. S., Ferguson, T., Stammers, A. N., Bohm, C., Arora, R. C., Duhamel, T. A., & Tangri, N. (2017). Prevalence of frailty in Canadians 18–79 years old in the Canadian Health Measures Survey. *BMC geriatrics*, *17*(1), 28.

Kelly, M. E., Duff, H., Kelly, S., Power, J. E. M., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. *Systematic reviews*, *6*(1), 259.

Khosravi, P., Rezvani, A., & Wiewiora, A. (2016). The impact of technology on older adults' social isolation. *Computers in Human Behavior*, *63*, 594-603.

Kim, M., Hsu, H.-Y., Kwok, O.-m., & Seo, S. (2018). The optimal starting model to search for the accurate growth trajectory in Latent Growth Models. *Frontiers in psychology*, *9*, 349.

Klein, A., & Moosbrugger, H. (2000). Maximum likelihood estimation of latent interaction effects with the LMS method. *Psychometrika*, *65*(4), 457-474.

Klein, B. E., Klein, R., Knudtson, M. D., & Lee, K. E. (2003). Relationship of measures of frailty to visual function: the Beaver Dam Eye Study. *Transactions of the American Ophthalmological Society*, *101*, 191.

Kobayashi, L. C., & Steptoe, A. (2018). Social isolation, loneliness, and health behaviors at older ages: longitudinal cohort study. *Annals of Behavioral Medicine*, *52*(7), 582-593.

Kraemer, H. C., Kiernan, M., Essex, M., & Kupfer, D. J. (2008). How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur approaches. *Health psychology*, *27*(2S), S101.

Kristensen, K., König, H.-H., & Hajek, A. (2019). The association of multimorbidity, loneliness, social exclusion and network size: findings from the population-based German Ageing Survey. *BMC public health*, *19*(1), 1-10.

Kuchel, G. A. (2018). Frailty and resilience as outcome measures in clinical trials and geriatric care: are we getting any closer?

Kuiper, J. S., Zuidersma, M., Zuidema, S. U., Burgerhof, J. G., Stolk, R. P., Oude Voshaar, R. C., & Smidt, N. (2016). Social relationships and cognitive decline: a systematic review and meta-analysis of longitudinal cohort studies. *International journal of epidemiology*, *45*(4), 1169-1206.

Kulminski, A., Yashin, A., Arbeev, K., Akushevich, I., Ukraintseva, S., Land, K., & Manton, K. (2007). Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: results from analyses of the National Long Term Care Survey. *Mechanisms of ageing and development*, *128*(3), 250-258.

Kwan, R. Y., Cheung, D. S., Lo, S. K., Ho, L. Y., Katigbak, C., Chao, Y.-Y., & Liu, J. Y. (2019). Frailty and its association with the Mediterranean diet, life-space, and social participation in community-dwelling older people. *Geriatric Nursing*, *40*(3), 320-326.

Landeiro, F., Barrows, P., Musson, E. N., Gray, A. M., & Leal, J. (2017). Reducing social isolation and loneliness in older people: a systematic review protocol. *BMJ open*, *7*(5), e013778.

Landi, F., Cesari, M., Calvani, R., Cherubini, A., Di Bari, M., Bejuit, R., Mshid, J., Andrieu, S., Sinclair, A. J., & Sieber, C. C. (2017). The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies"(SPRINTT) randomized controlled trial: design and methods. *Aging clinical and experimental research*, *29*(1), 89-100.

Lang, P.-O., Michel, J.-P., & Zekry, D. (2009). Frailty syndrome: a transitional state in a dynamic process. *Gerontology*, *55*(5), 539-549.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *The gerontologist*, *9*(3_Part_1), 179-186.

Leigh-Hunt, N., Bagguley, D., Bash, K., Turner, V., Turnbull, S., Valtorta, N., & Caan, W. (2017). An overview of systematic reviews on the public health consequences of social isolation and loneliness. *Public health*, *152*, 157-171.

Lennartsson, C., Rehnberg, J., & Dahlberg, L. (2021). The association between loneliness, social isolation and all-cause mortality in a nationally representative sample of older women and men. *Aging & mental health*, 1-8.

Levasseur, M., Lussier-Therrien, M., Biron, M. L., Raymond, É., Castonguay, J., Naud, D., Fortier, M., Sévigny, A., Houde, S., & Tremblay, L. (2022). Scoping study of definitions of social participation: update and co-construction of an interdisciplinary consensual definition. *Age and ageing*, *51*(2), afab215.

Levasseur, M., Richard, L., Gauvin, L., & Raymond, É. (2010). Inventory and analysis of definitions of social participation found in the aging literature: Proposed taxonomy of social activities. *Social Science & Medicine*, *71*(12), 2141-2149.

Li, C.-L., & Hsu, H.-C. (2015). Cognitive function and associated factors among older people in Taiwan: Age and sex differences. *Archives of Gerontology and Geriatrics*, *60*(1), 196-200.

Li, G., Thabane, L., Ioannidis, G., Kennedy, C., Papaioannou, A., & Adachi, J. D. (2015). Comparison between frailty index of deficit accumulation and phenotypic model to predict risk of falls: data from the global longitudinal study of osteoporosis in women (GLOW) Hamilton cohort. *PloS one*, *10*(3), e0120144.

Liao, M.-Y., Yeh, C.-J., Liao, C.-C., Lee, S.-H., Yang, S.-F., & Lee, M.-C. (2018). Effects of receiving and providing family support on mortality in non-frail, pre-frail and frail older adults in Taiwan: A 12-year follow-up longitudinal study. *European Geriatric Medicine*, *9*(5), 679-685.

Lubben, J. (2017). Addressing social isolation as a potent killer. *Public Policy & Aging Report*, *27*(4), 136-138.

Lubben, J., & Gironda, M. (2004). Measuring social networks and assessing their benefits. *Social networks and social exclusion: Sociological and policy perspectives*, 20-34.

Luciani, A., Dottorini, L., Battisti, N., Bertuzzi, C., Caldiera, S., Floriani, I., Zonato, S., Ferrari, D., & Foa, P. (2013). Screening elderly cancer patients for disabilities: evaluation of study of osteoporotic fractures (SOF) index and comprehensive geriatric assessment (CGA). *Annals of oncology*, *24*(2), 469-474.

Luger, E., Dorner, T. E., Haider, S., Kapan, A., Lackinger, C., & Schindler, K. (2016). Effects of a home-based and volunteer-administered physical training, nutritional, and social support program on malnutrition and frailty in older persons: a randomized controlled trial. *Journal of the American Medical Directors Association*, *17*(7), 671. e679-671. e616.

MacKinnon, D. P. (2011). Integrating mediators and moderators in research design. *Research on social work practice*, *21*(6), 675-681.

Maes, M., Qualter, P., Vanhalst, J., Van den Noortgate, W., & Goossens, L. (2019). Gender differences in loneliness across the lifespan: A meta–analysis. *European Journal of Personality*, *33*(6), 642-654.

Mair, C. A. (2019). Alternatives to Aging Alone?:"Kinlessness" and the Importance of Friends Across European Contexts. *The Journals of Gerontology: Series B*.

Makizako, H., Shimada, H., Doi, T., Yoshida, D., Anan, Y., Tsutsumimoto, K., Uemura, K., Liu-Ambrose, T., Park, H., & Lee, S. (2015). Physical frailty predicts incident depressive symptoms in elderly people: prospective findings from the Obu Study of Health Promotion for the Elderly. *Journal of the American Medical Directors Association*, *16*(3), 194-199.

Malini, F. M., Lourenço, R. A., & Lopes, C. S. (2016). Prevalence of fear of falling in older adults, and its associations with clinical, functional and psychosocial factors: The Frailty in Brazilian Older People-Rio de Janeiro Study. *Geriatrics & gerontology international*, *16*(3), 336-344.

Maltby, J., Hunt, S. A., Ohinata, A., Palmer, E., & Conroy, S. (2020). Frailty and Social Isolation: Comparing the Relationship between Frailty and Unidimensional and Multifactorial Models of Social Isolation. *Journal of Aging and Health*, 0898264320923245.

Martin, C. T., Kayser-Jones, J., Stotts, N. A., Porter, C., & Froelicher, E. S. (2005). Factors contributing to low weight in community-living older adults. *Journal of the American Academy of Nurse Practitioners*, *17*(10), 425-431.

Martin, F. C. (2017). Frailty, sarcopenia, falls and fractures. In *Orthogeriatrics* (pp. 47-61). Springer.

Mattie, H., Engø-Monsen, K., Ling, R., & Onnela, J.-P. (2018). Understanding tie strength in social networks using a local "bow tie" framework. *Scientific reports*, *8*(1), 1-9.

Maulik, P. K., Eaton, W. W., & Bradshaw, C. P. (2010). The effect of social networks and social support on common mental disorders following specific life events. *Acta Psychiatrica Scandinavica*, *122*(2), 118-128.

Maulik, P. K., Eaton, W. W., & Bradshaw, C. P. (2011). The effect of social networks and social support on mental health services use, following a life event, among the Baltimore Epidemiologic Catchment Area cohort. *The journal of behavioral health services & research*, *38*(1), 29-50.

McDermid, R. C., & Bagshaw, S. M. (2014). *Physiological reserve and frailty in critical illness*. Oxford University Press.

McDonough, P., & Walters, V. (2001). Gender and health: reassessing patterns and explanations. *Social science & medicine*, *52*(4), 547-559.

McIsaac, D. I., MacDonald, D. B., & Aucoin, S. D. (2019). Frailty for perioperative clinicians: a narrative review. *Anesthesia & Analgesia*, *130*(6), 1450-1460.

McPhee, J. S., French, D. P., Jackson, D., Nazroo, J., Pendleton, N., & Degens, H. (2016). Physical activity in older age: perspectives for healthy ageing and frailty. *Biogerontology*, *17*(3), 567-580.

Mehrabi, F., & Béland, F. (2020). Effects of social isolation, loneliness and frailty on health outcomes and their possible mediators and moderators in community-dwelling older adults: A scoping review. *Archives of Gerontology and Geriatrics*, *90*, 104119. https://doi.org/10.1016/j.archger.2020.104119

Mehrabi, F., & Béland, F. (2021). Frailty as a Moderator of the Relationship between Social Isolation and Health Outcomes in Community-Dwelling Older Adults. *International Journal of Environmental Research and Public Health*, *18*(4), 1675. https://doi.org/10.3390/ijerph18041675

Menec, V. H., Newall, N. E., Mackenzie, C. S., Shooshtari, S., & Nowicki, S. (2019). Examining individual and geographic factors associated with social isolation and loneliness using Canadian Longitudinal Study on Aging (CLSA) data. *PloS one*, *14*(2), e0211143.

Merchant, R. A., Liu, S. G., Lim, J. Y., Fu, X., & Chan, Y. H. (2020). Factors associated with social isolation in community-dwelling older adults: a cross-sectional study. *Quality of life research*, *29*(9), 2375-2381.

Min, J., Ailshire, J., & Crimmins, E. M. (2016). Social engagement and depressive symptoms: do baseline depression status and type of social activities make a difference? *Age and Ageing*, *45*(6), 838-843.

Mitchell, J. C. (1974). Social networks. *Annual review of anthropology*, *3*(1), 279-299.

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *TheScientificWorldJournal*, *1*, 323-336.

Miyawaki, C. E. (2015). Association of social isolation and health across different racial and ethnic groups of older Americans. *Ageing & Society*, *35*(10), 2201-2228.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., & Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*, *4*(1), 1.

Monroe, W. (1898). Discussion and reports. Social consciousness in children. *Psychological Review*, *5*(1), 68.

Morley, J. E., Vellas, B., Van Kan, G. A., Anker, S. D., Bauer, J. M., Bernabei, R., Cesari, M., Chumlea, W., Doehner, W., & Evans, J. (2013). Frailty consensus: a call to action. *Journal of the American Medical Directors Association*, *14*(6), 392-397.

Mulasso, A., Roppolo, M., Giannotta, F., & Rabaglietti, E. (2016). Associations of frailty and psychosocial factors with autonomy in daily activities: a cross-sectional study in Italian community-dwelling older adults. *Clinical interventions in aging*, *11*, 37.

Muthén, B., & Asparouhov, T. (2008). Growth mixture modeling: Analysis with non-Gaussian random effects. *Longitudinal data analysis*, *143165*.

Muthén, B., Asparouhov, T., Hunter, A. M., & Leuchter, A. F. (2011). Growth modeling with nonignorable dropout: alternative analyses of the STAR* D antidepressant trial. *Psychological methods*, *16*(1), 17.

Muthén, B. O., & Khoo, S.-T. (1998). Longitudinal studies of achievement growth using latent variable modeling. *Learning and individual differences*, *10*(2), 73-101.

Muthén, L., & Muthén, B. (2018). Mplus. *The comprehensive modelling program for applied researchers: user's guide*, *5*.

Muthén, L. K., & Muthén, B. (2017). *Mplus user's guide: Statistical analysis with latent variables, user's guide*. Muthén & Muthén.

Naito, R., Leong, D. P., Bangdiwala, S. I., McKee, M., Subramanian, S., Rangarajan, S., Islam, S., Avezum, A., Yeates, K. E., & Lear, S. A. (2021). Impact of social isolation on mortality and morbidity in 20 high-income, middle-income and low-income countries in five continents. *BMJ global health*, *6*(3), e004124.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699.

National Academies of Sciences, E., & Medicine. (2020). Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System.

Naud, D., Généreux, M., Bruneau, J.-F., Alauzet, A., & Levasseur, M. (2019). Social participation in older women and men: differences in community activities and barriers according to region and population size in Canada. *BMC public health*, *19*(1), 1-14.

Nesselroade, J. R., & Baltes, P. B. (1979). *Longitudinal research in the study of behavior and development*. Academic Press.

Newall, N. E., & Menec, V. H. (2017). Loneliness and social isolation of older adults: Why it is important to examine these social aspects together. *Journal of Social and Personal Relationships*, 0265407517749045.

Ní Mhaoláin, A. M., Fan, C. W., Romero-Ortuno, R., Cogan, L., Cunningham, C., Lawlor, B., & Kenny, R. A. (2012). Depression: a modifiable factor in fearful older fallers transitioning to frailty? *International journal of geriatric psychiatry*, *27*(7), 727-733.

Nicholson, N. R. (2012). A review of social isolation: an important but underassessed condition in older adults. *The journal of primary prevention*, *33*(2-3), 137-152.

Nicholson, N. R., Jr (2009). Social isolation in older adults: an evolutionary concept analysis. *Journal of advanced nursing*, *65*(6), 1342-1352.

O'Connell, M. L., Coppinger, T., & McCarthy, A. L. (2020). The role of nutrition and physical activity in frailty: a review. *Clinical nutrition ESPEN*, *35*, 1-11.

O'Caoimh, R., Sezgin, D., O'Donovan, M. R., Molloy, D. W., Clegg, A., Rockwood, K., & Liew, A. (2021). Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. *Age and ageing*, *50*(1), 96-104.

Okada, K. (2017). Negative estimate of variance-accounted-for effect size: How often it is obtained, and what happens if it is treated as zero. *Behavior research methods*, *49*(3), 979-987.

Okura, M., Ogita, M., Yamamoto, M., Nakai, T., Numata, T., & Arai, H. (2017). The relationship of community activities with cognitive impairment and depressive mood independent of mobility disorder in Japanese older adults. *Archives of gerontology and geriatrics*, *70*, 54-61.

Organization, W. H. (2017). Global strategy and action plan on ageing and health.

Palmer, R. F., Espino, D. V., Dergance, J. M., Becho, J., & Markides, K. (2012). The role of physical activity and diabetes status as a moderator: functional disability among older Mexican Americans. *Age and ageing*, *41*(6), 752-758.

Peek, M. K., Howrey, B. T., Ternent, R. S., Ray, L. A., & Ottenbacher, K. J. (2012). Social support, stressors, and frailty among older Mexican American adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *67*(6), 755-764.

Pérez-Tasigchana, R. F., Sandoval-Insausti, H., Donat-Vargas, C., Banegas, J. R., Rodríguez-Artalejo, F., & Guallar-Castillon, P. (2020). Combined impact of traditional and nontraditional healthy behaviors on frailty and disability: A prospective cohort study of older adults. *Journal of the American Medical Directors Association*, *21*(5), 710. e711-710. e719.

Peters, L. L., Boter, H., Buskens, E., & Slaets, J. P. (2012). Measurement properties of the Groningen Frailty Indicator in home-dwelling and institutionalized elderly people. *Journal of the American Medical Directors Association*, *13*(6), 546-551.

Peters, M. D., Godfrey, C. M., Khalil, H., McInerney, P., Parker, D., & Soares, C. B. (2015). Guidance for conducting systematic scoping reviews. *JBI Evidence Implementation*, *13*(3), 141-146.

Peterson, M. J., Giuliani, C., Morey, M. C., Pieper, C. F., Evenson, K. R., Mercer, V., Cohen, H. J., Visser, M., Brach, J. S., & Kritchevsky, S. B. (2009). Physical activity as a preventative

factor for frailty: the health, aging, and body composition study. *The Journals of Gerontology: Series A*, *64*(1), 61-68.

Pham, M. T., Rajić, A., Greig, J. D., Sargeant, J. M., Papadopoulos, A., & McEwen, S. A. (2014). A scoping review of scoping reviews: advancing the approach and enhancing the consistency. *Research synthesis methods*, *5*(4), 371-385.

Poli, S., Cella, A., Puntoni, M., Musacchio, C., Pomata, M., Torriglia, D., Vello, N., Molinari, B., Pandolfini, V., & Torrigiani, C. (2017). Frailty is associated with socioeconomic and lifestyle factors in community-dwelling older subjects. *Aging clinical and experimental research*, *29*(4), 721-728.

Preacher, K. J., Wichman, A. L., MacCallum, R. C., & Briggs, N. E. (2008). Relationships between LGM and multilevel modeling. *Latent growth curve modeling*, 71-79.

Provencher, V., Béland, F., Demers, L., Desrosiers, J., Bier, N., Ávila-Funes, J. A., Galand, C., Julien, D., Fletcher, J. D., & Trottier, L. (2017). Are frailty components associated with disability in specific activities of daily living in community-dwelling older adults? A multicenter Canadian study. *Archives of Gerontology and Geriatrics*, *73*, 187-194.

Putnam, R. D. (2000). *Bowling alone: The collapse and revival of American community*. Simon and schuster.

Ram, N., & Grimm, K. (2007). Using simple and complex growth models to articulate developmental change: Matching theory to method. *International journal of behavioral development*, *31*(4), 303-316.

Rico-Uribe, L. A., Caballero, F. F., Martín-María, N., Cabello, M., Ayuso-Mateos, J. L., & Miret, M. (2018). Association of loneliness with all-cause mortality: A meta-analysis. *PloS one*, *13*(1), e0190033.

Risbridger, S., Walker, R., Gray, W., Kamaruzzaman, S., Ai-Vyrn, C., Hairi, N., Khoo, P., & Pin, T. (2021). Social Participation's Association with Falls and Frailty in Malaysia: A Cross-Sectional Study. *The Journal of frailty & aging*, 1-7.

Roberts, B. W., Walton, K. E., & Viechtbauer, W. (2006). Patterns of mean-level change in personality traits across the life course: a meta-analysis of longitudinal studies. *Psychological bulletin*, *132*(1), 1.

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(7), 722-727.

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *Cmaj*, *173*(5), 489-495.

Rohde, N., D'Ambrosio, C., Tang, K. K., & Rao, P. (2016). Estimating the mental health effects of social isolation. *Applied research in quality of life*, *11*(3), 853-869.

Röhr, S., Wittmann, F., Engel, C., Enzenbach, C., Witte, A. V., Villringer, A., Löffler, M., & Riedel-Heller, S. G. (2021). Social factors and the prevalence of social isolation in a population-based adult cohort. *Social psychiatry and psychiatric epidemiology*, 1-10.

Rolfson, D. B., Majumdar, S. R., Tsuyuki, R. T., Tahir, A., & Rockwood, K. (2006). Validity and reliability of the Edmonton Frail Scale. *Age and ageing*, *35*(5), 526-529.

Romero-Ortuno, R., Fouweather, T., & Jagger, C. (2013). Cross-national disparities in sex differences in life expectancy with and without frailty. *Age and ageing*, *43*(2), 222-228.

Romero-Ortuno, R., Walsh, C. D., Lawlor, B. A., & Kenny, R. A. (2010). A frailty instrument for primary care: findings from the Survey of Health, Ageing and Retirement in Europe (SHARE). *BMC geriatrics*, *10*(1), 57.

Santini, Z. I., Fiori, K. L., Feeney, J., Tyrovolas, S., Haro, J. M., & Koyanagi, A. (2016). Social relationships, loneliness, and mental health among older men and women in Ireland: A prospective community-based study. *Journal of affective disorders*, *204*, 59-69.

Santini, Z. I., Jose, P. E., Cornwell, E. Y., Koyanagi, A., Nielsen, L., Hinrichsen, C., Meilstrup, C., Madsen, K. R., & Koushede, V. (2020). Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. *The Lancet Public Health*, *5*(1), e62-e70.

Scharlach, A. E., Davitt, J. K., Lehning, A. J., Greenfield, E. A., & Graham, C. L. (2014). Does the village model help to foster age-friendly communities? *Journal of aging & social policy*, *26*(1-2), 181-196.

Scheel-Hincke, L. L., Möller, S., Lindahl-Jacobsen, R., Jeune, B., & Ahrenfeldt, L. J. (2020). Cross-national comparison of sex differences in ADL and IADL in Europe: findings from SHARE. *European journal of ageing*, *17*(1), 69-79.

Schnittger, R. I., Walsh, C. D., Casey, A.-M., Wherton, J. P., McHugh, J. E., & Lawlor, B. A. (2012). Psychological distress as a key component of psychosocial functioning in community-dwelling older people. *Aging & mental health*, *16*(2), 199-207.

Seeman, T. E. (1996). Social ties and health: The benefits of social integration. *Annals of epidemiology*, *6*(5), 442-451.

Seeman, T. E., Bruce, M. L., & McAvay, G. J. (1996). Social network characteristics and onset of ADL disability: MacArthur studies of successful aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *51*(4), S191-S200.

Serra-Prat, M., Papiol, M., Vico, J., Palomera, E., Sist, X., & Cabré, M. (2016). Factors associated with frailty in community-dwelling elderly population. A cross-sectional study. *European Geriatric Medicine*, *7*(6), 531-537.

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health psychology*, *30*(4), 377.

Shankar, A., McMunn, A., Demakakos, P., Hamer, M., & Steptoe, A. (2017). Social isolation and loneliness: Prospective associations with functional status in older adults. *Health psychology*, *36*(2), 179.

Sharifian, N., Kraal, A. Z., Zaheed, A. B., Sol, K., & Zahodne, L. B. (2020). Longitudinal associations between contact frequency with friends and with family, activity engagement, and cognitive functioning. *Journal of the International Neuropsychological Society*, *26*(8), 815-824.

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*.

Shor, E., & Roelfs, D. J. (2015). Social contact frequency and all-cause mortality: A meta-analysis and meta-regression. *Social Science & Medicine*, *128*, 76-86.

Smith, K. J., & Victor, C. (2019). Typologies of loneliness, living alone and social isolation, and their associations with physical and mental health. *Ageing & Society*, *39*(8), 1709-1730.

Smith, L., Firth, J., Grabovac, I., Koyanagi, A., Veronese, N., Stubbs, B., Soysal, P., Yang, L., & Jackson, S. E. (2019). The association of grip strength with depressive symptoms and cortisol in hair: A cross-sectional study of older adults. *Scandinavian journal of medicine & science in sports*, *29*(10), 1604-1609.

Song, J., Lindquist, L. A., Chang, R. W., Semanik, P. A., Ehrlich-Jones, L. S., Lee, J., Sohn, M.-W., & Dunlop, D. D. (2015). Sedentary behavior as a risk factor for physical frailty independent of moderate activity: results from the osteoarthritis initiative. *American journal of public health*, *105*(7), 1439-1445.

Sourial, N., Wolfson, C., Bergman, H., Zhu, B., Karunananthan, S., Quail, J., Fletcher, J., Weiss, D., Bandeen-Roche, K., & Béland, F. (2010). A correspondence analysis revealed frailty deficits aggregate and are multidimensional. *Journal of clinical epidemiology*, *63*(6), 647-654.

Spector, W. D., & Fleishman, J. A. (1998). Combining activities of daily living with instrumental activities of daily living to measure functional disability. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *53*(1), S46-S57.

Statistics Canada. (2010). Canadian Community Health Survey (CCHS)-Healthy Aging questionnaire (2008-2009). 117-120. (Statistics Canada)

Statistics Canada. (2019). *Population projections for Canada (2018 to 2068), Provinces and Territories (2018 to 2043)*. Retrieved September 17, 2019 from https://www150.statcan.gc.ca/n1/pub/91-520-x/91-520-x2019001-eng.htm

Stewart, M., Anderson, J., Beiser, M., Mwakarimba, E., Neufeld, A., Simich, L., & Spitzer, D. (2008). Multicultural meanings of social support among immigrants and refugees. *International Migration*, *46*(3), 123-159.

Strandberg, T. E., & Pitkälä, K. H. (2007). Frailty in elderly people. *Lancet (London, England)*, *369*(9570), 1328-1329.

Takatori, K., & Matsumoto, D. (2021). Social factors associated with reversing frailty progression in community-dwelling late-stage elderly people: An observational study. *PloS one*, *16*(3), e0247296.

Tan, B. K. J., Man, R. E. K., Gan, A. T. L., Fenwick, E. K., Varadaraj, V., Swenor, B. K., Gupta, P., Wong, T. Y., Trevisan, C., & Lorenzo-López, L. (2020). Is sensory loss an understudied risk factor for frailty? A systematic review and meta-analysis. *The Journals of Gerontology: Series A*, *75*(12), 2461-2470.

Tanskanen, J., & Anttila, T. (2016). A prospective study of social isolation, loneliness, and mortality in Finland. *American journal of public health*, *106*(11), 2042-2048.

Theeke, L. A. (2010). Sociodemographic and health-related risks for loneliness and outcome differences by loneliness status in a sample of US older adults. *Research in gerontological nursing*, *3*(2), 113-125.

Theou, O., Walston, J., & Rockwood, K. (2015). Operationalizing frailty using the frailty phenotype and deficit accumulation approaches. In *Frailty in Aging* (Vol. 41, pp. 66-73). Karger Publishers.

Tugade, M. M., & Fredrickson, B. L. (2004). Resilient individuals use positive emotions to bounce back from negative emotional experiences. *Journal of personality and social psychology*, *86*(2), 320.

Uchino, B., Ong, A., Queen, T., & Kent de Grey, R. (2016). Theories of social support in health and aging. *Handbook of theories of aging (3rd. ed.). New York, NY: Springer*.

Uchino, B. N. (2006). Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of behavioral medicine*, *29*(4), 377-387.

Ukraintseva, S., Yashin, A. I., & Arbeev, K. G. (2016). Resilience versus robustness in aging.

Umberson, D., & Karas Montez, J. (2010). Social relationships and health: A flashpoint for health policy. *Journal of health and social behavior*, *51*(1_suppl), S54-S66.

United Nations. (2006). *Guidelines for review and appraisal of the Madrid international plan of action on ageing—Bottom-up participatory approach*. U. D. o. E. a. S. Affairs.

Uno, C., Okada, K., Matsushita, E., Satake, S., & Kuzuya, M. (2021). Friendship-related social isolation is a potential risk factor for the transition from robust to prefrailty among healthy older adults: a 1-year follow-up study. *European Geriatric Medicine*, *12*(2), 285-293.

Vaingankar, J. A., Chong, S. A., Abdin, E., Picco, L., Chua, B. Y., Shafie, S., Ong, H. L., Chang, S., Seow, E., & Heng, D. (2017). Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. *Geriatrics & gerontology international*, *17*(10), 1444-1454.

Valtorta, N., & Hanratty, B. (2012). Loneliness, isolation and the health of older adults: do we need a new research agenda? *Journal of the Royal Society of Medicine*, *105*(12), 518-522.

Valtorta, N. K., Kanaan, M., Gilbody, S., & Hanratty, B. (2016). Loneliness, social isolation and social relationships: what are we measuring? A novel framework for classifying and comparing tools. *BMJ open*, *6*(4), e010799.

Valtorta, N. K., Kanaan, M., Gilbody, S., & Hanratty, B. (2018). Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing. *European journal of preventive cardiology*, *25*(13), 1387-1396.

van Kan, G. A., Rolland, Y. M., Morley, J. E., & Vellas, B. (2008). Frailty: toward a clinical definition. *Journal of the American Medical Directors Association*, *9*(2), 71-72.

Vermeiren, S., Vella-Azzopardi, R., Beckwee, D., Habbig, A.-K., Scafoglieri, A., Jansen, B., Bautmans, I., Verté, D., Beyer, I., & Petrovic, M. (2016). Frailty and the prediction of negative health outcomes: a meta-analysis. *Journal of the American Medical Directors Association*, *17*(12), 1163. e1161-1163. e1117.

Vetrano, D. L., Palmer, K., Marengoni, A., Marzetti, E., Lattanzio, F., Roller-Wirnsberger, R., Lopez Samaniego, L., Rodríguez-Mañas, L., Bernabei, R., & Onder, G. (2019). Frailty and multimorbidity: a systematic review and meta-analysis. *The Journals of Gerontology: Series A*, *74*(5), 659-666.

Victor, C. R., Scambler, S. J., Bowling, A., & Bond, J. (2005). The prevalence of, and risk factors for, loneliness in later life: a survey of older people in Great Britain. *Ageing & Society*, *25*(6), 357-375.

Victor, C. R., & Yang, K. (2012). The prevalence of loneliness among adults: a case study of the United Kingdom. *The Journal of psychology*, *146*(1-2), 85-104.

Wade, K. F., Marshall, A., Vanhoutte, B., Wu, F. C., O'Neill, T. W., & Lee, D. M. (2017). Does pain predict frailty in older men and women? Findings from the English Longitudinal Study of Ageing (ELSA). *The Journals of Gerontology: Series A*, *72*(3), 403-409.

Wallace, L., Theou, O., Rockwood, K., & Andrew, M. K. (2018). Relationship between frailty and Alzheimer's disease biomarkers: a scoping review. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *10*, 394-401.

Walston, J., Hadley, E. C., Ferrucci, L., Guralnik, J. M., Newman, A. B., Studenski, S. A., Ershler, W. B., Harris, T., & Fried, L. P. (2006). Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *Journal of the American Geriatrics Society*, *54*(6), 991-1001.

Wang, B., He, P., & Dong, B. (2015). Associations between social networks, social contacts, and cognitive function among Chinese nonagenarians/centenarians. *Archives of Gerontology and Geriatrics*, *60*(3), 522-527.

Wang, J., Mann, F., Lloyd-Evans, B., Ma, R., & Johnson, S. (2018). Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review. *BMC psychiatry*, *18*(1), 156.

Wang, R., Feng, Z., Liu, Y., & Lu, Y. (2020). Relationship between neighbourhood social participation and depression among older adults: A longitudinal study in China. *Health & social care in the community*, *28*(1), 247-259.

Ware Jr, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical care*, 473-483.

Washburn, R. A. (2000). Assessment of physical activity in older adults. *Research quarterly for exercise and sport*, *71*(sup2), 79-87.

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): development and evaluation. *Journal of clinical epidemiology*, *46*(2), 153-162.

Weiss, R. S. (1973). Loneliness: The experience of emotional and social isolation.

Wen, Z., Marsh, H. W., Hau, K.-T., Wu, Y., Liu, H., & Morin, A. J. (2014). Interaction effects in latent growth models: Evaluation of alternative estimation approaches. *Structural Equation Modeling: A Multidisciplinary Journal*, *21*(3), 361-374.

Wenger, G. C., & Burholt, V. (2004). Changes in levels of social isolation and loneliness among older people in a rural area: a twenty–year longitudinal study. *Canadian Journal on Aging/la revue canadienne du vieillissement*, *23*(2), 115-127.

Wethington, E., & Pillemer, K. (2013). Social isolation among older people. *The handbook of solitude: Psychological perspectives on social isolation, social withdrawal, and being alone*, 242-259.

Wethington, E., & Pillemer, K. (2014). Social isolation among older people. *SOLITUDE*, 242.

Whitson, H. E., Cohen, H. J., Schmader, K., Morey, M. C., Kuchel, G., & Colon-Emeric, C. (2018). Physical resilience: not simply the opposite of frailty. *Journal of the American Geriatrics Society*, *66*(8), 1459.

Whitson, H. E., Duan-Porter, W., Schmader, K. E., Morey, M. C., Cohen, H. J., & Colón-Emeric, C. S. (2016). Physical resilience in older adults: systematic review and development of an emerging construct. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *71*(4), 489-495.

World Health Organization. (2002). *Active ageing: A policy framework*.

World Health Organization. (2007). *Global age-friendly cities: A guide*. World Health Organization.

World Health Organization. (2015). *World report on ageing and health* (9241565047).

World Health Organization. (2017). *10 facts on ageing and health*. https://www.who.int/news-room/fact-sheets/detail/10-facts-on-ageing-and-health

World Health Organization. (2020). *Decade of healthy ageing: baseline report*.

Xie, B., & Ma, C. (2021). Effect of social participation on the development of physical frailty: Do type, frequency and diversity matter? *Maturitas*, *151*, 48-54.

Yesavage, J. A., & Sheikh, J. I. (1986). 9/Geriatric depression scale (GDS) recent evidence and development of a shorter version. *Clinical gerontologist*, *5*(1-2), 165-173.

Yu, B., Steptoe, A., Chen, Y., & Jia, X. (2020). Social isolation, rather than loneliness, is associated with cognitive decline in older adults: the China Health and Retirement Longitudinal Study. *Psychological medicine*, 1-8.

Yu, B., Steptoe, A., Niu, K., & Jia, X. (2020). Social Isolation and Loneliness as Risk Factors for Grip Strength Decline Among Older Women and Men in China. *Journal of the American Medical Directors Association*, *21*(12), 1926-1930.

Zhang, X., Sun, M., Liu, S., Leung, C. H., Pang, L., Popat, U. R., Champlin, R., Holmes, H. M., Valero, V., & Dinney, C. P. (2018). Risk factors for falls in older patients with cancer. *BMJ supportive & palliative care*, *8*(1), 34-37.

Zhang, X., Warner, M. E., & Firestone, S. (2019). Overcoming barriers to livability for all ages: Inclusivity is the key. *Urban Planning*, *4*(2), 31-42.

Zunzunegui, M.-V., Béland, F., Sanchez, M.-T., & Otero, A. (2009). Longevity and relationships with children: the importance of the parental role. *BMC public health*, *9*(1), 351.

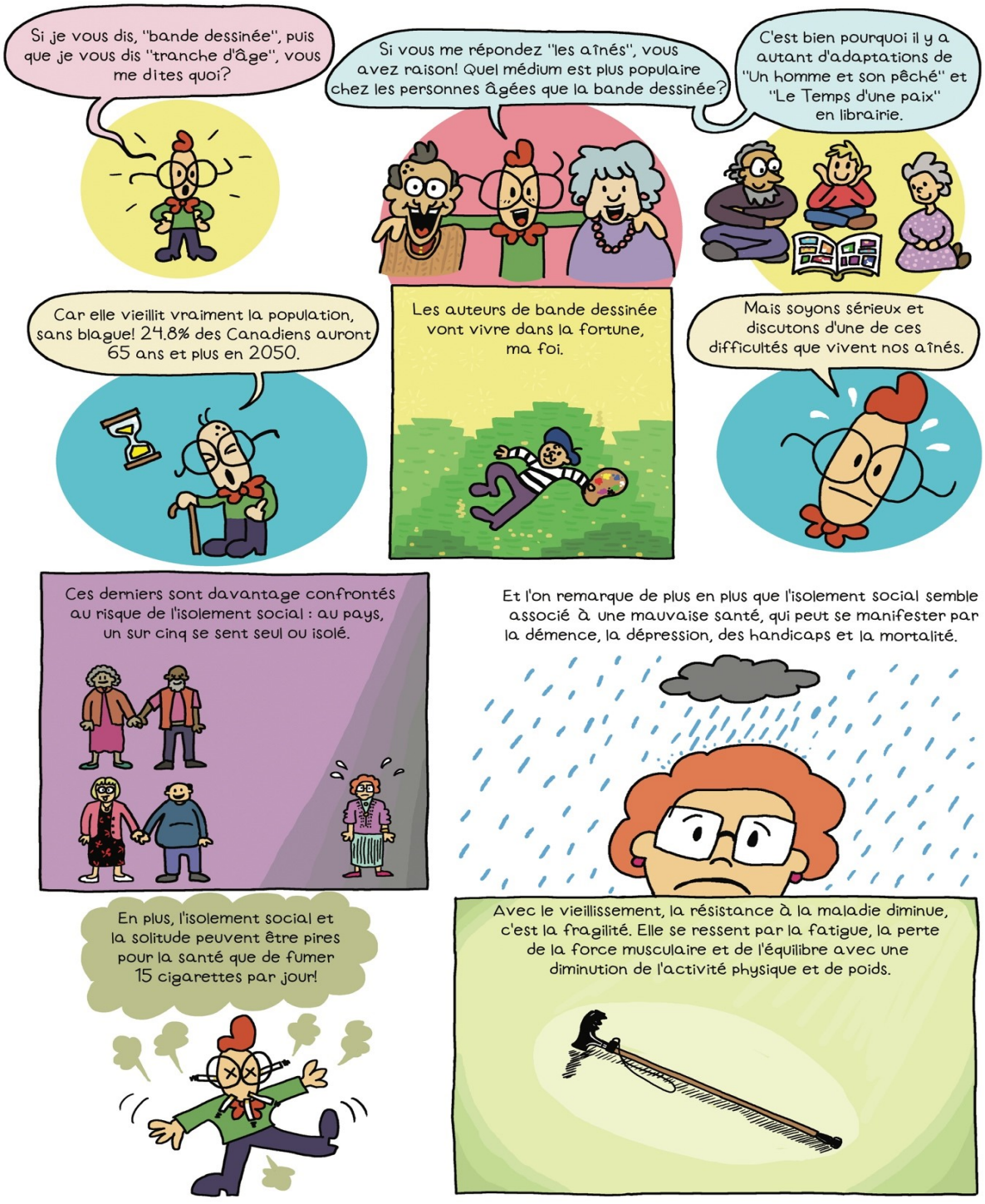
Zunzunegui, M.-V., Koné, A., Johri, M., Béland, F., Wolfson, C., & Bergman, H. (2004). Social networks and self-rated health in two French-speaking Canadian community dwelling populations over 65. *Social Science & Medicine*, *58*(10), 2069-2081.

Appendices

Appendix A: The Comic of this research study illustrated by Saturnome

The present research study was among the top 5 hot research topic that was selected in the “illustre recherche” competition at FAECUM through which the comic of this study was illustrated by Saturnome to raise awareness about social isolation and frailty among the public. The comic is displayed on the Facebook page of FAECUM:

https://www.facebook.com/FAECUM/photos/a.259784816692317 5/259784822692316 9/?type=3&thea ter.


Si je vous dis, "bande dessinée", puis que je vous dis "tranche d'âge", vous me dites quoi?
Si vous me répondez "les aînés", vous avez raison! Quel médium est plus populaire chez les personnes âgées que la bande dessinée?
C'est bien pourquoi il y a autant d'adaptations de "Un homme et son péché" et "Le Temps d'une paix" en librairie.
Car elle vieillit vraiment la population, sans blague! 24.8% des Canadiens auront 65 ans et plus en 2050.
Les auteurs de bande dessinée vont vivre dans la fortune, ma foi.
Mais soyons sérieux et discutons d'une de ces difficultés que vivent nos aînés.
Ces derniers sont davantage confrontés au risque de l'isolement social : au pays, un sur cinq se sent seul ou isolé.
Et l'on remarque de plus en plus que l'isolement social semble associé à une mauvaise santé, qui peut se manifester par la démence, la dépression, des handicaps et la mortalité.
En plus, l'isolement social et la solitude peuvent être pires pour la santé que de fumer 15 cigarettes par jour!
Avec le vieillissement, la résistance à la maladie diminue, c'est la fragilité. Elle se ressent par la fatigue, la perte de la force musculaire et de l'équilibre avec une diminution de l'activité physique et de poids.

Ainsi, le soutien social devrait diminuer la fragilité.

... et améliorer la santé et allonger la bonne vie.

-Fereshteh Mehrabi

Appendix B: Ethics certificates

Université de Montréal

Comité d'éthique de la recherche en santé

14 décembre 2017

Objet: Approbation éthique – « Social isolation, frailty and their adverses outcomes in the elderly: A longitudinal study in Quebec »

Mme Fereshteh Mehrabi,

Le Comité d'éthique de la recherche en santé (CERES) a étudié le projet de recherche susmentionné et a délivré le certificat d'éthique demandé suite à la satisfaction des exigences précédemment émises. Vous trouverez ci-joint une copie numérisée de votre certificat; copie également envoyée à votre directeur/directrice de recherche et à la technicienne en gestion de dossiers étudiants (TGDE) de votre département.

Notez qu'il y apparaît une mention relative à un suivi annuel et que le certificat comporte une date de fin de validité. En effet, afin de répondre aux exigences éthiques en vigueur au Canada et à l'Université de Montréal, nous devons exercer un suivi annuel auprès des chercheurs et étudiants-chercheurs.

De manière à rendre ce processus le plus simple possible et afin d'en tirer pour tous le plus grand profit, nous avons élaboré un court questionnaire qui vous permettra à la fois de satisfaire aux exigences du suivi et de nous faire part de vos commentaires et de vos besoins en matière d'éthique en cours de recherche. Ce questionnaire de suivi devra être rempli annuellement jusqu'à la fin du projet et pourra nous être retourné par courriel. La validité de l'approbation éthique est conditionnelle à ce suivi. Sur réception du dernier rapport de suivi en fin de projet, votre dossier sera clos.

Il est entendu que cela ne modifie en rien l'obligation pour le chercheur, tel qu'indiqué sur le certificat d'éthique, de signaler au CERES tout incident grave dès qu'il survient ou de lui faire part de tout changement anticipé au protocole de recherche.

Nous vous prions d'agréer, Madame, l'expression de nos sentiments les meilleurs,

Dominique Langelier, présidente
Comité d'éthique de la recherche en santé (CERES)
Université de Montréal

DL/GP/gp
c.c. Gestion des certificats, BRDV
François Béland, professeur titulaire, École de santé publique - Département d'administration de la santé
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Original ethics approval by Université de Montréal

Université de Montréal

N° de certificat
17-162-CERES-D

Comité d'éthique de la recherche en santé

CERTIFICAT D'APPROBATION ÉTHIQUE

Le Comité d'éthique de la recherche en santé (CERES), selon les procédures en vigueur, en vertu des documents qui lui ont été fournis, a examiné le projet de recherche suivant et conclu qu'il respecte les règles d'éthique énoncées dans la Politique sur la recherche avec des êtres humains *de l'Université de Montréal.*

Projet	
Titre du projet	**Social isolation, frailty and their adverses outcomes in the elderly: A longitudinal study in Quebec**
Étudiante requérante	**Fereshteh Mehrabi** [redacted] Candidate au Ph. D. en santé publique, École de santé publique - Département de gestion, d'évaluation et de politique de santé
Sous la direction de	François Béland, professeur titulaire, École de santé publique - Département d'administration de la santé, Université de Montréal

Financement	
Organisme	Non financé
Programme	
Titre de l'octroi si différent	
Numéro d'octroi	
Chercheur principal	
No de compte	

MODALITÉS D'APPLICATION

Tout changement anticipé au protocole de recherche doit être communiqué au CERES qui en évaluera l'impact au chapitre de l'éthique.

Toute interruption prématurée du projet ou tout incident grave doit être immédiatement signalé au CERES

Selon les règles universitaires en vigueur, un suivi annuel est minimalement exigé pour maintenir la validité de la présente approbation éthique, et ce, jusqu'à la fin du projet. Le questionnaire de suivi est [redacted] du CERES.

[redacted]

Dominique Langelier, présidente
Comité d'éthique de la recherche en santé
Université de Montréal

14 décembre 2017
Date de délivrance

1er septembre 2020
Date de fin de validité

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

3333 Queen-Mary
2e étage, bur. 220-3
Montréal QC H3V 1A2

Téléphone : 514-343-6111 poste 2604
ceres@umontreal.ca
www.ceres.umontreal.ca

Ethics renewal by Université de Montéal

Université de Montréal

Comité d'éthique de la recherche en sciences et en santé (CERSES)

19 août 2020

Objet: Certificat d'approbation éthique - 1er renouvellement – « Social Isolation, Frailty and Health Outcomes among community-dwelling older adults: A Longitudinal Study in Quebec »

Mme Fereshteh Mehrabi,

Le Comité d'éthique de la recherche en sciences et en santé (CERSES) a étudié votre demande de renouvellement pour le projet de recherche susmentionné et a délivré le certificat d'éthique demandé suite à la satisfaction des exigences qui prévalent. Vous trouverez ci-joint une copie numérisée de votre certificat; copie également envoyée à votre directeur/directrice de recherche et à la technicienne en gestion de dossiers étudiants (TGDE) de votre département.

Notez qu'il y apparaît une mention relative à un suivi annuel et que le certificat comporte une date de fin de validité. En effet, afin de répondre aux exigences éthiques en vigueur au Canada et à l'Université de Montréal, nous devons exercer un suivi annuel auprès des chercheurs et étudiants-chercheurs.

De manière à rendre ce processus le plus simple possible et afin d'en tirer pour tous le plus grand profit, nous avons élaboré un court questionnaire qui vous permettra à la fois de satisfaire aux exigences du suivi et de nous faire part de vos commentaires et de vos besoins en matière d'éthique en cours de recherche. Ce questionnaire de suivi devra être rempli annuellement jusqu'à la fin du projet et pourra nous être retourné par courriel. La validité de l'approbation éthique est conditionnelle à ce suivi. Sur réception du dernier rapport de suivi en fin de projet, votre dossier sera clos.

Il est entendu que cela ne modifie en rien l'obligation pour le chercheur, tel qu'indiqué sur le certificat d'éthique, de signaler au Comité tout incident grave dès qu'il survient ou de lui faire part de tout changement anticipé au protocole de recherche.

Nous vous prions d'agréer, Madame, l'expression de nos sentiments les meilleurs,

Insaf Salem Fourati
Responsable de l'évaluation éthique continue
Comité d'éthique de la recherche en sciences et en santé (CERSES)
Université de Montréal

c.c. Gestion des certificats, BRDV
François Béland, professeur titulaire, École de santé publique - Département d'administration de la santé
p.j. Certificat #17-162-CERES-D(1)

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

3333 Queen-Mary
2e étage, bur. 220-3
Montréal QC H3V 1A2

Téléphone : 514-343-6111 poste 2604
ceres@umontreal.ca
www.ceres.umontreal.ca

Université de Montréal

Comité d'éthique de la recherche en sciences et en santé (CERSES)

N^O de certificat
17-162-CERES-D(1)

CERTIFICAT D'APPROBATION ÉTHIQUE

- 1er renouvellement -

Le Comité d'éthique de la recherche en sciences et en santé (CERSES), selon les procédures en vigueur et en vertu des documents relatifs au suivi qui lui a été fournis conclu qu'il respecte les règles d'éthique énoncées dans la Politique sur la recherche avec des êtres humains *de l'Université de Montréal*

Projet	
Titre du projet	**Social Isolation, Frailty and Health Outcomes among community-dwelling older adults: A Longitudinal Study in Quebec**
Étudiante requérante	**Fereshteh Mehrabi** [redacted], Candidate au Ph. D. en santé publique, École de santé publique - Département de gestion, d'évaluation et de politique de santé
Sous la direction de	François Béland, professeur titulaire, École de santé publique - Département d'administration de la santé, Université de Montréal
Note :	Modification du titre; Modifications au protocole de recherche (méthodologie) 18 août 2020
Financement	
Organisme	Non financé
Programme	
Titre de l'octroi si différent	
Numéro d'octroi	
Chercheur principal	
No de compte	

MODALITÉS D'APPLICATION

Tout changement anticipé au protocole de recherche doit être communiqué au Comité qui en évaluera l'impact au chapitre de l'éthique. Toute interruption prématurée du projet ou tout incident grave doit être immédiatement signalé au Comité.

Selon les règles universitaires en vigueur, un suivi annuel est minimalement exigé pour maintenir la validité de la présente approbation éthique, et ce, jusqu'à la fin du projet. Le questionnaire de suivi est disponible sur la page web du Comité.

[redacted]

Insaf Salem Fourati
Responsable de l'évaluation éthique continue
Comité d'éthique de la recherche en sciences et en santé (CERSES)
Université de Montréal

19 août 2020
Date de délivrance du renouvellement ou de la réémission*

1er septembre 2021
Date du prochain suivi

14 décembre 2017
Date du certificat initial

1er septembre 2021
Date de fin de validité

*Le présent renouvellement est en continuité avec le précédent certificat

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

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Montréal QC H3V 1A2

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www.ceres.umontreal.ca

Comité d'éthique de la recherche en sciences et en santé (CERSES)

Bureau de la conduite responsable en recherche

Université de Montréal

16 août 2021

Fereshteh Mehrabi

François Béland

OBJET :	Projet # 2017-644 - Renouvellement de l'approbation éthique Social Isolation, Frailty and Health Outcomes among community-dwelling older adults: A Longitudinal Study in Quebec Financement : non financé

Bonjour,

Vous avez soumis au Comité d'éthique de la recherche en sciences et en santé (CERSES) de l'Université de Montréal, en date 13 août 2021, une demande de renouvellement pour votre projet cité en rubrique.

Votre demande de renouvellement a fait l'objet d'une évaluation. Suite à celle-ci, le tout étant jugé satisfaisant, j'ai le plaisir de vous informer que votre demande de renouvellement a été approuvée par le CERSES.

Ainsi, vous pouvez poursuivre votre projet de recherche pour un an, et ce, à compter du 01 septembre 2021 jusqu'au 01 septembre 2022.

Il est de votre responsabilité de compléter le prochain formulaire de renouvellement (formulaire F9) que nous vous ferons parvenir annuellement via Nagano 1 mois avant l'échéance de la présente approbation, à défaut de quoi l'approbation éthique délivrée par le CERSES sera suspendue.

Dans le cadre du suivi éthique continu, le Comité vous demande de vous conformer aux exigences suivantes en utilisant les formulaires Nagano prévus à cet effet :

- Soumettre, pour approbation préalable, toute demande de **modification** au projet de recherche ou à tout autre document approuvé par le Comité pour la réalisation du projet (formulaire F1).
- Soumettre, dès que cela est porté à votre connaissance, toutes **informations supplémentaires, nouveau renseignement et/ou correspondances diverses** (formulaire F2).
- Soumettre, dès que cela est porté à votre connaissance, tout **incident ou accident** lié à la réalisation du projet de recherche (formulaire F5).
- Soumettre, dès que cela est porté à votre connaissance, l'**interruption prématurée** du projet de recherche, qu'elle soit temporaire ou permanente (formulaire F6).
- Soumettre, dès que cela est porté à votre connaissance, toute **déviation** au projet de recherche susceptible de remettre en cause le caractère éthique du projet (formulaire F8).
- Soumettre une demande de **renouvellement** un mois avant l'échéance de la date d'approbation afin de renouveler l'approbation éthique (formulaire F9).
- Soumettre le rapport de la **fin du projet de recherche** (formulaire F10).

Finalement, nous vous rappelons que la présente décision vaut pour une année et peut être suspendue ou révoquée en cas de non-respect de ces exigences.

Le CERSES de l'Université de Montréal est désigné par le ministre de la Santé et des Services Sociaux aux fins de l'application de l'article 21 du Code civil du Québec. Il exerce ses activités en conformité avec la *Politique sur la recherche avec des êtres humains* (60.1) de l'Université de Montréal ainsi que l'*Énoncé de politique des trois conseils* (EPTC). Il suit également les normes et règlements applicables au Québec et au Canada.

Cordialement,

Pour la présidente du CERSES, Christine Grou,

Josée Côté
Responsable de l'évaluation éthique continue
Bureau de la conduite responsable en recherche
Université de Montréal
Horaire de travail : lundi au mercredi midi
suivi-ethique@umontreal.ca

Josée Côté

Ethics approval by the Research Ethics Board of the Integrated Health and Social Services University Network for West-Central Montreal

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal
Québec
Hôpital général juif

CENTRE GÉRIATRIQUE DONALD BERMAN MAIMONIDES GERIATRIC CENTRE
CENTRE D'HÉBERGEMENT FATHER DOWD RESIDENTIAL CENTRE
CENTRE D'HÉBERGEMENT HENRI-BRADET RESIDENTIAL CENTRE
CENTRE D'HÉBERGEMENT ST-ANDREW RESIDENTIAL CENTRE
CENTRE D'HÉBERGEMENT ST-MARGARET RESIDENTIAL CENTRE
CENTRE MIRIAM HOME AND SERVICES
CENTRE DE RÉADAPTATION CONSTANCE-LETHBRIDGE REHABILITATION CENTRE
CENTRE DE RÉADAPTATION MAB-MACKAY REHABILITATION CENTRE
CHSLD JUIF DE MONTRÉAL JEWISH ELDERCARE CENTRE
CLSC DE BENNY FARM
CLSC DE CÔTE-DES-NEIGES
CLSC MÉTRO
CLSC DE PARC-EXTENSION
CLSC RENÉ-CASSIN
HÔPITAL CATHERINE BOOTH HOSPITAL
HÔPITAL GÉNÉRAL JUIF JEWISH GENERAL HOSPITAL
HÔPITAL MOUNT SINAI HOSPITAL
HÔPITAL RICHARDSON HOSPITAL

Integrated Health and Social Services University Network for West-Central Montreal

BUREAU DE L'EXAMEN DE LA RECHERCHE
RESEARCH REVIEW OFFICE

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN (C)
Présidente, Comité d'éthique de la recherche Médical/biomedical
CIUSSS Centre-Ouest-de-L'Île-de-Montréal
3755 Côte-Ste-Catherine, A-925
Montréal, Québec, H3T 1E2
514-340-8222 local 22445
cer@jgh.mcgill.ca
jgh.ca/rec

Me. Alain Klotz, L.L.M.
Président, Comité d'éthique de la recherche Première ligne & psychocial
CIUSSS Centre-Ouest-de-L'Île-de-Montréal
3755 Côte-Ste-Catherine, A-925
Montréal, Québec, H3T 1E2
514-340-8222 local 22445
cer@jgh.mcgill.ca
jgh.ca/rec

October 10, 2017

Dr. François Béland
Groupe de Recherche Solidage
Jewish General Hospital
Contact: Fereshteh Mehrabi (fereshteh.mehrabi@umontreal.ca)

SUBJECT: **Ethics Protocol:** CODIM-MBM-17-146
Title: "Social isolation, frailty and their adverse outcomes in the elderly: a longitudinal study in Quebec"
Sponsor: N/A

Dear Dr. Béland,

Thank you for submitting your study to the Research Review Office for review.

The Research Ethics Committees of the West-Central Montreal Health (Federalwide Assurance Number: 0796) are designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), the membership requirements for Research Ethics Boards defined in Part C Division 5 of the Food and Drugs Regulations; acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

As this study involves no more than minimal risk in accordance with TCPS 2 article 6.12, this protocol received a delegated research ethics review. We are pleased to inform you that the study is granted Delegated Approval for the period of one year.

As this study is a secondary analysis of data collected as part of the FRéLE study, no consent forms are necessary. For your information, the above-mentioned protocol will be presented for

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal
Québec
Hôpital général juif

corroborative approval at the next meeting of the MBM Research Ethics Committee to be held on October 27, 2017.

Please note that it is the Investigator's responsibility to ensure that all necessary final approval letters (Feasibility) are granted before the study can be initiated at our site.

Delegated Approval Date:	**October 10, 2017**
Expiration date of Delegated Approval:	**October 9, 2018**

Your "Continuing Review Application" must be received by the Research Review Office one month before the expiration date above in order to ensure timely review. Otherwise, the study will be terminated.

Respectfully,

[redacted]

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Medical/Biomedical Research Ethics Committee

Resource person for this project:
Mrs. Kathleen Blagrave, MBM Research Ethics Coordinator
Telephone: 514 340-8222, ext. 26571
e-mail: kblagrave@jgh.mcgill.ca

3755, chemin de la Côte-Sainte-Catherine Road
Montréal (Québec) H3T 1E2
T. 514-340-8222
ciusss-centreouestmtl.gouv.qc.ca

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal
Québec
Integrated Health and Social Services University Network for West-Central Montreal

2018-10-09

Dr. François Béland
c/o: Fereshteh Mehrabi
email: fereshteh.mehrabi@umontreal.ca

Object: Project 2018-805, 17-146 - Continuing review ethics approval.
Social Isolation, Frailty and their Adverse Outcomes in the Elderly: A longitudinal Study in Quebec

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Dear Dr. Béland,

Thank you for the continuing review submission of the research project indicated above.

A delegated review of the research project was provided by member(s) of the Medical-Biomedical of the Integrated Health and Social Services University Network for West-Central Montreal. The research project was found to continue to meet scientific and ethical standards for conduct at the Integrated Health and Social Services University Network for West-Central Montreal.

The following documents were approved or acknowledged by the Medical-Biomedical of the Integrated Health and Social Services University Network for West-Central Montreal:

- Continuing Review Submission Form
- ◦ approved documents (Protocol-Fereshteh Mehrabi.docx)

This will be reported to the Medical-Biomedical and will be entered accordingly into the minutes of the next meeting, to be held on Medical-Biomedical meeting on 2018-10-26.

The approval of the research project is valid until 2019-10-10.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an Annual Renewal Submission Form (F9) to the REC prior to expiry. Please be advised that should the protocol reach its expiry before a continuing review has been submitted, the data collected after the expiry date may not be considered valid. However, should the research conclude for any reason prior to approval expiry, you are required to submit a Completion (End of a Study) Report (F10) to the REC once the data analysis is complete to give an account of the study findings and publication status.

Furthermore, should any revision to the project or other development occur prior to the next continuing review, you must advise the REC without delay. Regulation does not permit initiation of a proposed study modification prior to its approval by the REC.

The Research Ethics Committees of the Integrated Health and Social Services University Network for West-Central Montreal (Federalwide Assurance Number: 0796) are designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), and the membership requirements for Research Ethics Committee defined in Part C Division 5 of the Food and Drugs Regulations; and acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

Duties of Researchers:
Ethics approval may be withdrawn if the following stipulations are not met:

- To obtain prior written approval from the REC for any substantive modification to the research, including changes to the study procedures, financial arrangements and/or resource utilization, before initiating the change; except where urgent action is required to eliminate an immediate hazard to a study participant;
- To maintain confidentially, the updated Research Participants Registry is to be retained for the length of time required by regulations, and in accordance with institutional policy;
- To comply with all relevant regulations and guidelines governing the conduct of research involving human subjects and the requirements of the REC;
- To comply with all REC requests to report study information, including prompt reporting of unexpected or serious adverse events (SAEs) or alarming trends in expected SAEs, according to the policies and procedures of each institution where the study is conducted;
- To advise the REC and all study subjects of new significant findings emerging during the course of the study;
- To comply with quality assurance assessment as defined by each institution's policy;
- To maintain study records according to regulatory requirements,

Respectfully,

Vasiliki Bessy Bitzas
Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Medical/Biomedical Research Ethics Committee

FWA 00000796

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal
Québec
Integrated Health and Social Services University Network for West-Central Montreal

2019-10-16

Dr. François Béland
c/o: Fereshteh Mehrabi
email: fereshteh.mehrabi@umontreal.ca

Object: Project 2018-805, 17-146 - Continuing review ethics approval
Social Isolation, Frailty and their Adverse Outcomes in the Elderly: A longitudinal Study in Quebec

---

Dear Dr. Béland,

Thank you for the continuing review submission of the research project indicated above.

A delegated review of the research project was provided by member(s) of the Medical-Biomedical of the Integrated Health and Social Services University Network for West-Central Montreal. The research project was found to continue to meet scientific and ethical standards for conduct at the Integrated Health and Social Services University Network for West-Central Montreal.

The following documents were approved or acknowledged by the Medical-Biomedical of the Integrated Health and Social Services University Network for West-Central Montreal:

- Continuing Review Submission Form F9 - 11081
- - Please upload publications (if available) (Abstract.pdf)
  - approved documents (Protocol-Fereshteh Mehrabi.docx)

This will be reported to the Medical-Biomedical and will be entered accordingly into the minutes of the next meeting, to be held on 2019-11-22.

The approval of the research project is valid until 2020-10-10.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an Annual Renewal Submission Form (F9) to the REB prior to expiry. Please note that if the protocol approval expires before its renewal is granted, the data collected after the expiration date may not be considered valid. However, should the research conclude for any reason prior to approval expiry, you are required to submit a Completion (End of a Study) Report (F10) to the REB once the data analysis is complete to give an account of the study findings and publication status.

Furthermore, should any revision to the project or other development occur prior to the next continuing review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to its approval by the REB.

The Research Ethics Board of the Integrated Health and Social Services University Network for West-Central Montreal (Federalwide Assurance Number: 0796) are designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2018), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), and the membership requirements for Research Ethics Board defined in Part C Division 5 of the Food and Drugs Regulations; and acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

Duties of Researchers:
Ethics approval may be withdrawn if the following stipulations are not met:

- To obtain prior written approval from the REB for any substantive modification to the research, including changes to the study procedures, financial arrangements and/or resource utilization, before initiating the change; except where urgent action is required to eliminate an immediate hazard to a study participant;
- To maintain confidentially, the updated Research Participants Registry is to be retained for the length of time required by regulations, and in accordance with institutional policy;
- To comply with all relevant regulations and guidelines governing the conduct of research involving human subjects and the requirements of the REB;
- To comply with all REB requests to report study information, including prompt reporting of unexpected or serious adverse events (SAEs) or alarming trends in expected SAEs, according to the policies and procedures of each institution where the study is conducted;
- To advise the REB and all study subjects of new significant findings emerging during the course of the study;
- To comply with quality assurance assessment as defined by each institution's policy;
- To maintain study records according to regulatory requirements,

Respectfully,

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Medical/Biomedical Research Ethics Committee

FWA 00000796

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal

Québec

2020-10-10

Dr. François Béland
c/o: Fereshteh Mehrabi
email: fereshteh.mehrabi@umontreal.ca

Object: Project 2018-805, 17-146 - Continuing review ethics approval
Social Isolation, Frailty and their Adverse Outcomes in the Elderly: A longitudinal Study in Quebec

---

Dear Dr. Béland,

Thank you for the continuing review submission of the research project indicated above.

A delegated review of the research project was provided by member(s) of the Medical/Biomedical Research Ethics Committee of the CIUSSS West-Central Montreal REB. The research project was found to continue to meet scientific and ethical standards for conduct at the CIUSSS West-Central Montreal.

The following documents were approved or acknowledged by the Medical/Biomedical Research Ethics Committee of the CIUSSS West-Central Montreal:

- Continuing Review Submission Form F9-17649
- - Please upload publications (if available) (Mehrabi & Bleand 2020.pdf)
  - Documenation: (Protocol-Fereshteh Mehrabi.docx)
  - approved documents (Protocol-Fereshteh Mehrabi.docx)

This will be reported to the Medical/Biomedical Research Ethics Committee and will be entered accordingly into the minutes of the next meeting, to be held on 2020-10-30.

The approval of the research project is valid until 2021-10-10.

All research involving human subjects requires review at recurring intervals. To comply with the regulation for continuing review of at least once per year, it is the responsibility of the investigator to submit an Annual Renewal Submission Form (F9) to the REB prior to expiry. Please note that if the protocol approval expires before its renewal is granted, the data collected after the expiration date may not be considered valid. However, should the research conclude for any reason prior to approval expiry, you are required to submit a Completion (End of a Study) Report (F10) to the REB once the data analysis is complete to give an account of the study findings and publication status.

Furthermore, should any revision to the project or other development occur prior to the next continuing review,

you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to its approval by the REB.

The Research Ethics Board of the CIUSSS West-Central Montreal (Federalwide Assurance Number: 0796) is designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2018), in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998), and the membership requirements for Research Ethics Board defined in Part C Division 5 of the Food and Drugs Regulations; and acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

Duties of Researchers:

- To obtain prior written approval from the REB for any substantive modification to the research, including changes to the study procedures, financial arrangements and/or resource utilization, before initiating the change; except where urgent action is required to eliminate an immediate hazard to a study participant;
- To maintain confidentially, the updated Research Participants Registry is to be retained for the length of time required by regulations, and in accordance with institutional policy;
- To comply with all relevant regulations and guidelines governing the conduct of research involving human subjects and the requirements of the REB;
- To comply with all REB requests to report study information, including prompt reporting of unexpected or serious adverse events (SAEs) or alarming trends in expected SAEs, according to the policies and procedures of each institution where the study is conducted;
- To advise the REB and all study subjects of new significant findings emerging during the course of the study;
- To comply with quality assurance assessment as defined by each institution's policy;
- To maintain study records according to regulatory requirements,

Ethics approval may be withdrawn if those stipulations are not met.

Respectfully,

Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
Chair, Medical/Biomedical Research Ethics Committee

FWA 00000796

Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal

Québec

Annual Renewal- Harmonized

Protocol title: **Social Isolation, Frailty and their Adverse Outcomes among community-dwelling older adults: A longitudinal Study in Quebec**

Principal investigator: **Dr. François Béland**

First submit date: **2021-08-12**

Submitted by: **Mehrabi, Fereshteh**

Project's REB approbation date: **2017-10-10**

Nagano identifier: **17-146**

Project number(s): **2018-805, 17-146**

Form: **F9H-25036**

Form status: **Form approved**

Review and Decision- Research Review Office

1. **WCMH Reseach Ethics Sub-Committees**
   Medical/Biomedical Committee (MBM)

2. **REB Decision:**
   Approved - REB delegated review
   Please note that this decision is valid for the following participating site(s):
   CIUSSS-COMTL

3. **Renewal Period Granted:**
   2021-10-10 to 2022-10-10

4. **Date of the REC final decision & signature**
   2021-09-16
   Signature

   Dr. Vasiliki Bessy Bitzas, N, PhD, CHPCN(C)
   Chair, Medical/Biomedical Research Ethics Committee

   FWA 00000796

5. Do not select this option