The Role of Functional Social Isolation in Mediating the Association Between Baseline Depression and Subsequent Executive Function in the Canadian Longitudinal Study on Aging Comprehensive Cohort

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Background: Depression is a risk factor for decline in executive function. One mechanism that may link depression to executive function is functional social isolation, which pertains to the qualitative and behavioural aspects of social interactions. The extent to which functional social isolation mediates the association between depression and executive function over time is unknown.

Objective: To determine whether functional social isolation at follow-up (T2) mediates the association between depression (self-reported clinical depression or depressive symptoms) at baseline (T1) and executive function at T2 across age and sex.

Methods: Community-dwelling adults aged 45 to 85 from the Canadian Longitudinal Study on Aging (CLSA) Comprehensive Cohort were followed over three years (complete case analysis, n=14,133). Indirect (i.e., mediation) effects were assessed using percentile bootstrapping across moderators (age and sex) in conditional process analysis controlling for sociodemographic, physical health and health behaviour covariates.

Results: Functional social isolation was a significant mediator of the association between depressive symptoms (β = -0.0032, 95% CI: -0.0069, -0.0005; P_M = 8.0%) or self-reported clinical depression (β = -0.0644, 95% CI: -0.1282, -0.0166; P_M = 17.5%) and executive function only among women aged 75 and older, after controlling for T1 covariates.

Discussion: Functional social isolation may partially explain the association between depression and executive function in women aged 75 and older. Interventions that reduce either functional social isolation or depression in women aged 75 and older may promote executive function in this population.

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List of Abbreviations

ADL	Basic Activities of Daily Living
AFT	Animal Fluency Test
BMI	Body Mass Index
CES-D	Center for Epidemiological Studies Depression Scale
CES-D10	Center for Epidemiological Studies Short Depression Scale
CLSA	Canadian Longitudinal Study on Aging
COWAT	Controlled Oral Word Association Test
IADL	Instrumental Activities of Daily Living
MAT	Mental Alteration Test
MMSE	Mini Mental State Examination
P_M	Proportion mediated
SNST-VV	Stroop Neuropsychological Screening Test-Victoria Version
T1	Baseline
T2	Follow-up
TiMT	Time-Based Prospective Memory Test

Chapter 1

Introduction

Cognitive impairment is a global issue primarily driven by population aging (World Health Organization [WHO], 2017), with implications including loss of independence and reduced quality of life (Griffiths et al., 2020; Tariq & Barber, 2018). By 2050, it is estimated that 1.6 billion people globally will be over the age of 65, suggesting an urgent need for strategies that minimize cognitive decline and subsequent impairment in the population (National Institutes of Health [NIH], 2016). Fortunately, cognitive decline can be reduced by targeting modifiable risk factors, which could result in the prevention of up to 40% of dementia cases (Livingston et al., 2020). Investigating the impact of psychosocial factors on cognition is an especially important research priority, as depression and social isolation are included in the top five modifiable risk factors for dementia, each accounting for 4% of worldwide dementia cases even after accounting for communality, or the overlapping of risk factors (Livingston et al., 2020).

Depression is a common condition, with 11% of Canadians reporting a history of a major depressive disorder (Knoll & MacLennan, 2017). In addition to increasing risk for global cognitive decline and dementia, depression is a known risk factor for impairments in executive function, a subtype of cognition that is vital for everyday functional ability because of its role in decision-making, self-control and perspective-taking (Manchester et al., 2004; Trivedi & Greer 2014). High rates of both depression relapse and treatment-resistant depression suggest that depressive symptoms are difficult to treat and are often experienced chronically, predisposing individuals with depression to comorbid executive function impairments (Alexopoulos, 2019; Wiles et al., 2014). Shared risk factors between depression and executive function (e.g., vascular conditions, low socioeconomic status) also contribute to high rates of executive dysfunction in people with late-life depression (Wang & Blazer, 2015; Bennet & Thomas, 2014). Depression paired with executive function impairment is a particularly devasting combination that has been implicated in higher disability, poorer response to antidepressants, higher depression relapse rates, and higher suicidal risk compared to depression with no executive function impairment (Alexopoulos et al., 2002; DeBattista, 2005; Richard-Devantoy et al., 2012). Reducing the impact of depression on executive function may be an important strategy to minimize executive dysfunction, particularly in those with depression.

Depression likely impacts executive function through direct and indirect pathways that vary across subgroups. While much attention has focused on the physiological mechanisms linking depressive symptoms to executive function (Butters et al., 2008), very little attention has been given to modifiable factors that may mediate depression-induced cognitive impairment. Social isolation may explain, in part,

the association between depression and executive function, although few studies have directly tested this theory using mediation or related analyses (Cohrdes & Bretschneider, 2018; Semino et al., 2017; Wilson et al., 2007). Depression and social isolation are often associated (Almquist et al., 2017), and numerous studies suggest that social isolation is associated with cognitive decline independent of the impact of depression (Atti et al., 2010; Bae et al., 2020; Barnes et al., 2004; Bassuk et al., 1999; Béland et al, 2005; Bourassa et al., 2017; Carty et al., 2020; Chen et al., 2016; Conroy et al., 2010; Deng et al., 2018; Dickinson et al., 2011; Donovan et al., 2017; Estrella et al., 2021; Faramarzi et al., 2018; Ficker et al., 2014; Fratiglioni et al., 2000; Fu et al., 2018; Gow et al., 2013; Han et al., 2019; Holwerda et al., 2014; Huntley et al., 2018; James et al., 2011; D. Kim et al., 2017; G.E. Kim et al., 2019; Lara et al., 2019; Lee et al., 2020; Luchetti et al., 2020; Lyu et al., 2014; Murata et al., 2019; Nelson et al., 2013; Nguyen et al., 2002; O'Luanaigh et al., 2012; Raji et al., 2007; Rawtaer et al., 2017; Roystonn et al., 2020; Stenfors et al., 2013; Stinchcombe & Hammond, 2021; Tomioka et al., 2018; Tsuji et al., 2019; van Gelder et al., 2006; Vilalta-Franch et al., 2013; Wang et al., 2002; Wilson et al., 2007; Wilson et al., 2015; Windsor et al., 2014; Yu et al., 2020; Zahodne et al., 2014; Zahodne et al., 2018; Zunzunegui et al., 2003). For example, depression may induce social isolation as a result of social withdrawal, social dysfunction, or strained relationships (Porcelli et al., 2019). Consequently, social isolation may accelerate cognitive decline through lack of cognitive stimulation, reduced physical activity, or an overactive stress response (Eisele et al., 2012).

Furthermore, social isolation is multidimensional and complex, with potentially different health implications depending on the domain of social isolation. Social isolation is commonly split into two domains: structural, pertaining to objective social factors such as social participation, marital status and social network size; and functional, pertaining to the qualitative aspects of social support (Wister et al., 2019). While functional and structural domains of social isolation have both been identified as potential mediators between depression and cognition, functional social isolation may be more strongly tied to depression (Santini et al., 2020) and have a stronger influence on health-related outcomes (Costa-Cordella et al., 2021) compared to structural social isolation. For example, deficits in social perception may cause those with depression to feel socially isolated despite the presence of objective social network structures (e.g., large social network, being married) (Costa-Cordella et al., 2021; Kupferberg et al., 2016). Furthermore, the concept of functional social isolation incorporates the quality of social interactions (e.g., lack of emotional support and positive social interactions) rather than mere quantity, making functional social isolation more reflective of psychosocial stress and subsequent neurotoxic effects than structural social isolation.

Fortunately, social isolation is potentially modifiable, suggesting a possible target for promoting executive function, particularly in people with depression. The purpose of this thesis is to identify whether functional social isolation is a mediator between depression and executive function over time and in subgroups defined by age and sex. The identification of mediating factors is an important step in designing targeted interventions to support executive function, with the goal of maintaining quality of life in older age.

Chapter 2
Literature Review

2.1 Depression

Depression is the experience and persistence of depressive symptoms (American Psychiatric Association [APA], n.d.; Andresen et al., 1994). Depressive symptoms include, but are not limited to, irritability; inability to concentrate; fatigue; feelings of sadness, hopelessness, and worthlessness; lack of motivation; appetite and sleep changes; suicidal thoughts; loneliness; and social withdrawal (APA, n.d.; Andresen et al., 1994).

The devastating impacts of depression on the individual, their loved ones, and society are well established (Lépine & Briley, 2011). Depression exists on a spectrum, and impairs quality of life and increases risk for disease, disability and death regardless of a clinical depression diagnosis (Meeks et al., 2011; Rodríguez, 2012). Depressive symptoms not meeting the criteria of a clinical diagnosis are termed subthreshold depression, and are much less studied than clinical depression (Meeks et al., 2011). As a result, subthreshold depression is often not recognized and thus not addressed in the healthcare domain (Alexopoulos, 2019; Meeks et al., 2011). Subthreshold depression is up to three times more prevalent than major depression in older adults, with consequences including increased disability and healthcare costs, social isolation, reduced quality of life, risk for developing a depressive disorder, and suicidal ideation (Meeks et al., 2011).

Depressive symptoms are challenging to treat, suggesting the need for long-term management and tertiary prevention of associated health impacts. For example, because of high relapse rates and chronicity, depression may have a cumulative impact on health throughout life (Mulder, 2015). In addition, although clinical depression is treatable through pharmacological treatment and/or psychotherapy, treatment is not effective or preferred for many individuals. For example, one-third to one-half of primary care patients with depression are treatment-resistant, meaning their depressive symptoms did not remit in response to antidepressants (Wiles et al., 2014). Also, antidepressants are not as effective for older adults when compared to younger age groups, and some patients may be opposed to treatment for personal or health reasons (Alexopoulos, 2019). The challenges of treating depressive symptoms suggest the need for long-term management and tertiary prevention of associated health consequences.

In epidemiological studies, depression may be defined based on a clinical diagnosis (e.g., self-reported history of clinical depression, clinical assessment) or through a depression screening tool (e.g., self-

reported depression symptoms scale). It is important to note the distinction between a clinical depression diagnosis and a depression screening tool. In terms of administration, clinical diagnosis involves a comprehensive assessment of depression by a clinician, while depression screening tools are often self-administered and questionnaire-based (El-Den et al., 2018). While depression screening tools may be used by clinicians to help arrive at a diagnosis, they are not sufficient to diagnose an individual with clinical depression. Clinical depression measures may thus be more affected by help-seeking behaviour and access to healthcare systems, and reflect more severe depression compared to depression screening tools. Clinical depression measures may also be more likely to correctly identify those with depression given the comprehensiveness of a clinical assessment; however, clinical depression measures may be prone to misclassifying clinically relevant undiagnosed depression because clinical depression assessments are rarely administered on the entire sample under study. In contrast, depression screening tools are often administered on the entire sample because of ease of administration, and are thus more likely to identify those with clinically relevant depressive symptoms who have not undergone any clinical assessment (El-Den et al., 2018). Also, unlike clinical depression measures, depression screening tools are often continuous rather than binary, providing access to data from the entire spectrum of depression, including subthreshold depression levels.

2.2 Social Isolation

Humans are universally susceptible to profound psychological distress and physiological damage caused by social isolation (Holt-Lunstad, 2017). Social isolation increases risk of death at comparable magnitudes to mental health conditions, substance abuse, obesity, and physical inactivity (Holt-Lunstad et al., 2015). In terms of morbidity, social isolation increases risk for cognitive decline, depression, immune dysfunction, coronary heart disease, and stroke (Holt-Lunstad, 2017; Nicholson, 2012; Okely et al., 2019; Sörman et al., 2015). Social isolation may be a more relevant public health concern today than in the past because of several recent socio-cultural changes, including reductions in community involvement, religious attendance, and average household size; lower marriage rates; and higher rates of both divorce and childlessness (Holt-Lunstad, 2017). Older adults are especially vulnerable to social isolation because of small social networks, retirement, widowhood, health conditions, disability and cognitive decline (Nicholson, 2012). Social isolation is also gendered, as social participation and the health benefits of social support differ across men and women (Gariépy et al., 2016; Tomioka et al., 2018). Furthermore, increasing social isolation and social stress resulting from the recent COVID-19 pandemic disproportionally impacts older adults and women, putting these groups at higher risk of poor health outcomes (Armitage et al., 2020; Alon et al., 2020; Usher et al., 2020).

Social isolation can broadly be conceptualized as a lack of social connection (Holt-Lunstad, 2017) and includes structural and functional social support measures (Wister et al., 2019). Structural social support refers to the objective aspects of social support, and may include number of social contacts, marital status or social participation frequency (Wister et al, 2019). Functional support refers to qualitative aspects of social support, and may include social support availability, relationship quality, or the subjective desire to participate in more activities (Wister et al, 2019). While functional and structural aspects of social isolation are intertwined (Wister et al., 2019), they are typically measured as distinct constructs (Costa-Cordella et al., 2021; Santini et al., 2020). Although structural measures of social isolation are more often used in epidemiological studies than functional measures, functional measures may be better predictors of health outcomes (Chen et al., 2016; Costa-Cordella et al., 2021; Ficker et al., 2014; Holwerda et al., 2014) and more strongly tied to depression (Santini et al., 2020).

Note that the terminology regarding social isolation is inconsistent in the literature, where some studies refer to social isolation as purely structural (Guo et al., 2021; Menec et al., 2019), while others incorporate functional aspects (Evans, Llewellyn, Matthews, Woods, Brayne, & Clare, 2019; Newall & Menec, 2020; Wister et al., 2019). The terms "functional social isolation", referring to the lack of functional social support, and "structural social isolation", referring to the lack of structural social support, have previously been defined in the CLSA literature (Wister et al., 2019). This thesis will thus utilize the terms functional and structural social isolation when referring to these constructs.

2.3 Executive Function

Executive functions are higher-order cognitive processes responsible for self-control, perspective-taking, planning and working memory (Manchester et al., 2004). Executive functions comprise several distributed networks, including the pre-frontal cortex, cerebral cortex, and subcortical areas (Chung et al., 2014). Even when other cognitive functions are unaffected, impairment of executive functions can substantially disrupt everyday life and may increase risk for both depression and social isolation (Bennet & Thomas, 2014; Kremen et al., 2012; Manchester et al., 2004; Mast et al., 2004; Wang & Blazer, 2015). For example, extreme impairment of executive functions is associated with behavioural challenges and loss of independence, with substantial consequences to individuals, their loved ones, and society (Mograbi et al., 2014). Challenging behaviours specific to impairment of executive functions include lack of empathy, socially inappropriate behaviour, lack of emotional control, aggression, poor social skills, confusion, and difficulty following simple instructions (Hancock et al., 2010; Ogilvie et al., 2011; Von Hippel, 2007). While a certain level of decline in executive functioning can be attributed to normal aging (Kirova et al., 2015), more substantial declines often manifest at the earliest stages of dementia (Aretouli et al., 2013). In addition, men and women experience differences in biological and lifestyle risk factors

that result in differential decline in executive functioning (Stern et al., 2018). For example, risk factors such as depression are more prevalent among women (Mielke, 2018), while traumatic brain injuries (Li et al., 2016) and vascular disorders such as myocardial infarction and heart failure are more prevalent among men (M.Y. Kim et al., 2018). Preventative interventions that are tailored toward subgroups hold great promise, as many of the key risk factors associated with decline in executive functioning are modifiable and vary across subgroups (George et al., 2016; Tariq & Barber, 2018).

In population-based epidemiological studies, executive functions are commonly measured using performance-based tasks (Pickens et al., 2010). Some of these tasks target specific executive functions, while others assess multiple executive functions at once (Pickens et al., 2010). No single tool exists that adequately encompasses all aspects of executive function (Pickens et al., 2010).

2.4 Psychosocial Pathways to Cognitive Outcomes

Depression, measured on a continuous spectrum (e.g., depression screening tool) or assessed categorically (e.g., clinical diagnosis, positive depression screen derived from a depression screening tool), increases the risk for poor cognitive outcomes, including impairment in executive function. One mechanism that may link depression to cognition is social isolation, suggesting the possibility of an indirect (i.e., mediated) effect. The sections below will explore the relationship between depression and cognition, and the possibility of an indirect path through social isolation. Given the limited literature, studies that assessed depression (depressive symptoms or clinical diagnosis), social isolation (functional or structural), and cognition (overall cognition or executive function) will be explored below.

2.4.1 Depression as a Risk Factor for Cognitive Outcomes

Meta-analyses and systematic reviews demonstrate that depression increases the risk for poor cognitive outcomes across several domains, including executive function (Butters et al., 2008; Snyder, 2013; Trivedi & Greer 2014; Wiels et al., 2020). Depression can impact executive function directly by causing atrophy in the hippocampus and prefrontal cortex (Bora et al., 2012; Butters et al., 2008). Such brain changes are likely to be mediated by multiple interconnecting pathways (Butters et al., 2008). Biological mechanisms, including vascular disease, elevated glucocorticoid production, amyloid deposition, and neurofibrillary formation may explain why depression increases the risk for poor executive functioning (Butters et al., 2008). These processes result in higher total brain injury burden, thus increasing vulnerability to poor cognitive outcomes (Butters et al., 2008). Structural and functional brain changes from depression may accumulate across the life-course and persist despite depressive symptom reduction, as cognitive deficits appear to remain with little to no improvement in those with remitted depression (Douglas & Porter, 2009; Goeldner et al., 2013; J.H. Kim et al., 2019).

There is ongoing debate about whether depression is a true risk factor or a prodrome of cognitive impairment. A recent and very large population-based study found that depression severity increased dementia risk in a dose-response fashion over an eight-year follow-up period (Wu et al., 2020). A strong association over a long follow-up period lends support for depression as a true risk factor rather than a prodrome (Wu et al., 2020). Other literature demonstrates that current depression may be more predictive of cognition and incident dementia than historic depression (Eraydin et al., 2019; Gatz et al., 2005; Zullo et al., 2021), suggesting that depression may be more a prodrome of dementia than a risk factor. The long preclinical phase of dementia also makes it difficult to form conclusions as to whether depression acts primarily as a risk factor or prodrome for dementia (Wu et al., 2020).

When considering the relationships between depression and cognition, there is also the possibility of reverse causality, given the underrepresentation of longitudinal studies relative to cross-sectional studies (Bennet & Thomas, 2014; Butters et al., 2008; Kremen et al., 2012; Snyder, 2013; Trivedi & Greer 2014; Wang & Blazer, 2015; Wiels et al., 2020). Although there is more support for depression as a cause rather than a consequence of cognitive decline (Bennett & Thomas, 2014; Cui et al., 2007; Kremen et al., 2012), declines in executive function have been shown to increase depressive symptoms over time (Mast et al., 2004).

In addition, the association between depression and executive function may be explained by shared risk factors, such as social isolation, vascular changes (e.g., white matter hyperintensities in frontostriatal brain regions), inflammation, low socioeconomic status, low education, and comorbidities (Bennet & Thomas, 2014; Wang & Blazer, 2015). These alternative explanations highlight the complex relationship between depression and executive function.

2.4.2 The Effect of Depression on Cognition Mediated by Social Isolation

In addition to biological pathways, social mechanisms may explain how depression indirectly impacts executive function. In particular, social isolation (defined either as structural or functional) is an independent risk factor for poor cognitive functioning, irrespective of depressive symptoms (Lara et al., 2019). Possible mechanisms for an impact of social isolation on cognition include an amplified stress response, decreased physical activity, poor treatment compliance, and less participation in cognitively stimulating activities over and above those incurred by depressive symptoms alone (Fratiglioni et al., 2004; Hays et al., 2001; Liu et al., 2017). Furthermore, both functional and structural aspects of social isolation are associated with structural brain abnormalities even after controlling for depressive symptoms, cross-sectionally (structural and functional social isolation) and over time (functional social isolation) (van der Velpen et al., 2021). Perspectives from evolutionary theory additionally suggest that

higher-order cognition is social in origin, and that higher cortical regions responsible for executive function were evolved, in part, for social functioning (Adolphs, 2003; Ardila, 2008). Therefore, there are biological explanations for why social functioning and executive function are intertwined in humans.

As depression may increase risk for social isolation through social dysfunction and withdrawal (Porcelli et al., 2019), it is also plausible that social isolation may be causally located between depression and decline in executive function in a mediation relationship. Social isolation may therefore help to explain the association between depression and executive function. The following sections will explore social isolation, defined structurally or functionally, as a mediator between depression and global cognition and/or executive function.

2.4.2.1 Depression as a Risk Factor for Social Isolation

An understanding of the impact of depression on social isolation and the impact of social isolation on cognition is a piecemeal method to forming hypotheses about the role of social isolation as a mediator between depression and cognition. Depression and social isolation are distinct constructs that have been strongly linked and are known to impact each other bidirectionally (Almquist et al., 2017; Elmer & Stadtfeld, 2020; Kong et al., 2018; Nicholson, 2012; Rock et al., 2014; Semino et al., 2017; Wister et al., 2019). People with clinical depression or subthreshold depression are at risk of social dysfunction, as are people with remitted depression (Kupferberg et al., 2016; Rock et al., 2014). There are several factors that explain why people with depressive symptoms or a history of depression are at risk of social isolation. For example, people with depression are prone to less satisfying and more dysfunctional social relationships, which may reduce social networks or promote loneliness (Almquist et al., 2017; Nicholson, 2012). The limited number of longitudinal studies that directly assess the impact of depression on social isolation make it difficult to infer temporality (Almquist et al., 2017; Nicholson, 2012). This is an important consideration because, as mentioned above, social isolation increases risk of depression in addition to being a consequence of depression (Chou et al., 2011; Nicholson, 2012; Santini et al., 2020).

2.4.2.2 Social Isolation as a Risk Factor for Cognitive Outcomes

Similar to the relationship between depression and social isolation, the relationship between social isolation and cognition is also bidirectional and complex (Evans, Martyr, Collins, et al., 2019; Kelly et al., 2017; Kuiper et al., 2016). While most studies suggest that social isolation (functional or structural) reduces executive function, some studies show opposite (Sims et al., 2014; Wang et al., 2017) or null (Ayotte et al., 2013; La Fleur & Salthouse, 2017) associations for functional social isolation. It is hypothesized that social isolation may lead to impairments in executive function by amplifying stress, reducing physical activity, and limiting cognitive stimulation (Eisele et al., 2012). Reduced hippocampal

volume may play a role in mediating the association between social isolation and cognition through stress-induced pathways (G.E. Kim et al., 2019). The impact of social isolation on cognition via stress-induced pathways may be more important in the context of functional rather than structural social isolation, as the former incorporates the quality of social interactions (e.g., lack of emotional support and positive social interactions) unlike the latter. A small social network on its own is not necessarily a stressful experience, while a lack of emotional support may cause feelings of distress regardless of social network size. For example, small social networks, particularly in older age, may reflect trading off less satisfying or toxic social relationships for smaller, higher-quality social networks (English & Carstensen, 2014). Furthermore, some social relationships can be stressful or burdensome, result in lost autonomy or dependency, and promote poor health behaviours for particular subpopulations (Ang & Malhotra, 2016; Fu et al., 2018; Sims et al., 2014). Conflicting findings are likely a result of inconsistent definitions of social support, as well as differing impacts dependent on social support subtypes, gender, age and ethnicity (Atti et al., 2010; Fu et al., 2018; Kelly et al., 2017; Schwartz et al., 2019). Importantly, just as social isolation may reduce cognitive function, so may reductions in cognitive function increase social isolation. Despite some evidence of reverse causality, more research has investigated social isolation (functional or structural) as a risk factor compared to an outcome of cognitive decline (Okely et al., 2019; Sörman et al., 2015).

2.4.2.3 Mediation Studies and Related Analyses

While a piecemeal approach as described in Sections 2.4.2.1 and 2.4.2.2 can form an important basis for generating hypotheses about the role of social isolation as a mediator between depression and cognition, hypothesis testing can be further informed by studies that include all three variables in a single model. Mediation studies that explicitly assess social isolation as a mediator or connector between depression and cognitive function provide stronger support for mediation compared to methods that do not explicitly consider social isolation as a link between depression and cognitive function. Only three studies explicitly assessed social isolation as a connector/node or mediator between depression and cognitive outcomes (Casey et al., 2020; Cohrdes & Bretscheneider, 2018; Semino et al., 2017). Casey et al.'s (2020) study in community-dwelling older adults found that depressive symptoms predicted social network size (cross-sectionally), while social network size predicted executive function (longitudinally, controlling for depressive symptoms). The longitudinal association between depressive symptoms and social network size, however, was not considered (Casey et al., 2020). Cohrdes & Bretscheneider's (2018) population-based cross-sectional study found that reduced functional social support mediated the relationship between increasing depressive symptoms and decreasing executive function; however, this mediated relationship was only significant in women and in young to middle-aged adults. Among patients with

depressive symptoms in a geriatric psychiatry institution, social withdrawal strongly connected depressive symptoms to poor cognition in a cross-sectional network analysis (Semino et al., 2017). Only Cohrdes & Bretscheneider's (2018) study directly tested the indirect effect of depression on cognition through social isolation.

Consistent with the criteria for mediation proposed by Baron & Kenny (1986), other studies that have provided clues for mediation include those that found that the mediator (i.e., social isolation) was associated with the outcome (i.e., cognition) after accounting for the exposure (i.e., depression). While these studies are important for hypothesis generation, they cannot assess whether social isolation links depression and cognition as in Casey et al.'s (2020), Cohrdes & Bretscheneider's (2018) and Semino et al.'s (2017) analyses, and are thus relatively weaker in supporting mediation. An independent effect of social isolation on cognition can be assessed by accounting for depression through adjustment, stratification, matching, standardization, or restriction. Only adjustment, stratification and restriction have been used to account for depression in the literature.

Claims of mediation may be made in instances where the effect of an exposure changes upon the addition of a covariate into a regression model (Hayes et al., 2018). Only one study (Wilson et al., 2007) assessed how social isolation alone changed the effect of depression on executive function when added to a model, providing evidence that social isolation may act as a potential mediator. Wilson et al. (2007) found that loneliness (an indicator of functional social isolation) reduced the effect of depressive symptoms on risk of Alzheimer's disease by 50% over time, suggesting that loneliness may partially explain the association between depressive symptoms and Alzheimer's disease. Similarly, Cohrdes & Bretscheneider (2018) found that simultaneously accounting for functional social support and physical activity eliminated the association between depressive symptoms and executive function cross-sectionally; however, it is unclear whether functional social support was the primary driver of the eliminated association because functional social support alone was not added into the model.

Reports that social isolation predicts cognition after adjusting for depression also provide clues for potential mediation. Sixty-one studies reported on the effect of social isolation on cognition in models that adjusted for the effect of depression (no testing for interactions between depressive symptoms and social isolation), with 41 studies reporting on the effects of *both* depression and social isolation. Of the 41 studies mentioned above, six (15%) found that functional (Ficker et al., 2014; O'Luanaigh et al., 2012; Rawtaer et al., 2017; Wilson et al., 2007; Zahodne et al., 2014) or structural (Lee et al., 2020; Rawtaer et al., 2017) social isolation predicted decreasing cognition, where depression had no effect, while the majority of the remaining studies found a significant effect for both social isolation (functional or

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structural) and depression. The six studies mentioned above suggest that social isolation may have eliminated the association between depression and cognition; however, this cannot be confirmed given that a social isolation variable was not individually entered into any of the models. Of the 61 studies mentioned above (where depression was adjusted for and *at least* social isolation was reported on), 49 studies (80%) found that social isolation (functional or structural) predicted decreasing cognition, providing evidence that social isolation acts on cognition independently of depression (Atti et al., 2010; Bae et al., 2020; Barnes et al., 2004; Bassuk et al., 1999; Béland et al, 2005; Bourassa et al., 2017; Carty et al., 2020; Chen et al., 2016; Conroy et al., 2010; Deng et al., 2018; Dickinson et al., 2011; Donovan et al., 2017; Estrella et al., 2021; Faramarzi et al., 2018; Ficker et al., 2014; Fratiglioni et al., 2000; Fu et al., 2018; Gow et al., 2013; Han et al., 2019; Holwerda et al., 2014; Huntley et al., 2018; James et al., 2011; D. Kim et al., 2017; J.H. Kim et al., 2019; Lara et al., 2019; Lee et al., 2020; Luchetti et al., 2020; Lyu et al., 2014; Murata et al., 2019; Nelson et al., 2013; Nguyen et al., 2002; O'Luanaigh et al., 2012; Raji et al., 2007; Rawtaer et al., 2017; Roystonn et al., 2020; Stenfors et al., 2013; Stinchcombe & Hammond, 2021; Tomioka et al., 2018; Tsuji et al., 2019; van Gelder et al., 2006; Vilalta-Franch et al., 2013; Wang et al., 2002; Wilson et al., 2007; Wilson et al., 2015; Windsor et al., 2014; Yu et al., 2020; Zahodne et al., 2014; Zahodne et al., 2018; Zunzunegui et al., 2003). When comparing studies that assessed functional and structural support within the same study, results were more consistent for functional rather than structural social isolation in many countries (Chen et al., 2016; Estrella et al., 2021; Ficker et al., 2014; Gow et al., 2013; Holwerda et al., 2014; O'Luanaigh et al., 2012; Stinchcombe & Hammond, 2021) with some exceptions in Singapore (Rawtaer et al., 2017) and China (Yu et al., 2020) where structural social isolation, rather than loneliness, was associated with cognitive decline. Thus, there is likely a true association between social isolation and cognition in models controlling for depression, with more consistent support for functional rather than structural social isolation.

Evidence that social isolation still impacts cognition even after excluding people with depression also suggests that social isolation may act independently of depression, providing clues for potential mediation. It appears that higher social isolation (structural or functional) predicts decreasing cognition in people with depression (Dickinson et al., 2011; Fratiglioni et al., 2000; Guo et al., 2021; Hatch et al., 2015; Lam et al., 2017) and without depression (Evans, Llewellyn, Matthews, Woods, Brayne, Clare, & CFAS-Wales research team, 2019; Fratiglioni et al., 2000; Lara et al., 2019; Wang et al., 2002). In contrast, some studies did not find that social isolation (functional or structural) was associated with cognition in people with depression (Evans, Llewellyn, Matthews, Woods, Brayne, & Clare, 2019; Kuiper et al., 2020; Rej et al., 2015; Riddle et al., 2015) or in people without depression (Dickinson et al., 2011; Hatch et al., 2015; Lam et al., 2017). Evidence is thus mixed in terms of whether social isolation

(functional or structural) impacts cognition after restricting by depression, although nonsignificant findings may be attributable to underpowered analyses (Rej et al., 2015; Riddle et al., 2015; Dickinson et al., 2011; Lam et al., 2017).

The vast majority of studies found that higher levels of at least some social isolation measures, within structural or functional domains, were associated with worse cognition. Of the 61 studies mentioned above (depression and social isolation as simultaneous predictors of cognition), only 11 studies (18%) found no effect for any social isolation subtype on global cognitive or executive function outcomes (Caldas et al., 2020; Chi et al., 2000; Leggett et al., 2013; Rej et al., 2015; Riddle et al., 2015; Ryan, 1996; Sharifi et al., 2016; Yen et al., 2010; Zahodne et al., 2021; Zhang et al., 2019; Zullo et al., 2021), and only three studies (5%) found that higher social support (functional or structural) was associated with lower levels of cognition in particular populations, such as those defined by age group, sex and ethnicity (Roystonn et al., 2020; Sims et al., 2014; Zahodne, 2018). Reasons for inconsistent findings may include underpowered analyses (Chi et al., 2000; Rej et al., 2015; Riddle et al., 2015; Ryan, 1996), reliance on only structural social support measures (Sharifi et al., 2016; Yen et al., 2010; Zhang et al., 2019; Leggett et al., 2013), and use of multiple indicators of social isolation across subgroups (Roystonn et al., 2020; Sims et al., 2014; Zahodne, 2018). In general, it is reasonable to hypothesize that social isolation (functional or structural) generally reduces cognitive function.

2.4.2.4 Age and Sex as Moderators of the Mediated Effect of Social Isolation Between Depression and Cognition

2.4.2.4.1 Age

Social isolation may be a more important mediator between depression and cognition for certain subgroups. In particular, this proposed mediation relationship may vary across age because of differences in how depression and social isolation are addressed and experienced. Moderation by age for the effect of depression on social isolation may be explained by differences in mental healthcare utilization and risk of depression relapse. Older adults with depression may be at higher risk of social isolation than younger to middle-aged adults with depression, as older adults may be more likely than younger age groups to hold negative stereotypes towards mental illness, be underdiagnosed for depression, and experience depression relapse as well as being less likely to be supported by mental healthcare services (Conejero, 2018; Conner et al., 2010; Fässberg et al., 2012; Mitchell & Subramaniam, 2005; Ong, 2003; Segal et al., 2005). Mental health stigma and lack of mental healthcare support may result in fewer opportunities to reach out to loved ones for support or to engage in meaningful relationships with others who struggle with depression, resulting in loneliness and social withdrawal. As older adults experience higher rates of depression

relapse compared to younger age groups, the impact of depression on social isolation may be magnified with increasing age. Since depression has been linked to social withdrawal and isolation, it is possible that more episodes may have a cumulative effect on social relationships over time. This theory has been confirmed by a longitudinal study that found that the association between social disengagement and cognitive decline was more pronounced in those with a history of social disengagement than in those who had experienced it more recently (Bassuk et al., 1999). On the contrary, there is also some suggestion that older age groups may be less susceptible to the impact of clinical depression on social isolation. For example, one cross-sectional study found a significant interactive effect of age with depression on loneliness, where the association between clinically diagnosed depression and loneliness was stronger in the youngest-old group compared to older age groups (Peerenboom et al., 2015).

Age may also moderate the indirect (mediation) effect of social isolation by interacting with social isolation to produce differing impacts on cognition. The effect of social isolation on cognition may be magnified in older age as older adults may take longer to recover from stress, and may also experience a heightened stress response in reaction to stressors compared to younger age groups (Kiss et al., 2008; Ritvanen et al., 2006), but literature is conflicting. For example, some studies found that older age groups may be more vulnerable to the impact of low social support (defined structurally or functionally) on worsening cognitive outcome compared to younger age groups (Håkansson et al., 2009; Hatch et al., 2015; Wilson et al., 2015), while others found younger or middle-aged adults to be more vulnerable than older age groups (Atti et al., 2010; Cohrdes and Bretschneider, 2018). Other research suggests no moderation by age for the association between functional social support and cognition (Luchetti et al., 2020; Zahodne et al., 2014). In terms of recent Canadian research, a study using the CLSA dataset found that social factors (a combination of both functional and structural social isolation) were more important for adults over age 65 than middle-aged adults in mediating the association between sensory impairment and executive function in a multivariable model adjusting for age, sex, ethnicity, income, education, and physical health characteristics (Hämäläinen et al., 2019). On the contrary, another CLSA study found that the impact of functional social support on cognition may be especially important for those aged 45 to 54 compared to older age groups, although the scope of this study was descriptive and thus did not assess the effect of age on cognition after controlling for multiple covariates (Oremus et al., 2019). Two other CLSA studies did not find evidence of modification by age on the association between functional social support and memory, in either cross-sectional (Ohman, 2020) or longitudinal data (Yoo, 2021). Mixed findings may be because of study design differences (e.g., cross-sectional versus longitudinal) and differences in the cognitive domains assessed (e.g., memory, executive function, or the combination of memory and executive function).

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2.4.2.4.2 Sex and Gender

Similar to age, it is also possible that the role of social isolation as a mediator between depression and cognition varies across men and women, defined either by biological sex or by gender identity. With regard to the impact of depression on social isolation, differences in help-seeking behaviour, stigma/societal attitudes, and propensity for social withdrawal may explain variation across men and women. For example, men with depression are more likely to experience stigma, lose emotional and instrumental support over time, experience social disability, and avoid seeking out support to cope with their symptoms compared to women with depression (Houtjes et al., 2017; Scott & Collings, 2010; Seidler et al., 2016). On the contrary, women with depression may be more likely to socially withdraw over time compared to men with depression (Almquist, 2017).

Sex or gender may also moderate the indirect (mediation) effect of social isolation on the path between social isolation and cognition. The evidence on moderation by sex or gender is highly mixed, with some studies suggesting that social support (functional or structural) is especially protective for cognition in women (Béland et al., 2005; Cohrdes & Bretschneider, 2018; Guo et al., 2021; Tomioka et al., 2018; Lee et al., 2020), some suggesting differential impacts in men and women depending on structural social support subtype (Fu et al., 2018; Murata et al., 2019; Zunzunegui et al., 2003), and others suggesting no moderation of social isolation (functional or structural) by sex or gender (Fratiglioni, 2000; Holwerda et al., 2014; Rawtaer et al., 2017; Stenfors et al., 2013; Luchetti et al., 2020; Yu et al., 2020). While one meta-analysis found no gender differences for the association of lower structural social isolation and better cognitive outcomes (Evans, Martyr, Collins, et al., 2019), a recent systematic review suggested that both functional and structural social support, with the exception of marital status, may be more important for cognitive function in women compared to men (Costa-Cordella et al., 2021). Studies that assess sex as a moderator between functional social support and cognition are mixed in the CLSA. For example, some cross-sectional CLSA studies suggest that the positive impact of functional social support (Oremus et al., 2019; Rutter, 2019) or both functional and structural social support combined (Hämäläinen et al., 2019) on cognition is more important for women than men. In contrast, Ohman (2020) found that the positive association between functional social support and memory (cross-sectional) was stronger in males versus females. Another CLSA study found that sex did not moderate the association between functional social support and change in memory (Yoo, 2021). Mixed findings may be because of study design differences (e.g., cross-sectional versus longitudinal) and differences in the cognitive domains assessed (e.g., memory, executive function, or the combination of memory and executive function).

Taken together, preliminary evidence and theory suggest that depression and social isolation are experienced differently across age and sex/gender subgroups. Despite such differences, there are a lack of

studies that have explicitly considered age and sex/gender as moderators of the effect of depression on social isolation and the effect of social isolation on cognition. Limited evidence and contradictory findings make it difficult to infer which age and sex/gender subgroups may be most vulnerable to the effect of social isolation as a mediator between depression and cognition.

2.5 Literature Summary

The association between depression, social isolation and cognition is multidirectional and complex. While evidence is limited, there is support for social isolation, defined either structurally or functionally, as a mediator between depression and cognition. Increasing social isolation is likely important in predicting poor cognitive outcomes regardless of depression, and the few mediation studies that exist suggest that social isolation may link depression to cognition. Empirical evidence and theory suggest that age and sex may moderate the impact of depression on social isolation as well as the impact of social isolation on cognition. The only mediation study that considered age and sex found that functional social isolation mediated the relationship between depressive symptoms and executive function in women and young to middle-aged adults, but not in men or older adults. Additionally, CLSA research is inconclusive as to whether age or sex moderates the effect of social factors (functional or structural) on cognition.

Chapter 3
Rationale and Objective

3.1 Study Rationale

Gaps in the literature supporting social isolation (functional or structural) as a mediator between depression and executive function include a lack of studies that use rigorous methods to assess mediation and temporality, explore the moderating effects of age and sex, consider middle-aged adults, and focus on executive function as opposed to global cognition. The most rigorous methods for assessing mediation test whether indirect (mediation) effects are statistically significant while using longitudinal data to assess temporality. Only one study directly tested the indirect effect of depression on cognition through social isolation (functional); however, temporality could not be assessed because the study was cross-sectional (Cohrdes & Bretscheneider, 2018). In addition, studies that assessed age or sex as moderators of the association between depression and social isolation as well as the association between social isolation and executive function were sparse and conflicting. Such sparse and conflicting results make it difficult to hypothesize which subgroups may be most vulnerable to the psychosocial mechanisms linking depression to cognition. Also, while most studies focused on older adults, very few included middle-aged adults, an important population for upstream prevention of cognitive decline. Lastly, few studies isolated executive function from global cognition, demonstrating that more work is needed to assess executive function outcomes.

   In sum, an adequate understanding of how depression may impact executive function through psychosocial pathways and across different subgroups is lacking. My thesis has addressed this gap by examining whether functional social isolation, a potentially modifiable risk factor, may explain the link between depression and executive function over time and across age and sex in a large, community-dwelling population of middle-aged to older adults. Knowledge of such modifiable mechanisms is important for informing targeted interventions to buffer executive function decline, particularly in those experiencing depression.

3.2 Objective

The research objective was to determine whether functional social isolation at follow-up (T2) mediates the association between depression (self-reported clinical depression or depressive symptoms) at baseline (T1) and executive function at T2 across age and sex.

Chapter 4
Methodology

4.1 Search Methodology

Systematic literature searches using PubMed (legacy version, 1950 to present) and PsycINFO (1840 to present) were conducted and combined on June 9th, 2020. Updated results using the original search strategies were obtained on July 7th, 2021 based on the new PubMed version (Canese et al., 2020) and PsycINFO (1840 to present). Articles were excluded if they were conducted solely on children or adolescents, populations with bipolar or postpartum depression, or non-humans; if they were case reports, case series, opinion pieces, lectures or perspectives; if they were not available in English; if they did not include either global cognition or executive function as an outcome; if they did not include social isolation or depression as predictors; or if they were retracted.

Studies were included if they explicitly assessed social factors as mediators between depression (exposure) and cognition (outcome). Consistent with the criteria for mediation proposed by Baron and Kenny (1986), studies were also included if they assessed the effect of the mediator (social isolation) on the outcome (cognition) after accounting for the exposure (depression) in order to assess Path II of the mediation. Adjustment, stratification, matching, standardization or restriction were possible methods for accounting for depression. As fewer studies isolated executive function from global cognition, the scope of this literature review included global cognition along with executive function. Both structural and functional aspects of social isolation were also included given the limited number of applicable mediation studies. Search terms related to depression, social isolation, cognition, and adults were included.

The combined search produced 4039 articles after removing duplicates, with 77 remaining after exclusion criteria were applied. See Appendix A for the PRISMA flowchart and search strategies, and Appendix B for a summary of key literature.

4.2 Sample

4.2.1 Data Source

The CLSA consists of 51,338 community-dwelling Canadians age 45 to 85 at baseline, split into two cohorts: Comprehensive and Tracking (CLSA, n.d.a.). Only the Comprehensive cohort was used, given the advantages of that cohort for this study. These advantages included in-person data collection in the Comprehensive cohort, allowing for more in-depth assessments of executive function than the Tracking

cohort, which employed fewer cognitive tests and relied on telephone interviews (Raina et al., n.d.). For the Comprehensive cohort, participants were recruited through Provincial Health Registries, Telephone Sampling Random Digit Dialing, and the Québec Longitudinal Study on Nutrition and Aging (Raina et al., n.d.). In the Comprehensive cohort, sampling was stratified by sex, age group, province and data collection site (CLSA, n.d.a.). At the time of this thesis, two time-points of data were available: baseline (T1) and first follow-up (T2). Data collection for T2 occurred three years post-baseline. At T1, the Comprehensive cohort consisted of 30,097 individuals living within 50 km of 11 data collection sites within the following provinces: Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Nova Scotia, Ontario and Québec. Individuals were excluded if they were residing in the Canadian territories, First Nations reserves, and institutions; if they did not speak English or French; if they worked full-time for the Canadian Armed Forces; or if trained interviewers decided that the individual was unable because of cognitive impairment to provide consent or reliable information (Raina et al., n.d.).

4.2.2 Analytical Sample

Participants were included in the analytical sample if they were in the Comprehensive cohort at both T1 and T2. Participants who had missing data on any of the variables required for the analysis or who had unrealistic test scores were excluded. The determination of whether cognitive test scores were unrealistic was informed by the literature (Strauss et al., 2006), and any such scores were excluded to reduce the impact of measurement error. Since the executive function scores were standardized for those who tested in French or English exclusively, those who completed their executive function tests bilingually were also excluded. See Appendix C for the analytical sample flowchart (Figure C1), and missing data on executive function (Table C1) and covariates (Table C2).

4.3 Measures

4.3.1 Exposure

The main exposure variable was depression at baseline (T1), based on self-reported depressive symptoms or diagnosis of depression. Depressive symptoms were measured using the Center for Epidemiological Studies Short Depression Scale (CES-D10) (Radloff, 1977). The CES-D10 is a 10-item instrument that quantifies the frequency of depressive symptoms experienced in the past week, with higher scores indicating more depressive symptoms (see Appendix D for measurement details). O'Connell et al. (n.d.) have demonstrated measurement invariance of the CES-D10 across sex, age, education, language of administration, ethnicity, and cognition in the CLSA, making the CES-D10 an ideal measure for limiting

measurement bias. Self-reported clinical depression was assessed by the following question: "Has a doctor ever told you that you suffer from clinical depression?" (yes/no).

4.3.2 Outcome

The main outcome measure was standardized executive function score at follow-up (T2), with lower scores indicating lower function. The executive function score is a composite measure that was derived by summing z-scores from the following executive function tests: Mental Alteration Test (MAT), Stroop Neuropsychological Screening Test-Victoria Version (SNST-VV), Time-Based Prospective Memory Test (TiMT), Animal Fluency Test (AFT) and Controlled Oral Word Association Test (COWAT) (Raina et al., n.d.). Descriptions of these tests can be found in Appendix D. Z-scores for those who completed their tests in English or French were determined separately because of the impact of language on cognitive scores (Tuokko et al., 2019). A continuous measure of executive function was used rather than a categorical measure in order to maximize use of the information available, to avoid underestimating variation between subgroups, and to account for the possibility that the study time period may not be long enough to detect cognitive changes that meet a clinical threshold (Altman & Royston, 2006).

4.3.3 Mediator

The mediator was functional social isolation at follow-up (T2), with higher scores indicating more isolation. Functional social isolation was derived by reverse coding the Medical Outcomes Survey – Social Support Survey (MOS-SSS) (Sherbourne & Stewart, 1991). Functional social isolation refers to the perceived lack of social support availability (Sherbourne & Stewart, 1991), and was measured as a continuous variable. General considerations on the advantages of preserving the continuous nature of variables were discussed previously in Section 4.3.2. See Appendix D for measurement details.

4.3.4 Moderators of the Indirect (Mediated) Effect

Age group and sex at baseline were tested as moderators for the indirect (i.e., mediated) effect of depression on executive function through social isolation. Categories for age groups were 45 to 54, 55 to 64, 65 to 74 and 75+ years old. Categories for sex were male and female. See Appendix D for measurement details.

4.3.5 Covariates

Covariates were measured at baseline and included sociodemographic characteristics, physical health characteristics, health behaviours, functional social isolation, and executive function. Measurement details are in Appendix D. Covariate selection was informed by the literature review and by previous work on depression, social support, and cognitive function using baseline CLSA data (Ha, 2019; Iacono, 2019;

Oremus et al., 2020; Rutter, 2019). Variables flagged as potential confounders may be associated with the exposure, mediator and outcome. All of the covariates described below act outside of the casual pathways linking the exposure to the outcome and/or mediator.

Sociodemographic characteristics

In addition to their role as potential effect modifiers, age and sex were considered as potential confounders as they are associated with depression (Patten et al., 2015) and cognition (Li & Singh, 2014; Tuokko et al., 2020), and act outside of the causal pathway. Age group and sex categories are described under Section 4.3.4. Structural social support indicators (marital status and living arrangements) were controlled for because of their association with mental (Gariepy et al., 2016; Stahl et al., 2016), social (Holt-Lunstad, 2017) and cognitive health (Elovainio et al., 2018; Van Gelder, 2006). Education and income relate to socioeconomic status, a shared risk factor for depression and cognitive impairment (Bennet & Thomas, 2014). Education is classified by the highest level obtained, and income is classified as total household annual income. Province and urban/rural residence were controlled for as there are regional differences in social support and cognition in Canada (Oremus et al., 2019), and urban/rural residence has been associated with social support (Hu et al., 2018), depression (Hu et al., 2018) and cognition (Cassarino et al., 2016). Furthermore, participants were recruited based on age, sex, education and geography, suggesting the importance of considering these variables in analyses (CLSA, 2017).

Physical health characteristics

Functional impairment (Riddle et al., 2015), self-rated health (Ambresin et al., 2014; Bourassa et al., 2017), and number of chronic conditions (Benett & Thomas, 2014) were included because of their association with both depression and cognition. Functional impairment was defined as requiring assistance with one or more Basic Activities of Daily Living (ADL) or Instrumental Activities of Daily Living (IADL). Self-rated health was assessed on a Likert scale with values ranging from "Poor" to "Excellent". Chronic conditions included self-reported diagnosis of the following conditions known to impact cognition: high blood pressure/hypertension; diabetes/borderline high blood sugar; kidney disease/failure; cancer; under-active thyroid/hypothyroidism/myxedema; over-active thyroid/hyperthyroidism/Grave's disease; asthma; chronic obstructive pulmonary disease (COPD)/emphysema/chronic bronchitis; chronic cardiac conditions; stroke; and peripheral vascular disease. Chronic conditions were categorized into five categories (0, 1, 2, 3, 4+) to ensure adequate cell counts while minimizing residual confounding by accounting for increased care complexity associated with four or more chronic conditions relative to three or less (Thorpe et al., 2015).

Health behaviours

Smoking status and alcohol use were controlled for as they relate to depression (Jané-Llopis & Matytsina, 2006) and cognition (Ha, 2019; Peters et al., 2012; Rehm et al., 2019).

4.4 Analytical Strategy

4.4.1 Descriptive Analysis: Univariate and Bivariate

Univariate analyses were conducted by obtaining the mean and standard deviation for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and proportions for categorical variables. For bivariate analyses, Pearson correlation coefficients were reported when the variables were both continuous, a t-test or ANOVA was employed when one variable was continuous and the other was categorical, and a chi-square test was employed when both variables were categorical. Post hoc analyses were conducted to assess significant mean differences across categorical variables. All analyses were conducted on unweighted data.

4.4.2 Multivariable Analysis

4.4.2.1 Methodological Approach
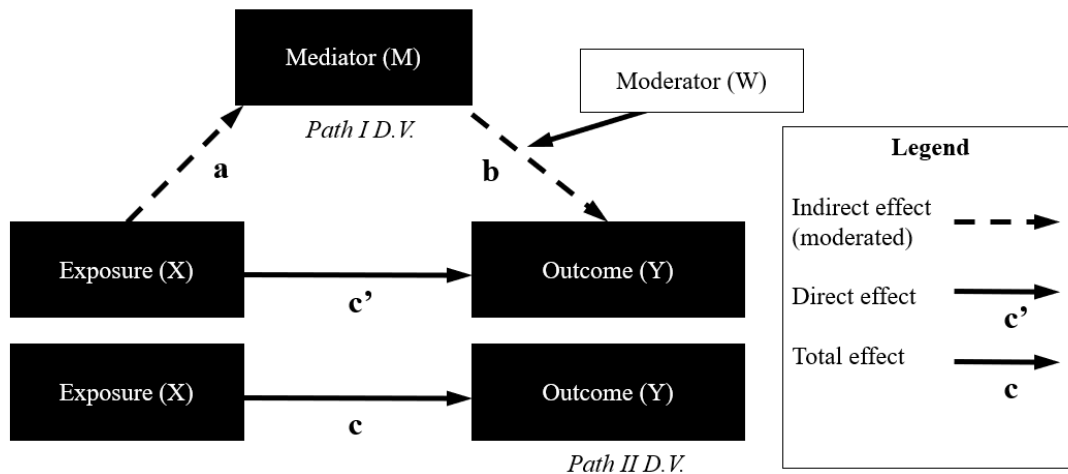
Figure 1: Simple Moderated Mediation Model Example: Conceptual Diagram. The mediator (M) and the outcome (Y) are both dependent variables (D.V.). M is dependent upon the exposure (X) (Path I), while Y is dependent upon X, M, W, and M*W (Path II).

Conditional process analysis, developed by Andrew Hayes (2018), combines mediation and moderation analyses into a single statistical model. This approach can be used to: (a) quantify and assess the direct and indirect pathways between an exposure and outcome through one or more intermediary variables (i.e., mediation) and; (b) examine whether such pathways are inhibited or enhanced across levels of one or

more effect modifiers (i.e., moderated mediation). The *indirect effect* is the regression coefficient that quantifies the difference between the effect of the exposure (X) on the outcome (Y) when the mediator is controlled for versus not controlled for. It is equivalent to the product of the effect of X on M, and the effect of M on Y holding X constant (i.e., ab). The indirect effect measures mediation, and can be tested to determine whether there is evidence of significant mediation. The *direct effect* (c') quantifies the effect of X on Y controlling for M. The *total effect* (c) quantifies the effect of X on Y when not controlling for M. The total effect is composed of the direct effect plus the indirect effect (see Equation 2 below). If there is evidence of moderated mediation, there will be multiple indirect effects to report, as the indirect effect will be a function of the moderator. Data must be unweighted and mediators must be continuous for conditional process analyses.

$$ab = c - c' \qquad [1]$$
$$c = c' + ab \qquad [2]$$

Conditional process analysis was chosen over the more traditional approaches to mediation analysis for several compelling reasons. Piecemeal approaches, such as Baron and Kenny's causal steps approach, determine mediation by conducting multiple tests – first, by testing the association between X and M, and second, by testing the association between M and Y controlling for X (Baron & Kenny, 1986). Conditional process analysis limits error from multiple testing, as one single inferential test is all that is needed to determine mediation (Hayes, 2018). Another advantage of having a single inferential test for mediation is that overall uncertainty can be expressed using a confidence interval (Hayes, 2018). The causal steps approach proposed by Baron & Kenny (1986) cannot quantify mediation using a single inferential test. Also, conditional process analysis directly quantifies the relationship between the moderator and the indirect (i.e., mediated) effect, and can thus estimate and test the indirect effect at each level of a moderator without the need to conduct separate analyses within moderator subgroups (Hayes, 2018). Separate mediation analyses among subgroups would be required to conduct a moderated mediation analysis using a causal steps approach, resulting in power loss and compromising the validity of subgroup comparisons. Conditional process analysis, on the other hand, uses the entire dataset to estimate the indirect effects at each level of the moderator, thus limiting the influence of subgroup sample size on the probability of detecting significance (Hayes, 2018). For the reasons described above, conditional process analysis is the primary method used for this thesis.

Recall that in mediation models, the total effect (c) is broken up into two components: the indirect effect (ab) and the direct effect (c') (Equation 2). As a supplement to conditional process analysis and to

aid in interpretation of indirect effect size, the proportion mediated (P_M) was calculated within subgroups where the indirect effect was significant in fully adjusted models (Equation 3). The P_M is a useful and intuitive statistic (De Heus, 2011; Ananth, 2019; Miočević et al., 2018) and the most frequently reported method for quantifying mediation (Miočević et al., 2018). To calculate the P_M, one simply divides the indirect effect by the total effect, which provides information about the strength of the mediation pathway relative to the effect of the exposure on the outcome. Despite its ease of interpretation, the P_M is only suited to the following conditions: samples must be greater than 500 and the effects of X and M on Y must be in the same direction (De Heus, 2011). The P_M also cannot be obtained for complex moderated mediation models where more than one indirect path includes interaction terms. Splitting the data and conducting a simple mediation analysis within strata for each moderator is thus necessary for calculating the P_M for complex moderated mediation models. It is also important to note that the P_M lacks guidelines for significance testing, and studies that report on the P_M do not include p-values or confidence intervals (Cohrdes & Bretschneider, 2018; Colich et al., 2020; Dong & Li, 2020; Huang et al., 2017). Given its limitations, the P_M was used as a supplement to help meaningfully interpret indirect effects in subgroups where the indirect effect was significant. Hayes's approach, using data from the whole dataset, remains the more statistically robust strategy for estimation and reliable subgroup comparisons (Hayes et al., 2018).

$$P_M = \frac{ab}{c} \qquad\qquad [3]$$

4.4.2.2 Model Building Approach
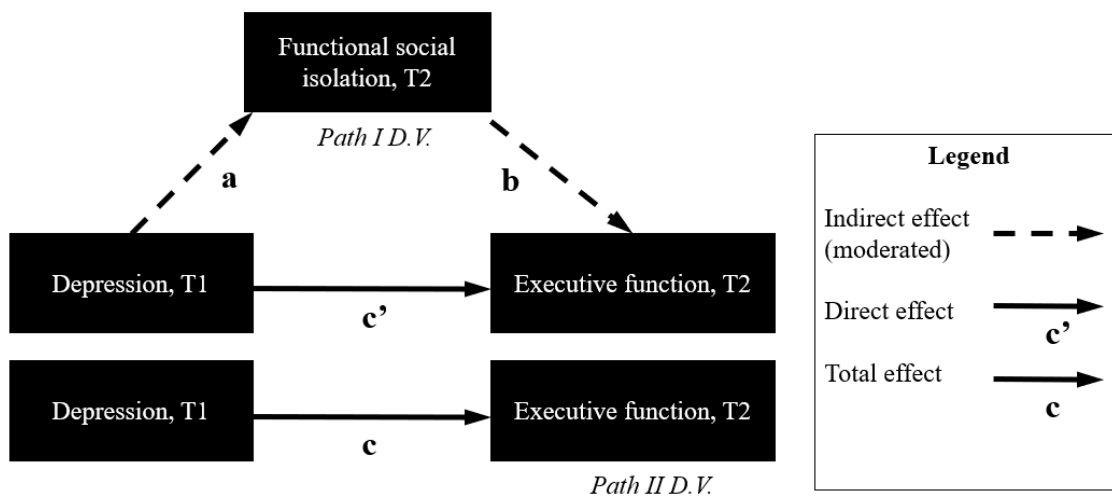
Figure 2: Proposed Mediation Conceptual Diagram. Interaction terms and covariates not shown. D.V. = dependent variable; T1 = baseline; T2 = follow-up.

The model building process was conducted on unweighted data according to the following steps: (1) construct a conceptual process diagram for the proposed mediation model (see Figure 2); (2) test interactions with age and sex at both indirect paths (Path I: X→M and Path II: M→Y) in fully adjusted models; (3a) if there are significant interactions, construct a moderated mediation model by including interaction terms at the paths where the interactions are significant, and then estimate indirect effects at levels of the moderator(s); or (3b) if no interactions are significant, keep the simple mediation model (unmoderated) from step 1 and estimate an overall indirect effect; and (4) conduct sensitivity analyses to address model limitations.

Testing Interactions

There is poor understanding of the moderating effects of age and sex on the association between depression and social isolation (i.e., Path I), and between social isolation and executive function (i.e., Path II). Given that the literature is inconclusive regarding the nature (i.e., two- versus three-way) and location (i.e., Path I only, Path II only, or both) of these interactions, interaction terms were tested for both paths in multiple linear regression models. Highest order interactions (i.e., three-way) were tested first and included in the model if significant, along with lower order terms. If higher-order interactions were nonsignificant, then lower order interactions were tested (i.e., two-way) and included in the model, if significant, along with lower order terms. Interaction terms were tested in fully adjusted models, and nonsignificant interactions were not included in the models.

Baseline outcome adjustment

Analyses controlled for baseline outcome measurements (i.e., functional social isolation and executive function), as recommended by Hayes (2018). Not controlling for baseline outcome measurements may inflate prospective associations (Stenfors et al., 2013) and result in regression toward the mean (Hayes, 2018; Ostermann et al., 2008).

4.4.2.3 Estimating Moderated Mediation

Mediation was tested and quantified using the indirect effect estimated across age and sex using the entire dataset. The proportion mediated (P_M) was calculated in the subgroup where the indirect effect was significant. Analyses were run using SAS 9.4 software (SAS Institute Inc., Cary, North Carolina). The PROCESS macro version 3.5 developed by Hayes (2018) was used to conduct moderated mediation analyses using ordinary least squares (OLS) regression-based path analysis. Goodness-of-fit was assessed using the R-squared (R^2) statistic, where the mediator and outcome were individually modelled as dependent variables.

The indirect effect is the product of two regression coefficients, which often results in non-normal sampling distributions (Hayes, 2018). Thus, a bootstrap confidence interval was used to handle non-normal sampling distributions (Hayes, 2018). Bootstrapping was conducted using resampling repeated 10,000 times with replacement (Hayes, 2018). Percentile bootstrapping was used over bias-corrected bootstrap as the former has a lower Type I error (Montoya & Hayes, 2017). Note that bootstrapping does not require assumptions regarding the distribution of residuals (Fox, 2015; Liu & Singh, 1995).

4.4.2.4 Models of Moderated Mediation

First, a moderated mediation model with two time-points was employed using conditional process analysis, followed by subsequent models adjusting for covariates in chunks. Models included depression at T1 as the exposure, functional social isolation at T2 as the mediator, executive function at T2 as the main outcome, and age group and sex at T1 as moderators. Separate analyses using CES-D10 and self-reported clinical depression as the exposure measures of depression were conducted. Models controlled for baseline mediator and baseline outcome measurements as recommended by Hayes (2018). See the data analysis table (Table 1) below.

4.4.2.5 Sensitivity Analyses

One path was chosen to be modelled cross-sectionally because only two time-points were available for modelling the mediation rather than the preferred three time-points (i.e., T1 depression, T2 social isolation, and T3 executive function). Path II was chosen to be modelled cross-sectionally (T2 functional social isolation → T2 executive function) given that cross-sectional and prospective results at Path II were generally consistent in terms of moderation. Path I was not chosen to be modelled cross-sectionally, as cross-sectional results (T1 depression → T1 functional social isolation) were not consistent with prospective results (T1 depression → T2 functional social isolation) in terms of moderation (data not shown). Sensitivity analyses that modelled the prospective Path II relationship between T1 functional social isolation and T2 executive function (Section 5.2.4) were conducted and reported in recognition of the limitations related to temporality at Path II. The prospective Path II models controlled for all covariates and tested for interactions with age and sex starting with three-way interactions and followed by two-way interactions. As stated previously, only highest order significant interactions (i.e., three-way > two-way), along with their lower order terms, were included. Sensitivity analyses that assessed the association between T1 functional social isolation and T2 executive functional were conducted, controlling for CES-D10 and self-reported clinical depression in separate models.

Table 1: Analysis Plan, Moderated Mediation Models

	Path I: X→M	Path II: M→Y[†]
Model 0 *Base Model*	**Exposure (X):** - Depression (T1) **Outcome (M):** - Functional social isolation (T2) **Baseline mediator and outcome covariates:** - Functional social isolation (T1) - Executive function (T1) **Moderators (W, Z)[‡]:** - W: Age group (T1) - Z: Sex (T1)	**Exposure (M):** - Functional social isolation (T2) **Outcome (Y):** - Executive function (T2) **Baseline mediator and outcome covariates:** - Functional social isolation (T1) - Executive function (T1) **Moderators (W, Z)[‡]:** - W: Age group (T1) - Z: Sex (T1)
Model 1	Same as Model 0, with adjustment for sociodemographic covariates at Path I and II. • **Sociodemographic covariates** (marital status, living arrangements, province, education, income, urban/rural residence)	
Model 2	Same as Model 0, with adjustment for sociodemographic and physical health covariates at Path I and II. • **Sociodemographic covariates** (see above) • **Physical health covariates** (self-rated health, number of chronic conditions, functional impairment)	
Model 3 *Fully Adjusted*	Same as Model 0, with adjustment for socio-demographic, physical health, and health behaviour covariates at Path I and II. • **Sociodemographic covariates** (see above) • **Physical health covariates** (see above) • **Health behaviour covariates** (smoking use, alcohol use)	

M = Functional social isolation at T2; T1 = Baseline; T2 = Follow-up; X = Depression (CES-D10 and self-reported clinical depression included in separate analyses); Y = Executive function at T2.
[†]Path II also controls for X.
[‡] Only significant highest order interactions, along with lower order terms, were included in the models.

Chapter 5

Results

5.1 Descriptive Analyses

Histograms for T1 depressive symptoms, T2 functional social isolation and T2 executive function can be found in Figures 3, 4 and 5, respectively. Descriptive results (univariate and bivariate) are summarized in Tables 2 to 4. The total column in Table 2 shows the proportions of the categorical variables in the analytical sample. It also shows measures of centrality and spread of the mediator (functional social isolation) and outcome (executive function) by the categorical exposure variable (self-reported clinical depression) and covariates, with group differences tested using either ANOVA or t-tests as appropriate. Correlation coefficients (Table 3) and stability of measures over time (Table 4) are reported for depressive symptoms, functional social isolation and executive function. Detailed results of ANOVA post hoc tests showing the mean differences for T2 functional social isolation and T2 executive function across each level of the covariates can be found in Appendix E, Table E1.
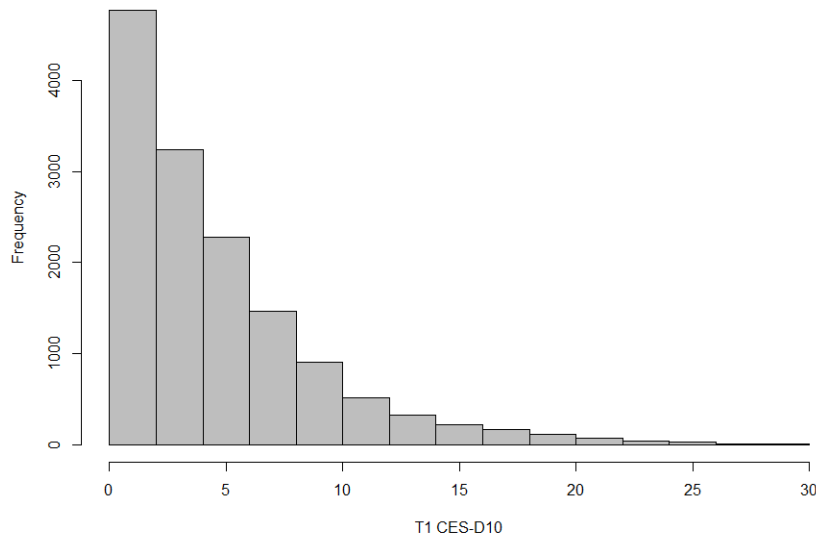
Figure 3: Distribution of Baseline (T1) Depressive Symptoms (CES-D10) – Unweighted Analytical Sample in the Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)
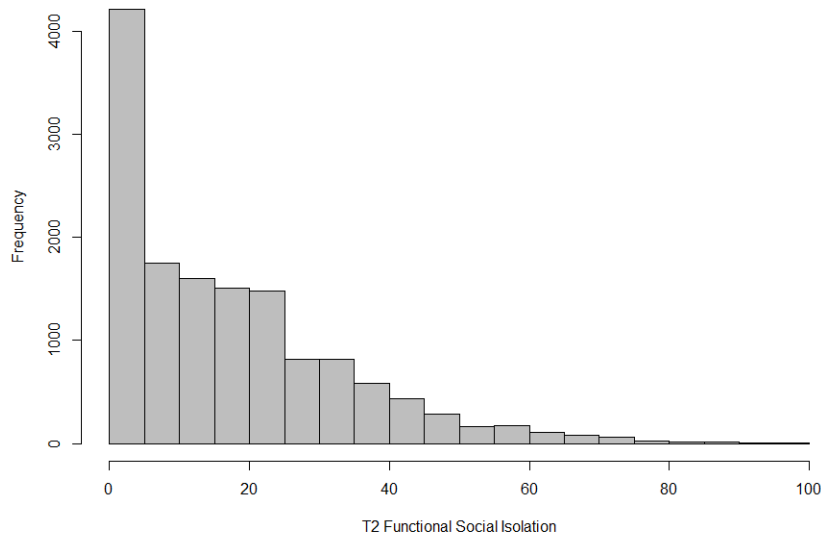
Figure 4: Distribution of Follow-up (T2) Functional Social Isolation – Unweighted Analytical Sample in the Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)
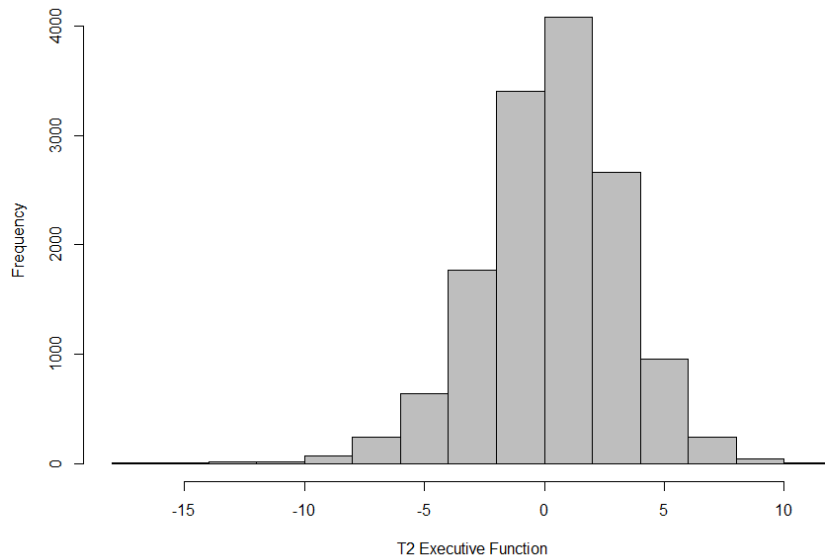
Figure 5: Distribution of Follow-up (T2) Executive Function – Unweighted Analytical Sample in the Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Table 2: Categorical Baseline Characteristics by Follow-up Functional Social Isolation and Executive Function – Unweighted Analytical Sample in the Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Characteristics (T1)	Total	Mediator (T2) Functional social isolation		Outcome (T2) Executive function
	%	$\bar{x}$ (SD)	Md (IQR)	$\bar{x}$ (SD)
Clinical depression (self-reported)				
Presence	15.63	**21.40 (18.40)**	18.42 (25.00)	0.35 (2.84)
Absence	84.37	**16.25 (15.91)**	13.16 (22.37)	0.30 (2.92)
Sociodemographic characteristics				
Age group (years)				
45-54	29.11	**15.41 (15.49)**[a]	11.84 (21.05)	**1.50 (2.49)**[a]
55-64	35.58	**16.78 (16.73)**[b]	13.16 (22.37)	**0.74 (2.54)**[b]
65-74	22.95	**17.21 (16.26)**[b]	13.16 (22.37)	**-0.59 (2.77)**[c]
75+	12.37	**21.39 (17.22)**[c]	18.42 (25.00)	**-2.08 (3.11)**[d]
Sex				
Female	49.42	17.30 (16.09)	14.47 (22.37)	0.27 (2.85)
Male	50.58	16.81 (16.75)	13.16 (23.69)	0.34 (2.96)
Marital status				
Partnered	73.44	**13.62 (13.79)**[a]	10.53 (21.05)	**0.50 (2.83)**[c]
Single/never married	7.95	**29.21 (20.59)**[b]	26.32 (28.95)	**0.33 (2.86)**[c]
Widowed	6.80	**24.14 (17.50)**[c]	22.37 (25.00)	**-1.43 (3.21)**[a]
Divorced	9.41	**26.13 (18.74)**[d]	23.68 (26.32)	**-0.02 (2.91)**[b]
Separated	2.41	**26.18 (19.55)**[cd]	25.00 (28.95)	**0.63 (2.64)**[c]
Living arrangements				
Lives alone	18.62	**27.88 (19.27)**	25.00 (26.31)	**-0.45 (3.08)**
Lives with others	81.38	**14.57 (14.62)**	10.53 (19.74)	**0.48 (2.84)**
Province				
Alberta	8.61	**17.97 (16.63)**[ab]	14.47 (22.37)	**0.46 (2.72)**[b]
British Columbia	22.83	**17.14 (16.70)**[b]	13.16 (23.69)	**0.77 (2.83)**[c]
Manitoba	10.14	**18.05 (16.10)**[ab]	14.47 (23.68)	**0.34 (2.92)**[b]
Newfoundland and Labrador	8.85	**15.12 (15.07)**[c]	11.84 (22.36)	**-0.26 (2.83)**[a]
Nova Scotia	9.52	**14.81 (14.49)**[c]	11.84 (21.05)	**-0.07 (2.87)**[a]
Ontario	24.06	**16.87 (17.11)**[b]	11.84 (22.37)	**0.35 (2.91)**[b]
Quebec	15.98	**18.47 (16.66)**[a]	15.79 (23.68)	**0.01 (3.04)**[a]
Education, highest level obtained				
Less than secondary school	3.96	**21.48 (17.40)**[a]	18.42 (26.31)	**-2.61 (3.03)**[a]
Secondary school graduation (no post-secondary)	8.31	**17.64 (16.53)**[c]	14.47 (22.37)	**-0.69 (2.82)**[b]
Some post-secondary	7.28	**19.43 (17.56)**[abc]	15.79 (25.00)	**-0.26 (2.76)**[c]
Post-secondary education (not university)	31.37	**18.20 (17.00)**[bc]	14.47 (23.68)	**-0.23 (2.76)**[c]
Post-secondary education (university)	49.08	**15.51 (15.60)**[d]	11.84 (21.05)	**1.14 (2.71)**[d]

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| Characteristics (T1) | Total | Mediator (T2) | | Outcome (T2) |
| | | Functional social isolation | | Executive function |
	%	$\bar{x}$ (SD)	Md (IQR)	$\bar{x}$ (SD)
Income				
<$20,000	3.76	**32.50 (21.78)**[a]	28.95 (32.90)	**-1.32 (3.21)**[a]
≥$20,000 and <$50,000	18.68	**23.22 (18.15)**[b]	21.05 (26.32)	**-0.96 (3.11)**[b]
≥$50,000 and <$100,000	35.48	**17.16 (15.83)**[c]	14.47 (22.37)	**0.11 (2.75)**[c]
≥$100,000 and <$150,000	21.86	**14.03 (14.35)**[d]	10.53 (21.05)	**0.92 (2.64)**[d]
≥$150,000	20.22	**11.56 (12.70)**[e]	7.89 (17.10)	**1.46 (2.50)**[e]
Rural/urban residence				
Rural	8.06	**14.44 (14.92)**	10.53 (22.36)	0.20 (2.86)
Urban	91.94	**17.28 (16.54)**	13.16 (23.69)	0.32 (2.91)
Physical health				
Self-rated health				
Excellent	21.89	**12.92 (14.26)**[a]	7.89 (19.73)	**0.79 (2.76)**[a]
Very good	43.41	**15.82 (15.24)**[b]	11.84 (22.37)	**0.47 (2.81)**[b]
Good	27.71	**20.22 (17.46)**[c]	17.11 (25.00)	**-0.07 (2.97)**[c]
Fair	6.08	**24.52 (19.92)**[d]	21.05 (28.95)	**-0.72 (3.16)**[d]
Poor	0.91	**28.99 (21.66)**[e]	25.00 (35.52)	**-0.67 (3.28)**[cd]
Number of chronic conditions				
0	35.73	**15.47 (15.60)**[a]	11.84 (21.05)	**0.92 (2.74)**[a]
1	31.43	**16.79 (16.26)**[b]	13.16 (22.37)	**0.39 (2.83)**[b]
2	18.96	**17.90 (16.77)**[c]	14.47 (23.03)	**-0.11 (2.95)**[c]
3	9.16	**19.61 (17.12)**[d]	17.11 (23.69)	**-0.70 (2.93)**[d]
4+	4.72	**22.36 (18.86)**[e]	19.74 (27.63)	**-1.29 (3.00)**[e]
Functional impairment				
Yes	7.05	**22.60 (18.37)**	19.74 (26.32)	**-1.22 (3.21)**
No	92.95	**16.63 (16.20)**	13.16 (22.37)	**0.42 (2.85)**
Health behaviours				
Smoking status				
Current user	7.90	**22.51 (18.68)**[a]	19.74 (26.31)	**0.11 (2.83)**[a]
Former user	42.81	**17.17 (16.36)**[b]	13.16 (23.69)	**0.06 (2.92)**[a]
Never user	49.28	**16.08 (15.93)**[c]	11.84 (22.37)	**0.55 (2.88)**[b]
Alcohol use				
Non-user	9.86	**20.63 (18.75)**[a]	17.11 (25.00)	**-0.39 (3.18)**[a]
Occasional user	11.43	**20.89 (18.72)**[a]	17.11 (26.32)	**-0.36 (2.96)**[a]
Regular user	78.72	**16.04 (15.60)**[b]	11.84 (22.37)	**0.49 (2.83)**[b]

IQR = interquartile range; Md = median; SD = standard deviation; T1 = Baseline; T2 = Follow-up; $\bar{x}$ = mean.
Tests used: t-test, ANOVA with post-hoc tests (Tukey).
Values where $p < 0.05$ are in **bolded** font. Different superscript letters indicate significant differences across categories of the variable.
The median and interquartile range are included for functional social isolation because the distribution is skewed.

Table 3: Correlation Matrix of Continuous Baseline Measures by Follow-up Functional Social Isolation and Executive Function –Analytical Sample, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Baseline (T1)	Follow-up (T2)	
	Mediator	**Outcome**
	Functional social isolation	Executive function
	r	*r*
CES-D10	**0.33**	**-0.08**
Functional social isolation	**0.75**	**-0.11**
Executive function	**-0.12**	**-0.76**

CES-D10 = Center for Epidemiologic Studies Short Depression Scale; *r* = Pearson's correlation coefficient; T1 = Baseline; T2 = Follow-up.

Tests used: Pearson's correlation coefficient, chi-square.

Values where p < 0.05 are in **bolded** font.

Table 4: Stability of Depressive Symptoms (CES-D10), Self-Reported Clinical Depression, Functional Social Isolation, and Executive Function Over Time – Analytical Sample in the Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

	Prevalence (%)			
Clinical depression (self-reported)				
T1	**15.63**			
T2	**13.94**			
	$\bar{x}$	*SD*	*Md*	*IQR*
CES-D10				
T1	**4.96**	**4.42**	**4.00**	**5.00**
T2	**4.76**	**4.29**	**4.00**	**5.00**
Functional social isolation				
T1	**17.38**	**16.31**	**13.16**	**22.37**
T2	**17.05**	**16.43**	**13.16**	**23.69**
Executive function				
T1	**0.46**	**2.77**	**0.60**	**3.58**
T2	**0.31**	**2.90**	**0.44**	**3.64**

CES-D10 = Center for Epidemiologic Studies Short Depression Scale; *IQR* = interquartile range; *Md* = median; *SD* = standard deviation; T1 = Baseline; T2 = Follow-up; $\bar{x}$ = mean.

Tests used: McNemar's test, paired t-test.

Values where p < 0.05 are in **bolded** font.

5.1.1 Bivariate Associations with Functional Social Isolation

Self-reported clinical depression (Table 2) and depressive symptoms (Table 3) at T1 were both significantly associated with functional social isolation at T2 in bivariate models. Mean functional social isolation was higher in those with self-reported clinical depression compared to those without self-reported clinical depression (21.40 vs. 16.25, $p < 0.0001$), and depressive symptoms were positively correlated with functional social isolation ($r = 0.33$, $p < 0.0001$).

As shown in Table 2, all T1 covariates were significantly associated with T2 functional social isolation in bivariate models, with the exception of sex. Increasing age was associated with higher functional social isolation, while those who were single/never married, widowed, divorced or separated had higher functional social isolation compared to those who were partnered. Living alone (versus with others) was also associated with higher functional social isolation. In terms of province, functional social isolation was highest in Quebec, Manitoba, and Alberta, and lowest in Nova Scotia and Newfoundland and Labrador. Functional social isolation was also highest among those with less than secondary school education, and lowest among those with university degrees. Functional social isolation increased with every decreasing income bracket. Urban (versus rural) residence was associated with higher functional social isolation. Compared with other sociodemographic covariates, the largest difference in functional social isolation was observed between the highest and lowest income bracket, as shown in Appendix E, Table E1.

Regarding physical health covariates, functional social isolation increased with every level of decreasing self-rated health and increasing number of chronic conditions. Functional social isolation was higher for participants who required assistance with activities of daily living compared to those who were functionally independent. Compared to other physical health covariates, the largest difference in functional social isolation was observed between poor and excellent self-rated health, as shown in Appendix E, Table E1.

Regarding health behaviour covariates, functional social isolation was highest among current smokers (versus never or former smokers). Functional social isolation was higher among non-users and occasional users of alcohol compared to regular users.

5.1.2 Bivariate Associations with Executive Function

As shown in Table 2, those with self-reported clinical depression had higher executive function scores compared to those without self-reported clinical depression; however, the association was non-significant

(0.35 vs. 0.30, p = 0.14). As shown in Table 3, depressive symptoms (r = -0.08, p < 0.0001) and functional social isolation (r = -0.11, p < 0.0001) were negatively correlated with executive function.

All T1 covariates were significantly associated with T2 executive function in bivariate models with the exception of sex and rural/urban residence (Table 2). Regarding sociodemographic covariates, executive function decreased with increasing age, and was lowest among those who were widowed and highest among those who were partnered, single/never married or separated. Those who were living alone had lower executive function scores compared to those who were living with others. In terms of province, those who were living in Newfoundland and Labrador, Nova Scotia or Quebec had the lowest mean executive function scores while those living in British Columbia had the highest. Executive function decreased with every level of decreasing educational attainment and income. Compared with other sociodemographic covariates, the largest differences in executive function were observed between the lowest and highest levels of educational attainment and the youngest and oldest age groups, as shown in Appendix E, Table E1.

Regarding physical health covariates, executive function scores were lowest for those reporting fair or poor health, and highest for those reporting excellent health (Table 2). Similarly, executive function scores were lower for those reporting relatively more chronic conditions compared to fewer chronic conditions. Executive function was lower for participants who required assistance with activities of daily living compared to those who were functionally independent. Compared with other physical health covariates, the largest difference in executive function was observed between those with the highest number of chronic conditions versus zero chronic conditions, as shown in Appendix E, Table E1.

Regarding health behaviour covariates, executive function was lower among former smokers and current smokers (versus never smokers) and non-users and occasional users of alcohol (versus regular users).

5.2 Multivariable Analyses

Results from model building, as informed by testing interactions, can be found under Section 5.2.1. The role of T2 functional social isolation as a mediator of the association between T1 depression measures (depressive symptoms or clinical depression) and T2 executive function is addressed across subgroups defined by age group and sex under Section 5.2.2. Moderated pathway effects and accompanying sensitivity analyses can be found under Sections 5.2.3 and 5.2.4, respectively. Covariate effects and model diagnostics can be found under Sections 5.2.5 and 5.2.6, respectively. Only fully adjusted results are summarized in the text below, while complete results (including partially adjusted effects) can be found in the tables.

5.2.1 Model Building

Conceptual models were built by testing interactions with age and sex at Path I (X→M) and Path II (M→Y), and including only significant interactions. Models that included depressive symptoms were run separately from models that included self-reported clinical depression, with consistent results in terms of the location (i.e., Path I versus Path II) and ordering (i.e., two-way versus three-way) of interaction terms. A finalized conceptual moderated mediation model was created, which was applicable regardless of whether depressive symptoms or self-reported clinical depression was modelled as the exposure (Figure 6, Section 5.2.1.2).

5.2.1.1 Testing Interactions

5.2.1.1.1 Path I: The Effect of Depression on Functional Social Isolation

Starting at Path I (X→M), the conceptual models were built by including the highest-order significant interactions of T1 depression with age and sex in fully adjusted linear regression models where T2 functional social isolation was the outcome. A three-way interaction was tested first and included if significant. Models that included depressive symptoms were run separately from models that included self-reported clinical depression, with consistent results across the two exposure measures as described below.

The three-way interaction of T1 depressive symptoms*age group*sex was significant in a fully adjusted Path I model (R^2-change = 0.0005, p-value = 0.0007). The three-way interaction of T1 self-reported clinical depression*age group*sex was also significant in a fully adjusted Path I model (R^2-change = 0.0004, p-value = 0.0025). Three-way interactions as described above were thus included in the conceptual moderated mediation models at Path I for both depression measures.

5.2.1.1.2 Path II: The Effect of Functional Social Isolation on Executive Function

Interactions at Path II (M→Y) were tested in the same way as Path I (X→M), starting with highest-order interactions. Models that included depressive symptoms as a covariate were run separately from models that included self-reported clinical depression, with consistent results across the two exposure measures as described below.

First, the three-way interaction of T2 functional social isolation*age group*sex was tested in a fully adjusted Path II model where T2 executive function was the outcome. The three-way interaction was not significant for the model where depressive symptoms were controlled for (R^2-change = 0.0001, p-value = 0.20), or for the model where self-reported clinical depression was controlled for (R^2-change = 0.0001, p-value =0.21) (data not shown). The three-way interaction of functional social isolation*age group*sex was thus not included in the conceptual model at Path II.

Next, the following two-way interactions were simultaneously tested where T2 executive function was the outcome: T2 functional social isolation*age group and T2 functional social isolation*sex. The two-way interaction of functional social isolation*age group was significant in models where depressive symptoms (R^2-change = 0.0005, p-value = 0.0011) or self-reported clinical depression (R^2-change = 0.0004, p-value = 0.0012) were controlled for. The two-way interaction of functional social isolation*sex was nonsignificant in both models where depressive symptoms (R^2-change = 0.0000, p-value = 0.88) or self-reported clinical depression (R^2-change = 0.0000, p-value = 0.88) were controlled for (data not shown). The two-way interaction of functional social isolation*age group was thus included in the conceptual moderated mediation models.

5.2.1.2 Final Moderated Mediation Conceptual Model
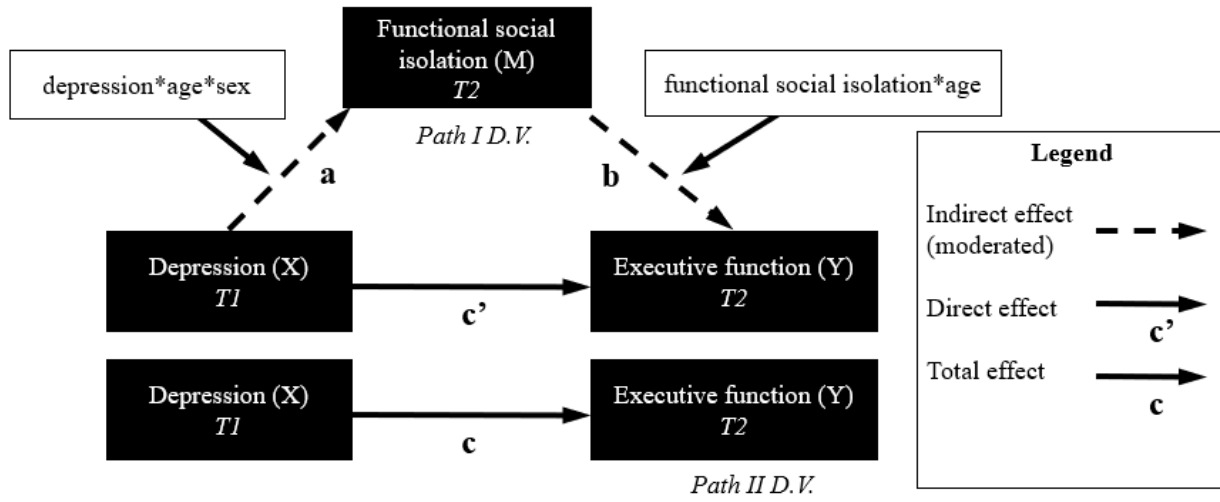
Figure 6: Final Conceptual Moderated Mediation Model, Pruned of Nonsignificant Interactions with Age and Sex. Covariates not shown. D.V. = dependent variable; M = functional social isolation; T1 = baseline; T2 = follow-up; X = depression (depressive symptoms or self-reported clinical depression in separate models); Y = executive function.

The relationship between depression (either depressive symptoms or self-reported clinical depression) and executive function, mediated by functional social isolation, is best conceptualized as a moderated mediation model, whereby age and sex are the moderators (see Figure 6). The multivariable data analysis table below reflects the final conceptual models, retaining only the highest-order significant interactions at their respective paths.

Table 5: Multivariable Data Analysis Table, Final Moderated Mediation Models Pruned of Nonsignificant Interactions with Age and Sex

	Path I: X→M	Path II: M→Y[†]

Model 0
Base Model
	Exposure (X):
	- Depression (T1)
	Outcome (M):
	- Functional social isolation (T2)
	Baseline mediator and outcome covariates:
	- Functional social isolation (T1)
	- Executive function (T1)
	Interaction terms[‡]:
	- *Three-way*:
	     depression*age group*sex
		Exposure (M):
		- Functional social isolation (T2)
		Outcome (Y):
		- Executive function (T2)
		Baseline mediator and outcome covariates:
		- Functional social isolation (T1)
		- Executive function (T1)
		Interaction terms[‡]:
		- *Two-way:*
		     functional social isolation*age group

Model 1	Same as Model 0, with adjustment for socio-demographic covariates at Paths I and II. • **Sociodemographic covariates at T1** (marital status, living arrangements, province, education, income, urban/rural residence)	

Model 2	Same as Model 0, with adjustment for socio-demographic and physical health covariates at Paths I and II.
	
	    • **Sociodemographic covariates at T1** (see above)
	    • **Physical health covariates at T1** (self-rated health, number of chronic conditions, functional impairment)	

Model 3
Fully Adjusted
	Same as Model 0, with adjustment for socio-demographic, physical health, and health behaviour covariates at Paths I and II.
	
	    • **Sociodemographic covariates at T1** (see above)
	    • **Physical health covariates at T1** (see above)
	    • **Health behaviour covariates at T1** (smoking use, alcohol use)	

M = Functional social isolation; T1 = Baseline; T2 = Follow-up; X = Depression (depressive symptoms or self-reported clinical depression included in separate analyses); Y = Executive function.
[†]Path II also controls for X.
[‡] Only significant highest-order interactions were included in the models. Lower-order terms corresponding to interaction effects were automatically controlled for. Sex and age group were controlled for in both paths (Path I and II) for all models (Models 0 to 3).

5.2.2 Moderated Indirect Effects and Proportion Mediated

The role of T2 functional social isolation as a mediator between T1 depression measures and T2 executive function is addressed in Tables 6a and 6b (depressive symptoms) and Tables 7a and 7b (self-reported clinical depression). Tables 6a and 7a apply interaction terms to the whole dataset (n=14,133) to estimate indirect effects, identifying subgroups where the mediation was significant. To aid in meaningfully interpreting the extent of mediation relative to the total effect of depression, a subset of the data was used to estimate the proportion mediated in the subgroup where the mediation was significant (see Tables 6b and 7b). As previously stated (Section 4.4.2), stratifying the data was necessary because the proportion mediated cannot be estimated in models with interaction terms occurring at both mediation paths. While results in Tables 6b and 7b give less precise estimates as a result of the smaller stratum of interest (women 75 years or older), indirect effect sizes approximate those using the whole dataset (Tables 6a and 7a).

After controlling for all covariates, T2 functional social isolation was a significant mediator of the effect of T1 depression on T2 executive function only among women aged 75 and older, in models both where the exposure was measured as depressive symptoms (β = -0.0032, 95% CI: -0.0069, -0.0005; Table 6a) or as self-reported clinical depression (β = -0.0644, 95% CI: -0.1282, -0.0166; Table 7a). Indirect effects for all other age and sex combinations were consistently nonsignificant with lower indirect effect sizes compared to women aged 75 and older in fully adjusted models. After controlling for all covariates, 8.01% of the total effect of depressive symptoms on executive function was attributed to mediation by functional social isolation in women aged 75 and older, with the remaining proportion attributed to the direct effect of depressive symptoms (Table 6b). For self-reported clinical depression, 17.53% of the total effect was attributed to mediation by functional social isolation in women aged 75 and older (Table 7b).

Table 6a: Indirect Effects of Depressive Symptoms (CES-D10) on Executive Function through Functional Social Isolation by Age and Sex, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

		Indirect effect β (95% Bootstrap CI)	
Moderators		**Base Model[†]**	**Fully Adjusted[†]**
Sex	**Age Group (years)**		
Male	*45-54*	-0.0005 (-0.0019, 0.0009)	-0.0001 (-0.0012,0.0010)
	55-64	**-0.0015 (-0.0030, -0.0004)**	-0.0009 (-0.0022, 0.0000)
	65-74	-0.0019 (-0.0042, 0.0002)	-0.0012 (-0.0032, 0.0006)
	75+	-0.0001 (-0.0034, 0.0035)	0.0001 (-0.0029, 0.0033)
Female	*45-54*	-0.0003 (-0.0013, 0.0006)	-0.0001 (-0.0008, 0.0006)
	55-64	**-0.0016 (-0.0032, -0.0004)**	-0.0010 (-0.0022, 0.0000)
	65-74	-0.0003 (-0.0012, 0.0003)	-0.0001 (-0.0008, 0.0004)
	75+	**-0.0037 (-0.0076, -0.0006)**	**-0.0032 (-0.0069, -0.0005)**

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; ΔR^2 = R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex.
Values where $p<0.05$ are in **bolded** font.
[†]Covariates:
  Base Model (Model 0): T1 mediator, T1 outcome, T1 depressive symptoms, age group, sex.
  Fully Adjusted (Model 3): Model 0 + sociodemographic, physical health and health behaviour factors.
  Note: Lower-order terms corresponding to interaction effects were automatically controlled for.
Sequential models adjusting for covariates in chunks (Models 1 and 2) can be found in Appendix F Table F1a.

Table 6b: Proportion of the Effect of Depressive Symptoms (CES-D10) on Executive Function Mediated by Functional Social Isolation in Women Aged 75 and Older, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=829)

Models[†]	Indirect effect β (95% Bootstrap CI)	Direct effect β (95% CI)	Total effect β (95% CI)	Proportion Mediated (%)
Base Model[†]	-0.0036 (-0.0094, 0.0008)	**-0.0481** **(-0.0897, -0.0064)**	**-0.0517** **(-0.0931, -0.0102)**	6.96
Fully Adjusted[†]	-0.0027 (-0.0079, 0.0008)	-0.0310 (-0.0747, 0.0127)	-0.0337 (-0.0773, 0.0099)	8.01

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; SE = Standard error; T1 = Baseline; T2 = Follow-up; X = Exposure; Y = Outcome.

Values where $p < 0.05$ are in **bolded** font

[†]Covariates:

  Base Model (Model 0): T1 mediator, T1 outcome, T1 depressive symptoms.

  Fully Adjusted (Model 3): Model 0 + sociodemographic, physical health and health behaviour factors.

Sequential models adjusting for covariates in chunks (Models 1 and 2) can be found in Appendix F Table F1b.

Table 7a: Indirect Effects of Self-Reported Clinical Depression on Executive Function through Functional Social Isolation by Age and Sex, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

		Indirect effect β (95% Bootstrap CI)	
Moderators		**Base Model**[†]	**Fully Adjusted**[†]
Sex	**Age Group (years)**		
Male	*45-54*	-0.0064 (-0.0219, 0.0072)	-0.0014 (-0.0130, 0.0099)
	55-64	**-0.0099 (-0.0225, -0.0013)**	-0.0051 (-0.0148, 0.0009)
	65-74	-0.0058 (-0.0188, 0.0032)	-0.0019 (-0.0108, 0.0054)
	75+	0.0102 (-0.0401, 0.0673)	0.0138 (-0.0330, 0.0677)
Female	*45-54*	-0.0024 (-0.0094, 0.0027)	-0.0002 (-0.0033, 0.0026)
	55-64	**-0.0082 (-0.0177, -0.0014)**	-0.0028 (-0.0090, 0.0012)
	65-74	-0.0004 (-0.0081, 0.0073)	0.0020 (-0.0031, 0.0100)
	75+	**-0.0753 (-0.1424, -0.0239)**	**-0.0644 (-0.1282, -0.0166)**

β = Regression coefficient value; CI = Confidence interval; M = Mediator; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z = Sex; Values where $p < 0.05$ are in **bolded** font.
[†]Covariates:
  Base Model (Model 0): T1 mediator, T1 outcome, T1 self-reported clinical depression, age group, sex.
  Fully Adjusted (Model 3): Model 0 + sociodemographic, physical health and health behaviour factors.
  Note: Lower-order terms corresponding to interaction effects were automatically controlled for.
Sequential models adjusting for covariates in chunks (Models 1 and 2) can be found in Appendix F Table F2a.

Table 7b: Proportion of the Effect of Self-Reported Clinical Depression on Executive Function Mediated by Functional Social Isolation in Women Aged 75 and Older, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=829)

Models[†]	Indirect effect β (95% Bootstrap CI)	Direct effect β (95% CI)	Total effect β (95% CI)	Proportion Mediated (%)
Base Model[†]	-0.0596 (-0.1490, 0.0077)	-0.3201 (-0.8798, 0.2396)	-0.3797 (-0.9354, 0.1760)	15.70
Fully Adjusted[†]	-0.0500 (-0.1381, 0.0109)	-0.2351 (-0.8047, 0.3344)	-0.2852 (-0.8513, 0.2810)	17.53

β = Regression coefficient value; CI = Confidence interval; M = Mediator; SE = Standard error; T1 = Baseline; T2 = Follow-up; X = Exposure; Y = Outcome.

Values where $p < 0.05$ are in **bolded** font

[†]Covariates:

  Base Model (Model 0): T1 mediator, T1 outcome, T1 self-reported clinical depression.

  Fully Adjusted (Model 3): Model 0 + sociodemographic, physical health and health behaviour factors.

Models adjusting for covariates in chunks (Models 1 and 2) can be found in Appendix F Table F2b.

5.2.3 Moderated Pathway Effects

In addition to assessing indirect effects, the mediated relationship can be further understood by honing in on the pathways from the exposure to the mediator (Path I) and the mediator to the outcome (Path II). The main Path I and Path II results are presented for depressive symptoms (Table 8) and self-reported clinical depression (Table 9). As stated previously, the interactions depression*age group*sex (Path I) and functional social isolation*age group (Path II) were significant regardless of whether depression was measured as depressive symptoms or as self-reported clinical depression.

5.2.3.1 Path I: The Effect of Depression on Functional Social Isolation in Women by Age Group

As shown in Table 8, the effect of T1 depressive symptoms on T2 functional social isolation in women varied by age (F-value = 3.22; p-value = 0.022), whereby depressive symptoms predicted significantly higher functional social isolation for women aged 45-54 (β = 0.1474; 95% CI: 0.0489, 0.2460), 55-64 (β = 0.2550; 95% CI: 0.1660, 0.3440) and 75 and older (β = 0.2477; 95% CI: 0.0664, 0.4291) in fully adjusted models. The effect of depressive symptoms on functional social isolation was not significant among women aged 65-74 in fully adjusted models (β = 0.0376; 95% CI: -0.0799, 0.1550).

As shown in Table 9, the association between self-reported clinical depression at T1 and functional social isolation at T2 was also moderated by age and sex in a three-way interaction in fully adjusted models (F-value = 4.82; p-value = 0.0024). Among women, the effect of self-reported clinical depression on functional social isolation varied by age; however, unlike depressive symptoms, self-reported clinical depression predicted significantly higher functional social isolation only in women aged 75 and older (β = 4.9339; 95% CI: 2.3739, 7.4938), and not in other age groups. The effect of self-reported clinical depression on functional social isolation was substantially higher in women aged 75 and older compared to women in other age groups.

5.2.3.2 Path I: The Effect of Depression on Functional Social Isolation in Men by Age Group

Similar to women, the effect of depressive symptoms at T1 on functional social isolation at T2 in men varied by age in fully adjusted models (F-value = 3.65; p-value = 0.012). The effect was significant among men aged 45-54 (β = 0.2484; 95% CI: 0.1339, 0.3629), 55-64 (β = 0.2459; 95% CI: 0.1450, 0.3468) and 65-74 (β = 0.3860; 95% CI: 0.2522, 0.5197), but nonsignificant for men aged 75 and older.

While the self-reported clinical depression*age group interaction was not statistically significant in men in fully adjusted models (F-value = 1.94; p-value = 0.12), the effect of self-reported clinical depression on T2 functional social isolation was only significant in younger men (45-54: β = 2.5072 [95%

CI: 1.0071, 4.0072]; 55-64: β = 1.3061 [95% CI: 0.0665, 2.5457]). Differences across age within men were less pronounced then differences across age within women, and standard errors were larger for men.

5.2.3.3 Path II: The Effect of Functional Social Isolation on Executive Function by Age Group

The association between functional social isolation at T2 and executive function at T2 was moderated by age in a two-way interaction in fully adjusted models including depressive symptoms (R^2-change = 0.0005, p-value = 0.0011) (Table 8) or self-reported clinical depression (R^2-change = 0.0004, p-value = 0.0012) (Table 9). The effect size of the association between functional social isolation and executive function increased from the youngest to the oldest age group both in models controlling for depressive symptoms and in those controlling for self-reported clinical depression. The association between functional social isolation and executive function was strongest for those aged 75 and older in fully adjusted models including depressive symptoms (β = -0.0130; 95% CI: -0.0184, -0.0077; Table 8) or self-reported clinical depression (β = -0.0131; 95% CI: -0.0185, -0.0077; Table 9) while it was weaker but still significant for those age 55-64 in fully adjusted models including depressive symptoms (β = -0.0038; 95% CI: -0.0076, -0.0001) or self-reported clinical depression (β = -0.0039; 95% CI: -0.0077, -0.0002). Associations were nonsignificant for the remaining age groups in fully adjusted models including depressive symptoms or self-reported clinical depression.

Table 8: Effects of Depressive Symptoms (CES-D10) on Functional Social Isolation (Path I) and Functional Social Isolation on Executive Function (Path II) by Age and Sex, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

	Path I: X→M β (95% CI)[†]	
	Base Model[†]	**Fully Adjusted**[†]
	X*W*Z (ΔR^2= 0.0006)	X*W*Z (ΔR^2=0.0005)
Age (W)	*Sex (Z): Males*	
	*X*W (F=4.41)*	*X*W (F=3.65)*
45-54	**0.3237 (0.2091, 0.4383)**	**0.2484 (0.1339, 0.3629)**
55-64	**0.2956 (0.1947, 0.3964)**	**0.2459 (0.1450, 0.3468)**
65-74	**0.4355 (0.3013, 0.5697)**	**0.3860 (0.2522, 0.5197)**
75+	0.0040 (-0.1899, 0.1978)	-0.0051(-0.1975, 0.1873)
	Sex (Z): Females	
	*X*W (F=3.87)*	*X*W (F=3.22)*
45-54	**0.2171 (0.1187, 0.3155)**	**0.1474 (0.0489, 0.2460)**
55-64	**0.3187 (0.2303, 0.4072)**	**0.2550 (0.1660, 0.3440)**
65-74	0.0673 (-0.0505, 0.1850)	0.0376 (-0.0799, 0.1550)
75+	**0.2596 (0.0774, 0.4418)**	**0.2477 (0.0664, 0.4291)**
	Path II: M→Y β (95% CI)[†]	
Age (W)	**Base Model**[†]	**Fully Adjusted**[†]
	M*W (ΔR^2 = 0.0005)	M*W (ΔR^2 =0.0005)
	Sex (Z): Males and Females	
45-54	-0.0015 (-0.0057, 0.0028)	-0.0005 (-0.0047, 0.0038)
55-64	**-0.0051 (-0.0089, -0.0013)**	**-0.0038 (-0.0076, -0.0001)**
65-74	-0.0043 (-0.0087, 0.0002)	-0.0032 (-0.0076, 0.0012)
75+	**-0.0141 (-0.0195, -0.0087)**	**-0.0130 (-0.0184, -0.0077)**

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; ΔR^2 = R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex.
Values where $p<0.05$ are in **bolded** font.
[†]Covariates:
  Base Model (Model 0): T1 mediator, T1 outcome, T1 depressive symptoms, age group, sex.
  Fully Adjusted (Model 3): Model 0 + sociodemographic, physical health and health behaviour factors.
  Note: Lower-order terms corresponding to interaction effects were automatically controlled for.
Models adjusting for covariates in chunks (Models 1 and 2) can be found in Appendix F Table F1a.

Table 9: Effects of Self-Reported Clinical Depression on Functional Social Isolation (Path I) and Functional Social Isolation on Executive Function (Path II) by Age and Sex, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

	Path I: X→M β (95% CI)[†]	
	Base Model[†]	**Fully Adjusted[†]**
	X*W*Z (ΔR^2=0.0004)	**X*W*Z (ΔR^2=0.0004)**
Age (W)	*Sex (Z): Males*	
	X*W (F=2.29)	*X*W (F=1.94)*
45-54	**3.2737 (1.7612, 4.7862)**	**2.5072 (1.0071, 4.0072)**
55-64	**1.8110 (0.5624, 3.0596)**	**1.3061 (0.0665, 2.5457)**
65-74	1.2454 (-0.4494, 2.9401)	0.5585 (-1.1214, 2.2384)
75+	-0.7211 (-3.6392, 2.1970)	-1.0551 (-3.9436, 1.8334)
	Sex (Z): Females	
	X*W (F=4.15)	*X*W (F=4.82)*
45-54	**1.2139 (0.0806, 2.3472)**	0.2763 (-0.8508, 1.4034)
55-64	**1.4940 (0.4822, 2.5058)**	0.7024 (-0.3053, 1.7101)
65-74	0.0764 (-1.2925, 1.4453)	-0.6071 (-1.9690, 0.7548)
75+	**5.3011 (2.7181, 7.8841)**	**4.9339 (2.3739, 7.4938)**
	Path II: M→Y β (95% CI)[†]	
Age (W)	**Base Model[†]**	**Fully Adjusted[†]**
	M*W (ΔR^2=0.0004)	**M*W (ΔR^2=0.0004)**
	Sex (Z): Males and Females	
45-54	-0.0019 (-0.0061, 0.0023)	-0.0006 (-0.0048, 0.0037)
55-64	**-0.0055 (-0.0092, -0.0017)**	**-0.0039 (-0.0077, -0.0002)**
65-74	**-0.0047 (-0.0091, -0.0002)**	-0.0033 (-0.0077, 0.0011)
75+	**-0.0142 (-0.0196, -0.0088)**	**-0.0131 (-0.0185, -0.0077)**

β = Regression coefficient value; CI = Confidence interval; M = Mediator; ΔR^2 = R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex.
Values where $p<0.05$ are in **bolded** font.
[†]Covariates:
  Base Model (Model 0): T1 mediator, T1 outcome, T1 self-reported clinical depression, age group, sex.
  Fully Adjusted (Model 3): Model 0 + sociodemographic, physical health and health behaviour factors.
  Note: Lower-order terms corresponding to interaction effects were automatically controlled for.
Models adjusting for covariates in chunks (Models 1 and 2) can be found in Appendix F Table F2a.

5.2.4 Sensitivity Analyses

Note that unlike Path I, Path II was chosen to be modelled cross-sectionally (T2 functional social isolation and T2 executive function) because only two time-points were available for modelling the mediation rather than the preferred three time-points (i.e., T1 depression, T2 social isolation, and T3 executive function). Sensitivity analyses were thus conducted to model the prospective association between functional social isolation at T1 and executive function at T2, controlling for all covariates (see Table 10). Results from the sensitivity analyses were consistent with the main analyses, whereby only age moderated Path II and effect sizes generally increased with age. See below for a description of results.

5.2.4.1 Testing Interactions

Model building for the Path II sensitivity analyses was conducted in the same way as for the main analyses, starting with three-way followed by two-way interactions. Just as in the main analyses, models that included depressive symptoms as a covariate were run separately from models that included self-reported clinical depression.

Consistent with the cross-sectional Path II results in Tables 8 and 9, T1 functional social isolation*age group*sex, was not significant in models of T2 executive function controlling for depressive symptoms (R^2-change = 0.0001; p-value = 0.30) or self-reported clinical depression (R^2-change = 0.0001; p-value = 0.31) (data not shown). Also consistent with the cross-sectional Path II results, T1 functional social isolation*sex was nonsignificant in the model controlling for depressive symptoms (R^2-change = 0.0000; p-value = 0.93) or self-reported clinical depression (R^2-change = 0.0001; p-value = 0.93) (data not shown). T1 functional social isolation*age group was significant in the model controlling for depressive symptoms (R^2-change = 0.0003; p-value = 0.011) or self-reported clinical depression (R^2-change = 0.0003; p-value = 0.011) (Table 10). The interaction of T1 functional social isolation*age group was thus included in the sensitivity analysis models.

5.2.4.2 Path II: The Effect of Functional Social Isolation on Executive Function by Age Group (Prospective)

Consistent with the cross-sectional Path II analyses (i.e., T2 functional social isolation and T2 executive function) in Tables 8-9, the association between T1 functional social isolation and T2 executive function was stronger at older compared to younger age groups, and significant in those aged 75 and older in fully adjusted models including depressive symptoms (β = -0.0097; 95% CI: -0.0147, -0.0046) or self-reported clinical depression (β = -0.0100; 95% CI: -0.0150, -0.0050), as shown in Table 10. Unlike the cross-sectional analyses, however, the prospective association was significant among those aged 65 to 74 in

fully adjusted models including self-reported clinical depression (β = -0.0041; 95% CI: -0.0082, -0.0001), as shown in Table 10. Also, unlike the cross-sectional analyses, the association in the fully adjusted prospective analyses were nonsignificant for those aged 55-64 in fully adjusted prospective models including depressive symptoms (β = -0.0012; 95% CI: -0.0045, 0.0021) or self-reported clinical depression (β = -0.0015; 95% CI: -0.0048, 0.0017).

Table 10: Sensitivity Analyses – Fully Adjusted Prospective Effects of Functional Social Isolation on Executive Function by Age and Sex, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Models	Moderator	Path II: M→Y	
		Effect of functional social isolation (T1) on executive function (T2) β (95% CI)	
	Age Group, years (W)	Controlling for depressive symptoms (CES-D10)	Controlling for self-reported clinical depression
		M*W (ΔR²=0.0003)	M*W (ΔR²=0.0003)
Fully Adjusted[†]	45-54	-0.0003 (-0.0035, 0.0042)	-0.0001 (-0.0039, 0.0037)
	55-64	-0.0012 (-0.0045, 0.0021)	-0.0015 (-0.0048, 0.0017)
	65-74	-0.0037 (-0.0078, 0.0004)	**-0.0041 (-0.0082, -0.0001)**
	75+	**-0.0097 (-0.0147, -0.0046)**	**-0.0100 (-0.0150, -0.0050)**

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y= Outcome; Z = sex.
[†]Model 3 Covariates: X, W, Z, Y (T1), sociodemographic factors (marital status, living arrangements, province, education, income, urban/rural residence), physical health factors (self-rated health, number of chronic conditions, functional impairment), health behaviour factors (smoking use, alcohol use).

5.2.5 Covariate Effects

Covariate effects, measured at T1, were mostly consistent between fully adjusted models that included either T1 depressive symptoms or self-reported clinical depression as described below. Fully adjusted covariate effect sizes can be found for models including depressive symptoms (Table 11) or self-reported clinical depression (Table 12).

5.2.5.1 Path I: The Effect of Covariates on Functional Social Isolation

As shown in Tables 11 and 12 (left-hand results column), sociodemographic covariates that were significantly associated with T2 functional social isolation in fully adjusted models included marital status, province and income. Being single/never married, divorced or separated was associated with higher levels of functional social isolation, on average, compared to having a partner. On the other hand, widowhood was not associated with functional social isolation compared to having a partner. In terms of province, only participants living in Quebec or Newfoundland and Labrador had lower levels of functional social isolation compared to people living in Ontario. Living in Nova Scotia (versus Ontario) was associated with lower functional social isolation only in models controlling for self-reported clinical depression. The association between income and functional social isolation was graded, whereby those with the lowest income had the highest levels of functional social isolation. Living alone, education, and rural residence were not associated with T2 functional social isolation in fully adjusted models.

Physical health covariates that were significantly associated with T2 functional social isolation in fully adjusted models included self-rated health and number of chronic conditions. Compared to those who reported excellent health, those who reported good or fair health had higher levels of functional social isolation, while results were nonsignificant for those reporting very good health. Poor health (versus excellent health) was associated with higher functional social isolation in models controlling for self-reported clinical depression but not in models where depressive symptoms were controlled for. Regarding the number of chronic conditions, only those with three chronic conditions had significantly higher levels of functional social isolation compared to having no chronic conditions. Functional impairment was not associated with functional social isolation in fully adjusted models. Health behaviour covariates that were significantly associated with T2 functional social isolation in fully adjusted models included smoking status, whereby current smokers had higher levels of functional social isolation compared to never users. Alcohol use, on the other hand, was not associated with functional social isolation.

In terms of baseline mediator and outcome, T1 functional social isolation was a significant predictor of T2 functional social isolation, while findings were nonsignificant for T1 executive function in fully adjusted models. Effect sizes for depression at Path I were not provided in Tables 11 and 12, given that depression is moderated at Path I (see Tables 8 and 9). The effect size of depression (along with interaction terms) for Path I can be found in Appendix F, Tables F3a and F4a.

5.2.5.2 Path II: The Effect of Covariates on Executive Function

As shown in Tables 11 and 12 (right-hand results column), neither depressive symptoms nor self-reported clinical depression were associated with T2 executive function. Sociodemographic covariates that were significantly associated with T2 executive function in fully adjusted models included province, education and income. Compared to Ontario, those living in Newfoundland and Labrador and in Nova Scotia had lower executive function scores, while those living in British Columbia and Manitoba had higher executive function scores. Executive function generally decreased with every decreasing level of education, although effect sizes were similar between completed post-secondary education (not university) and incomplete (i.e., some) post-secondary education. In terms of income, only those in the bottom two income brackets (<$50,000) had significantly lower executive function scores compared to those in the highest income bracket ($\geq$ $150,000). Marital status, living alone, and rural residence were not associated with executive function.

Physical health covariates that were significantly associated with T2 executive function in fully adjusted models were self-rated health and functional impairment. Compared to those who reported excellent health, those who reported fair health had lower levels of executive function. Those with functional impairment had lower executive function compared to those without functional impairment. Number of chronic conditions and health behaviour covariates (i.e., smoking and alcohol use) were not significantly associated with T2 executive function.

In terms of baseline mediator and outcome, T1 executive function was a significant predictor of T2 executive function, while findings were nonsignificant for T1 functional social isolation in fully adjusted models. Effect sizes for T2 functional social isolation at Path II were not provided in Tables 11 and 12, given that functional social isolation is moderated at Path II (see Tables 8 and 9). The effect size of T2 functional social isolation (along with interaction terms) for Path II can be found in Appendix F, Tables F3b and F4b.

Table 11: Covariate Effects on Functional Social Isolation and Executive Function Controlling for Depressive Symptoms (CES-D10), Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Independent Variables	Path I: X→M Functional social isolation (T2) $R^2 = 0.58$ β (95% CI)	Path II: M→Y Executive function (T2) $R^2 = 0.60$ β (95% CI)
Exposure (T1)		
CES-D10	*CES-D10*age group*sex[†]*	-0.0047 (-0.0125, 0.0031)
Mediator (T2)		
Functional social isolation		*Functional social isolation*age group[†]*
Baseline mediator and outcome (T1)		
Functional social isolation	**0.6792 (0.6665, 0.6919)**	0.0002 (-0.0027, 0.0031)
Executive function	-0.0616 (-0.1355, 0.0122)	**0.6931 (0.6804, 0.7057)**
Sociodemographic characteristics (T1)		
Marital status (ref: partnered)		
Single/never married	**2.8432 (1.9591, 3.7274)**	0.0584 (-0.0933, 0.2100)
Widowed	0.2122 (-0.7222, 1.1465)	-0.0949 (-0.2538, 0.0640)
Divorced	**1.7090 (0.9042, 2.5137)**	0.0085 (-0.1293, 0.1462)
Separated	**1.4000 (0.1653, 2.6348)**	0.0739 (-0.1372, 0.2851)
Lives alone (ref: lives with others)	0.0508 (-0.0226, 0.1242)	0.0036 (-0.0090, 0.0161)
Province (ref: Ontario)		
Alberta	0.5372 (-0.1691, 1.2434)	0.0574 (-0.0634, 0.1782)
British Columbia	-0.0976 (-0.6202, 0.4250)	**0.1137 (0.0243, 0.2031)**
Manitoba	-0.0038 (-0.6715, 0.6639)	**0.1369 (0.0228, 0.2511)**
Newfoundland and Labrador	**-1.0483 (-1.7514, -0.3453)**	**-0.1822 (-0.3025, -0.0619)**
Nova Scotia	-0.6669 (-1.3501, 0.0163)	**-0.1385 (-0.2553, -0.0216)**
Quebec	**-0.8954 (-1.4949, -0.2959)**	0.0618 (-0.0408, 0.1644)
Education, highest level obtained (ref: university degree)		
Post-secondary diploma/ degree (not university)	0.2676 (-0.1687, 0.7038)	**-0.2966 (-0.3711, -0.2221)**
Some post-secondary	0.1661 (-0.5580, 0.8902)	**-0.2897 (-0.4135, -0.1660)**
Secondary school graduation (no post-secondary)	-0.1713 (-0.8664, 0.5238)	**-0.3562 (-0.4750, -0.2374)**
Less than secondary school	-0.8297 (-1.8325, 0.1731)	**-0.8248 (-0.9961, -0.6536)**
Income (ref: ≥ $150,000)		
≥$100,000 and <$150,000	**0.7484 (0.1916, 1.3051)**	-0.0346 (-0.1299, 0.0607)
≥$50,000 and <$100,000	**0.9794 (0.4329, 1.5258)**	-0.0912 (-0.1848, 0.0025)
≥$20,000 and <$50,000	**2.2750 (1.5727, 2.9773)**	**-0.2518 (-0.3722, -0.1314)**
<$20,000	**3.9291 (2.7730, 5.0853)**	**-0.2513 (-0.4494, -0.0531)**
Rural (ref: urban)	-0.0908 (-0.7610, 0.5794)	-0.0558 (-0.1704, 0.0589)
Physical health (T1)		
Self-rated health (ref: excellent)		
Very good	0.2485 (-0.2234, 0.7204)	-0.0011 (-0.0818, 0.0796)
Good	**1.0304 (0.4866, 1.5741)**	-0.0651 (-0.1581, 0.0280)
Fair	**1.4328 (0.5481, 2.3176)**	**-0.2229 (-0.3742, -0.0715)**
Poor	1.0400 (-0.9255, 3.0055)	0.1839 (-0.1521, 0.5199)

Independent Variables	Path I: X→M Functional social isolation (T2) $R^2 = 0.58$ β (95% CI)	Path II: M→Y Executive function (T2) $R^2 = 0.60$ β (95% CI)
Number of chronic conditions (ref: 0)		
1	0.2519 (-0.1895, 0.6932)	-0.0250 (-0.1004, 0.0505)
2	0.1215 (-0.4074, 0.6504)	-0.0269 (-0.1172, 0.0635)
3	**0.7469 (0.0517, 1.4420)**	-0.0708 (-0.1897, 0.0480)
4+	0.5404 (-0.3868,1.4676)	-0.1281 (-0.2866, 0.0305)
Functional impairment (ref: no impairment)	0.0783 (-0.6549, 0.8116)	**-0.2198 (-0.3448, -0.0948)**
Health behaviours (T1)		
Smoking status (ref: never used)		
Former user	0.1500 (-0.2324, 0.5324)	-0.0479 (-0.1130, 0.0173)
Current user	**1.3601 (0.6617, 2.0586)**	-0.0660 (-0.1853, 0.0534)
Alcohol use (ref: non-user)		
Occasional user	-0.0144 (-0.7909, 0.7621)	0.0781 (-0.0547, 0.2109)
Regular user	-0.2839 (-0.8986, 0.3308)	0.1050 (-0.0001, 0.2101)

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; ref = reference group; T1 = Baseline; T2 = Follow-up; X = Exposure; Y = Outcome.

Values where $p<0.05$ are in **bolded** font.

[†]Moderators (age group and sex) as well as interaction terms (i.e., Path I: CES-D10*age group*sex; Path II: functional social isolation*age group) and their corresponding lower-order interaction effects were controlled for. Full results can be found in Appendix F Tables F3a (Path I) and F3b (Path II).

Table 12: Covariate Effects on Functional Social Isolation and Executive Function Controlling for Self-Reported Clinical Depression, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Independent Variables	Path I: X→M Functional social isolation (T2) $R^2 = 0.58$ β (95% CI)	Path II: M→Y Executive function (T2) $R^2 = 0.60$ β (95% CI)
Exposure (T1)		
Clinical depression (self-reported)	*Clinical depression (self-reported)*age group*sex[†]*	-0.0467 (-0.1339, 0.0404)
Mediator (T2)		
Functional social isolation		*Functional social isolation*age group[†]*
Baseline mediator and outcome (T1)		
Functional social isolation	**0.6953 (0.6831, 0.7075)**	-0.0001 (-0.0029, 0.0028)
Executive function	-0.0683 (-0.1424, 0.0057)	**0.6933 (0.6807, 0.7059)**
Sociodemographic characteristics (T1)		
Marital status (ref: partnered)		
Single/never married	**2.8441 (1.9582, 3.7300)**	0.0594 (-0.0922, 0.2110)
Widowed	0.2631 (-0.6739, 1.2001)	-0.0971 (-0.2561, 0.0618)
Divorced	**1.6188 (0.8120, 2.4255)**	0.0127 (-0.1251, 0.1504)
Separated	**1.4342 (0.1970, 2.6715)**	0.0736 (-0.1376, 0.2847)
Lives alone (ref: lives with others)	0.0455 (-0.0280, 0.1190)	0.0037 (-0.0088, 0.0162)
Province (ref: Ontario)		
Alberta	0.4906 (-0.2173, 1.1985)	0.0580 (-0.0628, 0.1787)
British Columbia	-0.1306 (-0.6544, 0.3933)	**0.1139 (0.0246, 0.2033)**
Manitoba	-0.0375 (-0.7069, 0.6319)	**0.1374 (0.0232, 0.2515)**
Newfoundland and Labrador	**-1.1002 (-1.8052, -0.3952)**	**-0.1828 (-0.3031, -0.0624)**
Nova Scotia	**-0.7119 (-1.3969, -0.0268)**	**-0.1394 (-0.2562, -0.0225)**
Quebec	**-1.0095 (-1.6106, -0.4084)**	0.0649 (-0.0378, 0.1675)
Education, highest level obtained (ref: university degree)		
Post-secondary diploma/ degree (not university)	0.2758 (-0.1618, 0.7133)	**-0.2972 (-0.3717, -0.2227)**
Some post-secondary	0.1858 (-0.5400, 0.9115)	**-0.2907 (-0.4144, -0.1670)**
Secondary school graduation (no post-secondary)	-0.1099 (-0.8073, 0.5876)	**-0.3591 (-0.4780, -0.2402)**
Less than secondary school	-0.7238 (-1.7288, 0.2812)	**-0.8309 (-1.0023, -0.6596)**
Income (ref: ≥ $150,000)		
≥$100,000 and <$150,000	**0.7597 (0.2020, 1.3174)**	-0.0346 (-0.1299, 0.0607)
≥$50,000 and <$100,000	**1.0342 (0.4870, 1.5813)**	-0.0915 (-0.1851, 0.0022)
≥$20,000 and <$50,000	**2.3647 (1.6611, 3.0683)**	**-0.2519 (-0.3723, -0.1314)**
<$20,000	**4.1191 (2.9607, 5.2775)**	**-0.2519 (-0.4501, -0.0537)**
Rural (ref: urban)	-0.1034 (-0.7757, 0.5688)	-0.0558 (-0.1704, 0.0589)
Physical health (T1)		
Self-rated health (ref: excellent)		
Very good	0.3858 (-0.0860, 0.8577)	-0.0035 (-0.0840, 0.0770)
Good	**1.3790 (0.8397, 1.9183)**	-0.0707 (-0.1627, 0.0214)
Fair	**2.1503 (1.2777, 3.0229)**	**-0.2340 (-0.3830, -0.0851)**

Independent Variables	Path I: X→M Functional social isolation (T2) $R^2 = 0.58$ β (95% CI)	Path II: M→Y Executive function (T2) $R^2 = 0.60$ β (95% CI)
Poor	**2.2251 (0.2723, 4.1778)**	0.1666 (-0.1665, 0.4997)
Number of chronic conditions (ref: 0)		
1	0.2560 (-0.1865, 0.6985)	-0.0242 (-0.0997, 0.0512)
2	0.1116 (-0.4192, 0.6424)	-0.0252 (-0.1157, 0.0652)
3	**0.7609 (0.0635, 1.4583)**	-0.0689 (-0.1878, 0.0500)
4+	0.5209 (-0.4095, 1.4513)	-0.1251 (-0.2838, 0.0336)
Functional impairment (ref: no impairment)	0.1587 (-0.5776, 0.8951)	**-0.2195 (-0.3446, -0.0944)**
Health behaviours (T1)		
Smoking status (ref: never used)		
Former user	0.1712 (-0.2120, 0.5544)	-0.0479 (-0.1130, 0.0173)
Current user	**1.3685 (0.6686, 2.0685)**	-0.0659 (-0.1853, 0.0534)
Alcohol use (ref: non-user)		
Occasional user	-0.0551 (-0.8333, 0.7232)	0.0784 (-0.0544, 0.2112)
Regular user	-0.3052 (-0.9214, 0.3109)	0.1047 (-0.0004, 0.2098)

β = Regression coefficient value; CI = Confidence interval; M = Mediator; ref = reference group; T1 = Baseline; T2 = Follow-up; X = Exposure; Y = Outcome.

Values where $p<0.05$ are in **bolded** font.

[†]Moderators (age group and sex) as well as interaction terms (i.e., Path I: self-reported clinical depression*age group*sex; Path II: functional social isolation*age group) and their corresponding lower-order interaction effects were controlled for. Full results can be found in Appendix F Tables F4a (Path I) and F4b (Path II).

5.2.6 Model Diagnostics

Assumptions of linear regression did not appear to be violated for Path I or Path II. Figures G1 to G3 (Appendix G) visually demonstrate linearity between all pathways. As shown in Figures G4 to G7, assumptions regarding the distribution of residuals (i.e., normality, homoscedasticity) appear valid. There were no influential outliers, as no observation surpassed the Cook's D threshold of 1 (Kleinbaum et al., 2013). In addition, no issues were detected regarding multicollinearity for Path I or Path II regardless of whether depressive symptoms or self-reported clinical depression was modelled as the exposure. Variance inflation factor (VIF) values for all main effects were less than 10, consistent with guidelines (Kleinbaum et al., 2013).

5.2.7 Missing Outcome Data

Missing data on T2 executive function were substantial. Supplementary analyses were thus conducted to flag potential biases. Table H1 in Appendix H summarizes the associations between the variables used in the analyses and missing data on T2 executive function. Compared to those with complete T2 executive function, participants who had missing scores on executive function at T2 were more likely to have self-reported clinical depression and higher depressive symptom scores at T1, higher T1 functional social isolation and lower T1 executive function scores.

Chapter 6

Discussion

6.1 Summary of Study Findings

This study investigated whether T2 functional social isolation was a mediator between T1 depression and T2 executive function across age and sex subgroups, after controlling for T1 functional social isolation and executive function, as well as sociodemographic, physical health and health behaviour covariates. Functional social isolation significantly mediated the relationship between depression (depressive symptoms or self-reported clinical depression) and executive function, but only in women aged 75 and over. To elaborate, in women aged 75 and older, depression (increasing depressive symptoms or the presence of self-reported clinical depression) predicted higher functional social isolation, which in turn, predicted decreasing executive function. In contrast, functional social isolation was not a significant mediator for females that were younger than 75 or males of any age group. Temporality was apparent at both fully adjusted paths of the mediation relationship within women aged 75 and older, as demonstrated by the main (Path I) and sensitivity (Path II) analyses. In other words, T1 depression (depressive symptoms or self-reported clinical depression) was associated with T2 functional social isolation, and T1 functional social isolation was associated with T2 executive function.

6.2 Discussion of Mediation Results

Results were generally consistent with other mediation literature that assessed the role of social factors between depression and cognition. For example, a CLSA study (cross-sectional) found that decreasing social engagement mediated the relationship between sensory impairment and decreasing executive function more strongly for women compared to men and for older compared to middle-aged adults (Hämäläinen et al., 2019); however, results are difficult to compare given that the exposure used in the current study was depression and not sensory impairment. Another mediation study in a German community-dwelling population (cross-sectional) similarly found that decreasing functional social support was a significant mediator for the relationship between increasing depressive symptoms and decreasing executive function in women but not men; however, unlike the current study, mediation was not significant in older age groups (Cohrdes & Bretscheneider, 2018). Inconsistent results may be because Cohrdes & Bretscheneider (2018) assessed indirect effects by age and sex separately instead of combining them, and age was only split into two categories (< 65 and ≥ 65) in their study instead of the four age groups in the current study. Splitting age into only two categories (< 65 and ≥ 65) and combining males

and females could dilute a potentially significant effect in women aged 75 and older. Inconsistent results may thus have more to do with differences in defining subgroups rather than true contradictory findings.

A positive association between depression and functional social isolation (Path I) and a negative association between functional social isolation and executive function (independent of depression) (Path II) is consistent with biological explanations and epidemiological evidence. Depression is linked to abnormalities in social communication and social perception, contributing to interpersonal difficulties and social withdrawal (Kupferberg et al., 2016; Wenzler et al., 2017). For example, people with depression tend to be hyper-sensitive to social rejection and have impairments in emotional recognition as well as emotional expressivity (e.g., smiling) (Davies et al., 2016; Kupferberg et al., 2016). Abnormal social tendencies in people with depression may thus result in dwindling perceived social support over time (Davies et al., 2016; Kupferberg et al., 2016; Wenzler et al., 2017). Likewise, a negative association between functional social isolation and executive function independent of depression is consistent with the literature. Many epidemiological studies demonstrate that both functional and structural social isolation impacts cognition after controlling for depression (Deng et al., 2018; Faramarzi et al., 2018; Fu et al., 2018; Han et al., 2019; Huntley et al., 2018; Kim et al., 2019; Lara et al., 2019; Lee et al., 2020; Luchetti et al., 2020; Murata et al., 2019; Roystonn et al., 2020; Tomioka et al., 2018; Tsuji et al., 2019; Yu et al., 2020; Zahodne et al., 2018). Furthermore, functional aspects of social isolation are associated with smaller grey and white matter volumes as well as smaller total brain volume even after controlling for depressive symptoms (van der Velpen et al., 2021). Functional social isolation may also result in executive function decline by reducing physical activity, limiting cognitive stimulation, and amplifying the stress response (Eisele et al., 2012). Evolutionary theories additionally suggest that humans developed executive function, in part, to establish the social connections necessary for survival (Adolphs, 2003; Ardila, 2008). Taken together, it is biologically plausible for depression to increase functional social isolation, and for functional social isolation to reduce executive functioning (independent of depression).

There may be several reasons why functional social isolation was found to mediate the effect of depression on executive function only in women aged 75 and older in the current study, including chronic depression, other socioenvironmental factors, survival effects, adaptive homeostasis and prodromal relationships. The first three explanations (chronic depression, other socioenvironmental factors, and survival effects) have to do with the moderating effect of age and sex on Path I, while the last two explanations (adaptive homeostasis and prodromal relationship) relate to the moderating effect of age at Path II. Compared to other subgroups, adults aged 75 and older may experience a stronger effect of depression on functional social isolation because of the cumulative social and cognitive effects of

depression across the life course. Chronic depression can be defined as depressive symptoms experienced over a long duration, and chronic depression is associated with higher social isolation compared to non-chronic depression (Visentini et al., 2018). In addition to the effects of older age, a longer lifetime duration of depression is more likely to occur in older women than older men because depression remains higher among women compared to men throughout the life course (Albert, 2015; Davison et al., 2019). Chronic depression may be better captured in measures of historical depression, such as the self-reported clinical depression measure used in this study, rather than current depressive symptoms, such as the CES-D10. Chronic depression may therefore explain why women aged 75 and older with self-reported clinical depression were, by far, the most vulnerable to functional social isolation compared to other subgroups with self-reported clinical depression in this study.

In addition, other socioenvironmental factors, such as structural social isolation, life-space mobility and caregiving burden, may contribute to differing effects of depression on functional social isolation across subgroups. Structural aspects of social isolation, such as a small social network and low social engagement, are intertwined with both depression (Kupferberg et al., 2016) and functional social isolation (Wister et al., 2019) and may amplify their effects. Combined with an already small social network in older age, it is possible that older women with self-reported clinical depression may be especially prone to feeling socially isolated. For example, Menec et al. (2019) found that structural social isolation was highest in women aged 75 and older compared to all other age and sex subgroups in the CLSA. It is thus possible that higher structural social isolation may intensify the effect of self-reported clinical depression on functional social isolation in women aged 75 and older. Furthermore, older women (versus older men) report lower life-space mobility, defined as the ability to travel within one's environment (Caldas et al., 2020). Lower life-space mobility restricts one's ability to participate in social activities and has been associated with cognitive decline and dementia (Caldas et al., 2020). Lower life-space mobility may be an additional barrier to social participation in older women with depression, as people with depression are already prone to social withdrawal compared to those without depression (Kupferberg et al., 2016). Caregiving burden may also contribute to a relatively strong relationship between self-reported clinical depression and functional social isolation in women aged 75 and older. To demonstrate, depression (Adelman et al., 2014), being female (Adelman et al., 2014) and older age (Chiao et al., 2015) are risk factors for caregiver burden, and caregiving burden is a risk factor for social isolation (Victor et al., 2020). The wider social context, therefore, may play a role in amplifying functional social isolation in women aged 75 and older with self-reported clinical depression.

Survival effects, occurring at Path I and in the context of selective pressures, are also important for understanding why mediation was only significant in women aged 75 and older but not in men of the same age group. Population-based studies demonstrate that depression-related mortality, including suicide, is higher among older men compared to older women (Diniz et al., 2014; Jeong et al., 2013; Kiely et al., 2019). Social isolation is also more deadly in older men compared to older women (Yang et al., 2013). Furthermore, depression combined with loneliness, an indicator of social isolation, is especially lethal in older men because of suicidality, cardiovascular disease and decreased motivation to pursue health-promoting behaviours (Holwerda et al., 2016). To demonstrate, Holwerda et al. (2016) found that severe depression combined with loneliness was associated with excess mortality in older men but not older women. It is thus possible that older men with depression do not have high levels of functional social isolation because social support acts as a survival advantage, resulting in low, nonsignificant effect sizes at Path I and consequently, nonsignificant mediation.

Adaptive homeostasis may explain the moderating effect of age between functional social isolation and executive function (i.e., Path II). Older adults may be more vulnerable to the effects of functional social isolation on executive function because of a diminishing ability to cope with stress. Social isolation often results in distress (Eisele et al., 2012; Holt-Lunstad, 2017), and biological processes associated with aging may amplify the effects of social isolation on cognition by diminishing one's ability to cope. Adaptative homeostasis enables organisms to successfully cope with stress, including emotional and psychological stressors (Pomatto & Davies, 2017). Declines in adaptive homeostasis occur with advancing age (Pomatto & Davies, 2017), which may explain why older adults exhibit heightened stress responses in reaction to stressors (Ritvanen et al., 2006) and take longer to recover from stress (Kiss et al., 2008) compared to younger adults. Such declines in adaptive homeostasis contribute to cellular senescence, increasing the risk for age-associated disease (Pomatto & Davies, 2017). The accumulation of senescent cells in the nervous system may thus increase the rate of cognitive decline in older versus younger individuals (Kritsilis et al., 2018), supporting the current findings that those in the oldest age group (75+) experienced the strongest association between functional social isolation and executive function.

Another possibility for why the relationship between functional social isolation and executive function (i.e., Path II) was only significant in older but not younger age group relates to a prodromal relationship. It is possible that functional social isolation acts as a preclinical symptom (prodrome) of cognitive impairment, similar to depression (Bennett & Thomas, 2014). Neuropsychiatric symptoms (e.g., irritability, agitation) and mild behavioural impairments (e.g., emotional dysregulation, social inappropriateness) are prevalent in those with early signs of cognitive impairment, and may disrupt social

relationships (Mortby et al., 2018; Peters et al., 2012). Although mitigated by sensitivity analyses that controlled for T1 executive function for the association between T1 functional social isolation and T2 executive function, the long preclinical course of dementia and the relatively short follow-up period of the study makes it possible that functional social isolation is also a prodrome for declining executive function.

6.3 Strengths of the Study

The strengths of the study include the quantification of mediation effects and error across age and sex; the incorporation of more than one time-point, two depression measures and numerous covariates; and the national scope of the sample. Conditional process analysis using PROCESS allowed the quantification of indirect effects and error while minimizing the number of tests, providing greater statistical robustness compared to traditional mediation approaches such as Baron and Kenny's causal steps approach (Baron & Kenny, 1986). In addition, the current study was able to provide estimates based on age and sex simultaneously rather than independently. Reporting by age and sex simultaneously provides greater relevance to particular age and sex subgroups (e.g., women aged 75+) compared to larger subgroups (e.g., women of all ages). As the current findings suggest, subgroup heterogeneity is important to consider.

Another strength of the study was the ability to incorporate many different measures, with implications for temporality, reproducibility and the minimization of confounding bias. For example, the study was able to assess temporality between all paths of the mediation by incorporating two time-points in PROCESS and conducting sensitivity analyses using linear regression. The inclusion of two depression measures (depressive symptoms and self-reported clinical depression) was another strength of the study, providing some evidence of reproducibility. In addition, the availability of a broad range of relevant covariates and the large sample size allowed for the inclusion of numerous covariates not controlled for in other similar studies, reducing the potential for confounding.

Lastly, the study was national in scope and additional measures were put into place to ensure adequate representation of the Canadian population (CLSA, 2017; Raina et al., 2019). For example, strategies such as stratified sampling as well as oversampling in underrepresented populations were employed (CLSA, 2017). Although with the conditional process analysis it was not possible to employ weighting, the stratified sampling strategy supported generalizability of the sample.

6.4 Limitations of the Study

Despite its strengths, the study has various limitations primarily related to missing data, generalizability and temporality. Poorer mental, social, physical and cognitive health among those who were excluded because of missing T2 executive function may have resulted in an underestimation of Path II effects and consequently, underestimated indirect effects. For example, those who were missing T2 executive function data were more likely to experience depression (self-reported clinical depression or higher depressive symptoms), functional social isolation, poor health, and lower executive function at T1 (Appendix H, Table H1). Consequently, those with both higher functional social isolation and lower executive function were likely excluded, pulling the effects closer to the null. Further, those who remained in the sample were healthier and thus less likely to experience executive function decline, potentially resulting in underestimated Path II effects. A healthier analytic sample also has implications for external validity, limiting the ability to apply the results to the general population. External validity is already a major concern in the CLSA, as CLSA participants are more likely to be Canadian-born, educated, affluent, and healthy compared to the overall Canadian population (Raina et al., 2019). Inability to incorporate survey weights may have also reduced external validity and may limit comparisons with other CLSA studies using weighted analyses. However, although weights could not be incorporated in the conditional process analyses, O'Connell et al. (2019) suggest that applying weights may not impact analyses of cognition in the CLSA (2019).

In addition, there are temporality concerns with the current study. As mentioned previously, three years may not be long enough to differentiate risk factors from prodromes of cognitive decline. While excluding those with cognitive impairment in the current study and controlling for T1 executive function may have addressed temporality concerns, the long preclinical phase of dementia makes it difficult to form conclusions as to whether depression or functional social isolation act primarily as risk factors or prodromes for decreasing executive function. Also, temporality could not be maintained at all paths when estimating the indirect effect. Although mitigated by sensitivity analyses, the reliance on two time-points rather than the preferred three made it impossible to estimate the indirect effect when all paths were modelled prospectively.

6.5 Implications and Future Directions

The current study may be the first to assess the role of social isolation as a mediator between depression and cognition according to subgroups defined by both age and sex simultaneously. Functional social isolation explains a small but potentially meaningful portion of the association between depression and executive function in women aged 75 and older, suggesting that social interventions aimed at eliminating

functional social isolation could reduce the impact of depression on executive function in this subpopulation. Socially stimulating group interventions, for example, have the potential to improve cognitive outcomes for lonely older adults (Pitkala et al., 2011). Nonetheless, the findings should be interpreted cautiously, as most of the effect of depression on executive function did not occur through functional social isolation, suggesting the direct role of depression or the indirect role of other mediators in explaining the relationship between depression and executive function. While mediation by functional social isolation is potentially meaningful, caution must be taken as small effect sizes suggest that depression and functional social isolation have relatively minor roles as predictors of executive function. It is also important to keep in mind that effects are likely underestimated given biases related to missing outcome data, and three years may not be long enough to differentiate depression and functional social isolation as true risk factors versus prodromes of declining executive function.

This study provides a broad look at how functional social isolation links depression to executive function. For a more detailed investigation, future studies should investigate other mediators. For example, future studies could investigate whether mediation varies by subtype of functional social isolation (e.g., emotional/informational, affectionate, tangible, positive social interactions). Investigating structural social isolation as a mediator is also warranted, given the classic distinction between functional and structural social factors in the context of cognitive outcomes (Costa-Cordella et al., 2021). In addition, future studies should investigate other possible mediators, beyond social factors, that may explain the association between depression and executive function. For example, cardiovascular risk factors, physical activity or sleep disturbance could also be explored as mediators.

In addition, future studies could examine issues related to directionality to address temporality limitations. Given the potential for bidirectionality between depression and functional social isolation, future studies could assess whether depression mediates the association between functional social isolation and executive function. Such studies would provide a more complete understanding of how mental and social factors work together to influence executive function. Also, to estimate the indirect effect where all paths are prospective, future studies could measure the exposure, mediator and outcome in sequence across three time-points. Future follow-up data from the CLSA will make it possible to estimate indirect effects where all paths are prospective.

Lastly, the extent of missing cognitive data, especially at follow-up, warrants further investigation. Future studies could thoroughly investigate the determinants of missing cognitive data in the CLSA and

other such longitudinal studies, and explore strategies for minimizing missing data on cognitive performance tests in the future.

6.6 Conclusion

A global mental health crisis exacerbated by the COVID-19 pandemic (Krendl et al., 2021) calls for a greater understanding of the downstream effects of depression and social isolation on age-related cognitive decline, and in particular, executive function. Executive function plays a crucial role in maintaining independence in older age, highlighting the need to promote executive function in an aging population. Identifying mediators between depression and executive function can inform strategies to promote executive function, particularly in those with depression. By addressing a major gap in the literature, this study contributes to an understanding of how depression impacts executive function, and for whom. Results suggest that increasing functional social isolation mediates the association between depression (higher depressive symptoms or self-reported clinical depression) and decreasing executive function in women aged 75 and older. In contrast, functional social isolation does not mediate the association between depression and executive function for other age and sex subgroups. Future studies can build upon these findings by investigating different subtypes of social isolation, examining depression as the mediator between functional social isolation and executive function, and exploring other possible mediators beyond social factors.

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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.

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Zahodne, L. B., Watson, C. W. M., Seehra, S., & Martinez, M. N. (2018). Positive Psychosocial Factors and Cognition in Ethnically Diverse Older Adults. *Journal of the International Neuropsychological Society*, *24*(3), 294-304.

Zahodne, L. B., Sharifian, N., Kraal, A. Z., Sol, K., Zaheed, A. B., Manly, J. J., & Brickman, A.M. (2021). Positive Psychosocial Factors and Cognitive Decline in Ethnically Diverse Older Adults. *Journal of the International Neuropsychological Society*, *27*(1), 69-78.

Zhang, Z., Li, L. W., Xu, H., & Liu, J. (2019). Does Widowhood Affect Cognitive Function Among Chinese Older Adults? *SSM-Population Health*, *7*, 100329.

Zullo, L., Clark, C., Gholam, M., Castelao, E., von Gunten, A., Preisig, M., & Popp, J. (2021). Factors Associated with Subjective Cognitive Decline in Dementia-Free Older Adults—A Population-Based Study. *International Journal of Geriatric Psychiatry, 36*(8), 1188- 1196.

Zunzunegui, M. V., Alvarado, B. E., Del Ser, T., & Otero, A. (2003). Social Networks, Social Integration, and Social Engagement Determine Cognitive Decline in Community-Dwelling Spanish Older Adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *58*(2), S93-S100.

Appendix A

Literature Search Strategy

Table A1: PubMed Search Strategy

	Predictor	Outcome	Population	Additional variable of interest
Concept	Depression	Cognition	Older Adults OR Middle Age (45+)	Social support availability
Author Keywords	Depressive Symptoms OR Depression OR Mood OR Affect	Cognitive Abilit*[tiab] OR Cognitive Function*[tiab] OR Cognitive Impairment*[tiab] OR Executive Function*[tiab] OR Executive Control*[tiab] OR Executive Dysfunction[tiab]	Elderly[TW] OR Older Adult* OR Middle Age	Social Support[tiab] OR Support Relations* OR Social Engagement* OR Social Participation OR Social Capital OR Social Withdrawal OR Social Erosion OR Loneliness OR Social Network OR Marital Status
MeSH terms	Depression[MeSH] OR Affect[MeSH] OR Depressive disorder[MeSH:noexp]	Cognition[MeSH:noexp] OR Cognition Disorders[MeSH] OR Executive Function[MeSH] OR Dementia[MeSH]	Aged[MeSH] OR Middle Aged[MeSH]	Social Support[MeSH] OR Interpersonal Relations[MeSH] OR Social Interaction[MeSH] OR Social Isolation[MeSH]
Restrictions (filters)	None			

Search strategy: (Depressive Symptoms OR Depression OR Mood OR Affect OR Depression[MeSH] OR Affect[MeSH] OR Depressive disorder[MeSH:noexp]) AND (Cognitive Abilit*[tiab] OR Cognitive Function*[tiab] OR Cognitive Impairment*[tiab] OR Executive Function*[tiab] OR Executive Control*[tiab] OR Executive Dysfunction[tiab] OR Cognition[MeSH:noexp] OR Cognition Disorders[MeSH] OR Executive Function[MeSH] OR Dementia[MeSH]) AND (Elderly[TW] OR Older Adult* OR Middle Age OR Aged[MeSH] OR Middle Aged[MeSH]) AND (Social Support[tiab] OR Support Relations* OR Social Engagement* OR Social participation OR Social capital OR Social withdrawal OR Social erosion OR Loneliness OR Social network OR Marital Status OR Social Support[MeSH] OR Interpersonal Relations[MeSH] OR Social Interaction[MeSH] OR Social Isolation[MeSH])

Number of results: 2528

Date of search: June 9th, 2020 (updated July 7th, 2021 using the same search strategy in the new PubMed)

Table A2: PsycINFO Search Strategy

	Predictor	Outcome	Additional variable of interest
Concept	Depression	Cognition	Social Support Availability
Author Keywords	"Depression*" OR "Depressive"	"Cognitive Function" OR "Cognitive Abilit*" OR "Cognition" OR "Cognitive Disorders" OR "Cognitive Impairment" OR "Executive Function*" OR "Executive Control*" OR "Executive Dysfunction" OR "Dementia"	"Social Networks" OR "Social Network" OR "Social Support*" OR "Social Relations*" OR "Interpersonal Relations*" OR "Social Interaction" OR "Social Engagement" OR "Social Isolation" OR "Social Participation" OR "Social Capital" OR "Social Withdrawal" OR "Social Erosion" OR "Loneliness" OR "Marital Status"
Restrictions (filters)	Limit to **Adults 18 years and older** Limit to **Peer-Reviewed Journals only**		

Search strategy: ((**Keywords**: ("depression*")) *OR* (**abstract**: ("depression*")) *OR* (**Keywords**: ("depressive")) *OR* (**abstract**: ("depressive"))) *AND* ((**Keywords**: ("Social Networks")) *OR* (**abstract**: ("Social Networks")) *OR* (**Keywords**: ("Social Support*")) *OR* (**abstract**: ("Social Support*")) *OR* (**Keywords**: ("Social Relations*")) *OR* (**abstract**: ("Social Relations*")) *OR* (**Keywords**: ("Interpersonal Relations*")) *OR* (**abstract**: ("Interpersonal Relations*")) *OR* (**Keywords**: ("Social Interaction")) *OR* (**abstract**: ("Social Interaction")) *OR* (**Keywords**: ("Social Engagement")) *OR* (**abstract**: ("Social Engagement")) *OR* (**Keywords**: ("Social Isolation")) *OR* (**abstract**: ("Social Isolation")) *OR* (**Keywords**: ("Social Participation")) *OR* (**abstract**: ("Social Participation")) *OR* (**Keywords**: ("Social Capital")) *OR* (**abstract**: ("Social Capital")) *OR* (**Keywords**: ("Social Withdrawal")) *OR* (**abstract**: ("Social Withdrawal")) *OR* (**Keywords**: ("Social Erosion")) *OR* (**abstract**: ("Social Erosion")) *OR* (**Keywords**: ("Loneliness")) *OR* (**abstract**: ("Loneliness")) *OR* (**Keywords**: ("Social Network")) *OR* (**abstract**: ("Social Network")) *OR* (**Keywords**: ("Marital Status")) *OR* (**abstract**: ("Marital Status"))) *AND* ((**Keywords**: ("Cognitive Function")) *OR* (**abstract**: ("Cognitive Function")) *OR* (**Keywords**: ("Cognitive Abilit*")) *OR* (**abstract**: ("Cognitive Abilit*")) *OR* (**Keywords**: ("Cognition")) *OR* (**abstract**: ("Cognition")) *OR* (**Keywords**: ("Cognitive Disorders")) *OR* (**abstract**: ("Cognitive Disorders")) *OR* (**Keywords**: ("Cognitive Impairment")) *OR* (**abstract**: ("Cognitive Impairment")) *OR* (**Keywords**: ("Executive Function*")) *OR* (**abstract**: ("Executive Function*")) *OR* (**Keywords**: ("Executive Control*")) *OR* (**abstract**: ("Executive Control*")) *OR* (**Keywords**: ("Executive Dysfunction")) *OR* (**abstract**: ("Executive Dysfunction")) *OR* (**Keywords**: ("Dementia")) *OR* (**abstract**: ("Dementia"))) *AND* **Age Group**: Adulthood (18 yrs & older) *AND* **Peer-Reviewed Journals only**

Number of results: 1109

Date of search: July 7th, 2021

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┌─────────────────────────────────────────┐
│         4039 records identified         │
│  2528 (PubMed legacy) + 402 (new PubMed) + │
│             1109 (PsycINFO)             │
└─────────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────────┐
│   3460 records after duplicates removed  │
└─────────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────────┐
│  3460 records screened by title and abstract │
└─────────────────────────────────────────┘
                    │            ┌──────────────────┐
                    │───────────▶│  3286 excluded   │
                    ▼            └──────────────────┘
┌─────────────────────────────────────────┐
│  174 full-text articles assessed for eligibility │
└─────────────────────────────────────────┘
                    │            ┌──────────────────┐
                    │───────────▶│ 97 full-text articles │
                    ▼            │    excluded*     │
┌─────────────────────────────────────────┐  └──────────────────┘
│ 77 total studies included in qualitative synthesis │
│            on July 7th, 2021            │
└─────────────────────────────────────────┘
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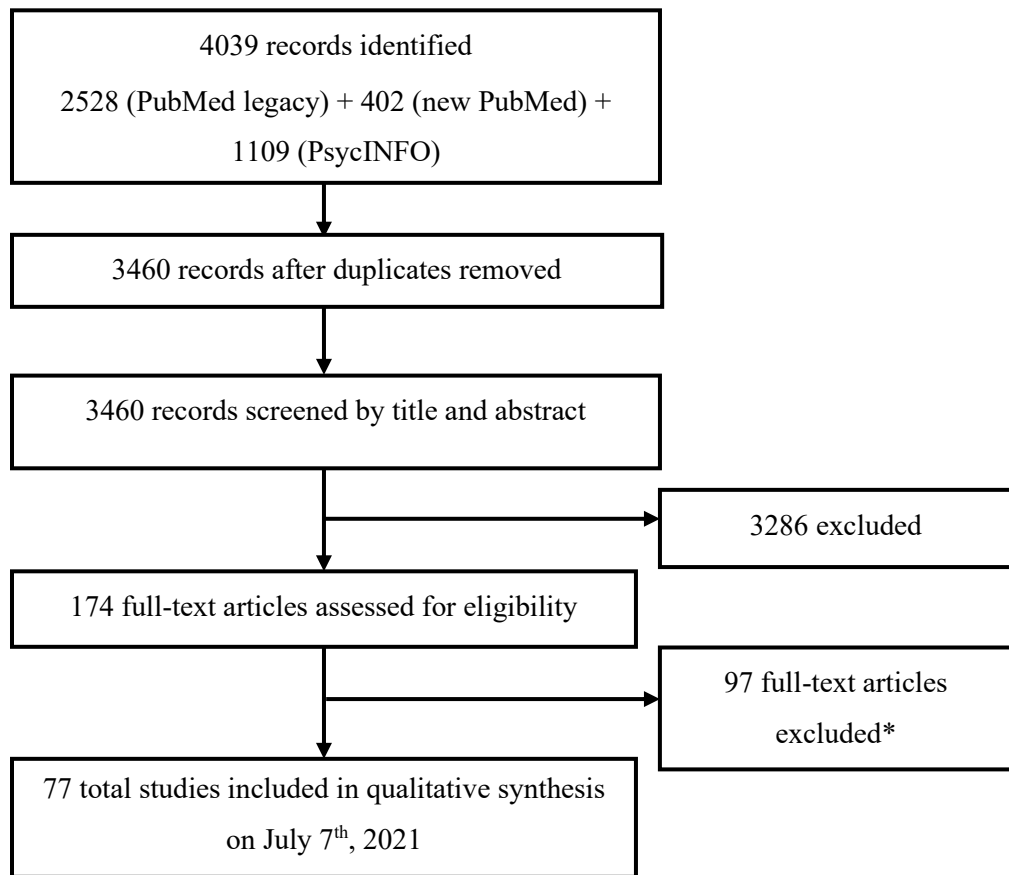
Figure A1. PRISMA Flowchart

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*Articles were excluded according to the following criteria:

-Conducted solely on children or adolescents, populations with bipolar or postpartum depression, or non-humans
-Case reports, case series, opinion pieces, lectures or perspectives
-Not available in English
-Did not include either global cognition or executive function as an outcome
-Retracted

Appendix B

Summary of Key Literature

Table B1: Summary of Relevant Literature

Study	Population, Design, Sample Characteristics	Independent Variables	Dependent Variables	Analysis Method	Assessed Moderation by Gender/Sex or Age?	Results and Conclusions
Atti, A. R., Forlani, C., De Ronchi, D., Palmer, K., Casadio, P., Dalmonte, E., & Fratiglioni, L. (2010). Cognitive Impairment After Age 60: Clinical and Social Correlates in the "Faenza Project". *Journal of Alzheimer's Disease, 21*(4), 1325-1334. **CATEGORIES:** **Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	7389 dementia-free older adults aged 60-102. Cross-sectional. Italian municipality.	<u>Exposures</u>: Social factors (age, gender, education, marital status, socioeconomic status); life habits (smoking, alcohol); medical conditions (depressive symptoms, neurological diseases, anxiety symptoms, vascular diseases, vascular risk factors).	<u>Outcome</u>: Cognitive Impairment No Dementia (CIND) – Mini Mental State Examination (MMSE)	<u>Analysis</u>: Logistic regression.	Results were stratified by age and gender.	Both depression and marital status were strongly associated with CIND. Being unmarried predicted CIND after controlling for depression and other covariates (OR=1.71). Depressive symptoms predicted CIND after controlling for marital status and other covariates (OR=1.92). <u>Gender/sex</u>: Unmarried status was associated with CIND in men only (OR=2.1). <u>Age</u>: Not being married was associated with CIND only in younger elderly people (OR=2.6).

| Bae, S. M. (2020). The Association Between Health-Related Factors, Physical and Mental Diseases, Social Activities, and Cognitive Function in Elderly Koreans: A Population-Based Cross-Sectional Study. *Psychogeriatrics*, *20*(5), 654-662.

CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable | 5678 adults aged 60+.

Cross-sectional.

Korea. | Exposures/ Covariates: Gender, age, education, marital status, depressive symptoms, body mass index, regular exercise, activities of daily living, instrumental activities of daily living, hand grip strength, social activities, socioeconomic status, diabetes, smoking, alcohol consumption, attendance at school reunions, volunteer work, and participation in political or civic organizations | Outcome: Cognition (global) | Analysis: Hierarchical multiple regression | Moderation by age or gender was not considered or reported on. | Depressive symptoms, marital status and social activities (structural) were associated with cognition in the same fully adjusted model. |
| Barnes, L. L., De Leon, C. M., Wilson, R. S., Bienias, J. L., & Evans, D. A. (2004). Social Resources and Cognitive Decline in a Population of Older African Americans and Whites. *Neurology, 63*(12), 2322-2326.

CATEGORIES: Depression and Social | 6102 older adults aged 65+.

Longitudinal, 3 follow-ups during an average follow-up of 5.3 years.

Chicago, United States. | Exposure: Social networks, social engagement

Covariates: Depressive symptoms, marital status, age, sex, education, race, total annual income, cognitive and physical activity, comorbidity | Outcome: Cognitive decline. | Analysis: Linear mixed effects models. | Non-significant interaction term for sex (i.e., the association between social resources and cognitive decline is not moderated by sex). | Higher level of social engagement and higher number of social networks were positively associated with cognition and reduced cognitive decline.

In a model that added depressive symptoms with several other covariates, the associations between social networks and social engagement with cognitive decline remained similar to original models. Thus, depression did not confound the association |

Isolation/Support in the Same Model with Cognition as Dependent Variable						between social support and cognitive decline. The association between depression and cognition was not reported on.
Bassuk, S. S., Glass, T. A., & Berkman, L. F. (1999). Social Disengagement and Incident Cognitive Decline in Community-Dwelling Elderly Persons. *Annals of Internal Medicine, 131*(3), 165-173. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	2812 community-dwelling older adults aged 65+. Longitudinal, 4 time-points over 12 years. Connecticut, United States.	<u>Exposure</u>: Social engagement (number of social ties) <u>Covariates</u>: Depressive symptoms, other socio-demographic factors (age, initial cognition, sex, ethnicity, education, income, housing, disability, sensory impairment, smoking status, cardiovascular profile, alcohol, physical activity).	<u>Outcome</u>: Cognitive decline (transition from high to medium or low; transition from medium to low).	<u>Analysis</u>: Polytomous logistic regression.	Moderation by age or gender was not considered or reported on.	Compared to extensive social ties, having fewer social contacts was associated with increased odds of decline in any given interval, holding depression and all other covariates constant. Availability and adequacy of emotional support was not associated with incident cognitive decline. Availability and adequacy of emotional support did not confound the association between social ties and cognitive decline. Temporal ordering: The association between social disengagement and cognitive decline was more pronounced in those with a history of social disengagement than those who experienced it more recently. Even in the highest initial cognition category, disengagement was still associated with incident cognitive decline. The relationship between depressive symptoms and cognition was not reported on in a

						model controlling for social support.
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. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1571 community-dwelling older adults aged 65+. Longitudinal, 4 time-points over 7 years. Suburban municipality of Spain.	Exposure: Social ties (structural) and social engagement (functional); social integration (structural). Covariates: Gender, education, depressive symptoms, chronic conditions, functional limitations.	Outcome: Rate of change in cognitive function.	Analysis: Repeated multivariate measures models: growth models	Social ties and social integration were modelled as interactions with age. Social ties and social integration were modelled as interactions with gender.	Depressive symptoms were associated with a higher rate of change in cognitive decline over time, after controlling for all covariates and main exposures, including social support variables. Interaction with age: Having more family ties was associated with less cognitive decline until 80 years of age. A protective association of social integration with change in cognitive decline was more significant as age increased. Interaction with gender: Having friends was associated with slower cognitive decline in women but not men, after controlling for depression among other covariates.
Bourassa, K. J., Memel, M., Woolverton, C., & Sbarra, D. A. (2017). Social Participation Predicts Cognitive Functioning in Aging Adults Over Time: Comparisons with Physical Health, Depression, and Physical Activity. *Aging &*	19,832 adults aged 50+. Longitudinal, 3 time-points over 6 years. 19 European Union countries (multinational) – SHARE study.	Exposures (time-varying): Social participation (structural), depressive symptoms, physical activity, self-rated health. Covariates (time-invariant): Age, gender, income.	Outcome: Cognition (memory and executive function).	Analysis: Latent curve growth model.	Moderation by age or gender was not considered or reported on.	Depression and social participation (as well as self-rated health and physical activity) all were significant in predicting executive function at all time-points when all were included in the final model along with covariates. Steeper executive function decline was also predicted by lower social participation, lower self-rated health, lower physical

Mental Health, 21(2), 133-146. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**						activity, and higher depressive symptoms.
Brown, C. L., Robitaille, A., Zelinski, E. M., Dixon, R. A., Hofer, S. M., & Piccinin, A. M. (2016). Cognitive Activity Mediates the Association Between Social Activity and Cognitive Performance: A Longitudinal Study. *Psychology and Aging, 31*(8), 831. **CATEGORIES: Depression as a Mediator Between Social Isolation/Support and Cognitive Outcomes**	755 older adults (community-dwelling). Longitudinal, 7 waves. Victoria Longitudinal Study (Canada).	<u>Exposure</u>: Social activity (structural). <u>Covariates (time-varying)</u>: Age, functional health. <u>Covariates (time-invariant)</u>: Baseline depression, age, cognition, social activity, physical activity, cognitive activity, years of education, sex. <u>Mediators</u>: Depressive symptoms, cognitive activity, physical activity, and vascular health conditions.	<u>Outcome</u>: Cognition (4 domains: episodic memory, fluency, reasoning, vocabulary).	<u>Analysis</u>: Multilevel structural equation modelling (SEM).	Moderation by age or gender was not considered or reported on.	<u>Within-person</u>: Social activity did not predict depression after adjusting for covariates. Higher depressive symptoms predicted lower scores on some cognitive domains, including reasoning, fluency and vocabulary performance. The indirect effect of depression was not significant. Thus, depression did not mediate the association between social activity and cognition. Cognitive activity; however, was a significant mediator. <u>Between-person</u>: Social activity did not predict depression after adjusting for covariates. Depression was not associated with cognition. The indirect effect of depression was not significant. Thus, depression did not mediate the association between social activity and cognition. Cognitive activity; however, was a significant mediator.

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						Suggestions for further research: Satisfaction with social activity should be investigated in relation to depressive symptoms, social activity and cognition.
Caldas, V., Fernandes, J., Vafaei, A., Gomes, C., Costa, J., Curcio, C., & Guerra, R. O. (2020). Life-Space and Cognitive Decline in Older Adults in Different Social and Economic Contexts: Longitudinal Results from the IMIAS Study. *Journal of Cross-Cultural Gerontology*, *35*(3), 237-254. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1486 community-dwelling older adults. Longitudinal. North America, South America, Europe.	Exposure / Covariates: Life space mobility, gender, research site, education, living arrangements, social support, depressive symptoms, chronic disease.	Outcome: Cognition.	Analysis: Quantile regressions.	Moderation by age or gender was not considered or reported on.	Depressive symptoms, but not social support (structural or functional), was associated with cognition in fully adjusted models. Depressive symptoms were negatively associated with cognition. Life-space mobility was associated with cognition in fully adjusted models.
Carty, C. L., Noonan, C., Muller, C., Saner, D., Reiman, E. M., Buchwald, D., ... & Nelson, L. A. (2020). Risk Factors for Alzheimer's Disease and Related	7,090 American Indians and non-Hispanic Whites aged 55+. Longitudinal. USA.	Exposures: Age, sex, marital status, rurality, tobacco use, hypertension, depression, hyperlipidemia, or diabetes.	Outcome: Alzheimer's disease and related dementias.	Analysis: Generalized estimating equations.	Moderation by age or gender was not considered or reported on.	Depression was consistently positively associated with Alzheimer's disease and related dementias for both American Indians and non-Hispanic Whites, while being married was protective only in American Indians (fully adjusted).

Dementia Diagnoses in American Indians. *Ethnicity & Disease, 30*(4), 671. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**						
Casey, A. N. S., Liu, Z., Kochan, N. A., Sachdev, P. S., & Brodaty, H. (2020). Cross-Lagged Modeling of Cognition and Social Network Size in the Sydney Memory and Ageing Study. *The Journals of Gerontology: Series B.* **CATEGORIES: Social Isolation/Support as a Mediator Between Depression and Cognitive Outcomes**	1,037 community-dwelling older adults. Longitudinal. Australia.	<u>Exposure</u>: Social network size. <u>Covariates</u>: Age, sex, education, medical conditions, depressive symptoms.	<u>Outcome</u>: Executive function.	<u>Analysis</u>: Cross-lagged panel models, structural equation modelling.	Moderation by age or gender was not considered or reported on.	Fully adjusted models: Depressive symptoms predicted social network size (concurrent paths, same time-point), while social network size predicted executive function (cross-lagged panel, over time) (Supplementary Table 6). Note that the association between depressive symptoms and social network size over time was not assessed.
Chen, T. Y., & Chang, H. Y. (2016). Developmental Patterns of Cognitive Function and	3155 adults age 65+ (nationally representative).	<u>Exposures (time-invariant)</u>: Baseline age, sex, and education.	<u>Outcome</u>: Cognitive function and cognitive trajectories	<u>Analysis</u>: Multinomial logistic regression;	Moderation by age or gender was not considered or reported on.	Those with more depressive symptoms were more likely to be in the starting high and declining group and the starting low declining group compared to the

Associated Factors Among the Elderly in Taiwan. *Scientific Reports, 6,* 33486. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	Longitudinal, 5 waves across 14 years. Taiwan	Exposures (time-variant): Health status (e.g., depressive symptoms), social support (functional and structural), physical function, health behaviours.	(starting low and declining; starting high and declining; high-stable).	group-based trajectory model.		high-stable group after controlling for covariates including social support. Those with less emotional social support (functional) were associated with starting low and declining compared to high-stable after controlling for depression and other covariates. Social interaction (structural) had no effect on cognitive decline.
Chi, I., & Chou, K. L. (2000). Depression Predicts Cognitive Decline in Hong Kong Chinese Older Adults. *Aging & Mental Health, 4*(2), 148-157. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	260 adults aged 70+, community-based. Longitudinal – baseline and 3 years later. Hong Kong.	Exposure: Depression at baseline. Covariates: Social support (structural and functional), sociodemographic, physical health, smoking, exercise, baseline cognition.	Outcome: Cognitive function.	Analysis: Multiple regression	Moderation by age or gender was not considered or reported on.	Increasing depressive symptoms was associated with decreasing cognitive score after controlling for all covariates, including social support. In this full model including depressive symptoms, social support variables (number of relatives felt close to, number of friends felt close to, and satisfaction with relationships with relatives living together) were not associated with cognitive score.
Cohrdes, C., & Bretschneider, J. (2018). Can Social Support and Physical Activity Buffer Cognitive Impairment in Individuals with Depressive Symptoms? Results from a	3661 adults aged 18-79. Cross-sectional. German Health and Examination Interview for Adults.	Exposure: Depressive symptoms. Covariates: Age, sex, socioeconomic status. Mediators: Perceived social support	Outcome: Executive function (global measure).	Analysis: Multiple linear regression.	Mediation analysis was used, where age and sex were moderators.	Increasing depressive symptoms predicted decreasing executive function with a small effect size (holding constant age, sex, and socioeconomic status). Perceived social support and physical activity mediated this relationship. Social support and physical activity eliminated the association

Representative Sample of Young to Older Adults. *Journal of Affective Disorders, 239*, 102-106. **CATEGORIES: Social Isolation/Support as a Mediator Between Depression and Cognitive Outcomes**		(functional), physical activity.				between depressive symptoms and executive function. Thus, full mediation by both social support and physical activity (entered in the same model) was evident. Increasing depressive symptoms significantly predicted low social support versus high social support (path a: X→M), holding age, sex, and socioeconomic status constant. Moderated mediation by sex: Full mediation by social support and physical activity was demonstrated in women and not men. Depression was associated with executive function in women only (holding age and socioeconomic status constant). Moderated mediation by age: Mediation by social support was only significant among those younger than 65. No mediation by social support or physical activity was demonstrated in adults over 65 years. Depressive symptoms and executive functioning were associated, but only in those age 65 or older (controlling for only socioeconomic status and sex). Conclusion: Women and young to middle-aged adults may benefit the most from social support and physical activity, as demonstrated

						by two additional sets of mediation analyses. Considerations: Depressive symptom severity was less severe and less prevalent in men versus women and those aged 65+ versus those younger than 65.
Conroy, R. M., Golden, J., Jeffares, I., O'Neill, D., & McGee, H. (2010). Boredom-Proneness, Loneliness, Social Engagement and Depression and Their Association with Cognitive Function in Older People: A Population Study. *Psychology, Health & Medicine, 15*(4), 463-473. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	802 adults aged 65+. Cross-sectional. Irish Republic.	Exposure: Social support cluster variable (widowed, living alone, low social support). Covariates: Depression, age, sex, education, marital status, loneliness, social support, social activity, rural designation, self-rated heath, illness/disability, boredom-proneness, physical activity.	Outcome: Cognitive impairment.	Analysis: Multinomial logistic regression and cluster analysis around latent variables.	Moderation by age or gender was not considered or reported on.	The social support cluster (widowed, living alone, with low functional social support) was not associated with age-adjusted cognitive impairment while holding depression and physical disability constant. In a full (non-clustered) model controlling for both social support and depression covariates, depression and reduced social activity increased odds for low cognition and possible cognitive impairment at comparable magnitudes. Low functional social support and loneliness were associated with increased odds of possible cognitive impairment.
Deng, J., Cao, C., Jiang, Y., Peng, B., Wang, T., Yan, K., ... & Wang, Z. (2018). Prevalence and	1781 adults aged 60+. Cross-sectional.	Exposures: Social activities (structural), depression, age, marital status,	Outcome: Dementia.	Analysis: Multivariate logistic regression.	Moderation by age or gender was not considered or reported on.	In a full model including all exposures/covariates, being single and having depression increased odds of dementia. In the full model, a higher frequency

Effect Factors of Dementia Among the Community Elderly in Chongqing, China. *Psychogeriatrics, 18*(5), 412-420. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	China.	tobacco, exercise, labour intensity, housework, outdoor activities, media consumption, body mass index, hypertension, coronary heart disease.				of social activities was associated with lower odds of dementia.
Dickinson, W. J., Potter, G. G., Hybels, C. F., McQuoid, D. R., & Steffens, D. C. (2011). Change in Stress and Social Support as Predictors of Cognitive Decline in Older Adults with and without Depression. *International Journal of Geriatric Psychiatry, 26*(12), 1267-1274. **CATEGORIES: Social Isolation/Support and Depression Interaction or Moderation Models; Depression and**	112 depressed and 101 non-depressed adults aged 60+. Longitudinal. United States.	<u>Exposure</u>: Change in social support (structural and functional aspects) <u>Covariates</u>: Depression, age, sex, education. <u>Stratification by</u>: Depression.	<u>Outcome</u>: One-year change in Consortium to Establish a Registry in Alzheimer's Disease (CERAD).	<u>Analysis</u>: Multiple linear regression.	Moderation by age or gender was not considered or reported on.	Decreased social interaction and instrumental social support predicted cognitive decline, holding depression, age, sex and education constant. This was apparent for some tests of executive function but not for others. Social network size (structural) and subjective (functional) social support were not associated with changes in cognition. Depression was only associated with poorer performance on one test of executive function and not others after controlling for specific functional social support factors and other covariates. Decreasing social interaction predicted decreasing cognition in one test of executive function in people with depression. There

						were no such associations in people without depression.
Social Isolation/Support in the Same Model with Cognition as Dependent Variable						
Donovan, N. J., Wu, Q., Rentz, D. M., Sperling, R. A., Marshall, G. A., & Glymour, M. M. (2017). Loneliness, Depression and Cognitive Function in Older US Adults. *International Journal of Geriatric Psychiatry, 32*(5), 564-573. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	8382 adults aged 65+. Longitudinal, 12 years. United States.	Exposure: Loneliness. Covariates: Sociodemographic factors, depression, social network (structural) and health conditions.	Outcome: Cognitive decline.	Analysis: Repeated measures analysis, generalized linear regression models.	Moderation by age or gender was not considered or reported on.	Over 12 years, baseline loneliness predicted accelerated cognitive decline while holding baseline sociodemographic factors, depression, social network and health conditions constant. Thus, loneliness impacted long-term cognition independent of baseline depression, yet, the impact of loneliness became marginally significant after controlling for the impact of depressive symptoms over time (i.e., depression confounded the association between loneliness and cognition). Those with depressive symptoms (even at the subclinical level) experienced quicker cognitive decline after controlling for baseline sociodemographic factors, social network, health conditions and loneliness. About half of those with loneliness reported clinical depression, suggesting that these two variables may be linked.
Estrella, M. L., Durazo-Arvizu, R. A., Gallo, L. C., Tarraf, W., Isasi, C.	2,818 middle-aged and older adults.	Exposure: Psychosocial factors (structural and functional).	Outcome: Individual tests of cognitive function (global	Analysis: Linear regression.	Moderation by age or gender was not	Functional but not structural aspects of social support were associated with better executive functioning after controlling for

R., Perreira, K. M., ... & Lamar, M. (2021). Psychosocial Factors Associated with Cognitive Function Among Middle-Aged and Older Hispanics/Latinos: The Hispanic Community Health Study/Study of Latinos and its Sociocultural Ancillary Study. *Journal of Alzheimer's Disease, (Preprint),* **1-17.** **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	Cross-sectional. Hispanic/Latino community in the USA.	Covariates: Age, sex, education, Hispanic/Latino background, income, language, depressive symptoms.	cognition, memory, executive function).		considered or reported on.	depressive symptoms and other covariates. Note that the models did not include different social factors simultaneously in one model. Effect of depressive symptoms was not reported on.
Evans, I. E., Llewellyn, D. J., Matthews, F. E., Woods, R. T., Brayne, C., Clare, L., & CFAS-Wales research team. (2019). Living Alone and Cognitive Function in Later Life. *Archives of Gerontology and*	2197 adults aged 65+, community-based. No depression nor cognitive impairment. Longitudinal (baseline and 2-year follow-up). Wales.	Exposure: Living alone (structural) Covariates: Baseline age, gender, education, social isolation (structural and functional composite measure), social activity (structural),	Outcomes: Loneliness, limited social activity, cognitive function.	Analysis: Linear regression.	Moderation by age or gender was not considered or reported on.	Cross-sectional: Living alone was not associated with poorer baseline cognition after controlling for all covariates (age, gender, education, social isolation, loneliness, social activity, marital status, ADL). On the other hand, social isolation, loneliness, marital status and social activity were associated with baseline cognition in the fully-adjusted model.

Geriatrics, 81, 222-233. **CATEGORIES: Social Support Predicting Cognition in Populations with No Depression**		loneliness (functional), marital status, activities of daily living (ADL).				Longitudinal: Living alone, loneliness, social activity and marital status were not associated with follow-up cognitive function after controlling for all covariates. On the other hand, social isolation was associated with follow-up cognition in the fully-adjusted model. Thus, in people without depression, living alone was not associated with cognition at baseline or over time. Unlike the other social support variables, social isolation was associated with poorer baseline cognition and poorer cognition over time.
Evans, I. E., Llewellyn, D. J., Matthews, F. E., Woods, R. T., Brayne, C., & Clare, L. (2019). Social Isolation, Cognitive Reserve, And Cognition in Older People with Depression and Anxiety. *Aging & Mental Health, 23*(12), 1691-1700. **CATEGORIES: Social Support Predicting Cognition in Populations with Depression**	123 adults, aged 65+, with depression or anxiety. Longitudinal (baseline and 2 years later). Wales.	Exposure: Social isolation (structural and functional composite measure). Covariates: Baseline age, gender, education, cardiovascular risk. Moderator: Cognitive reserve.	Outcome: Cognition.	Analysis: Linear regression.	Moderation by age or gender was not considered or reported on.	Despite having the same amount of contact with family and friends, older adults with depression or anxiety had more perceived isolation and loneliness than those without (bivariate associations). When considering those with depression or anxiety, social isolation was associated with poor baseline cognition but not change in cognition two years later after controlling for all covariates. Cognitive reserve was not a moderator for either association.

Faramarzi, M., Kamar, M. Z., Kheirkhah, F., Karkhah, A., Bijani, A., & Hosseini, S. R. (2018). Psychosocial Predictors of Cognitive Impairment in the Elderly: A Cross-Sectional Study. *Iranian Journal of Psychiatry, 13*(3), 207. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1612 adults aged 60+. Cross-sectional. Iran.	Exposures: Depression, social support (structural and functional composite measure), living alone, age, education, smoking.	Outcome: Cognitive impairment.	Analysis: Backwards multivariate logistic regression was used. Afterwards, the model was adjusted for all significant baseline characteristics determined at the bivariate level.	Moderation by age or gender was not considered or reported on.	Presence of depression predicted cognitive impairment after controlling for social support and other demographic factors (OR=1.64). Higher social support score categories were negatively associated with cognitive impairment, after controlling for depression and other demographic factors (OR=0.32,0.29). Magnitude of odds ratios for social support and depression were similar.
Ficker, L. J., Lysack, C. L., Hanna, M., & Lichtenberg, P. A. (2014). Perceived Cognitive Impairment Among African American Elders: Health and Functional Impairments in Daily Life. *Aging & Mental Health, 18*(4), 471-480.	501 adults aged 55 to 95. Cross-sectional. African American.	Exposure: Depressed mood, social functioning (feeling loved, feeling appreciated, feeling important, having lack of physical comfort and feeling engaged) Covariates: Age, education, marital status, health problems,	Outcome: Perceived cognitive impairment (binary).	Analysis: Logistic regression.	Moderation by age or gender was not considered or reported on.	Depression was not associated with the presence of perceived cognitive impairment after controlling for social functioning and other variables (age, education, marital status, health problems, cardiovascular risk, chronic pain and mobility). Higher social functioning (perceived social support) was protective against perceived cognitive impairment after controlling for depression and other variables (age, education,

CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable		cardiovascular risk, chronic pain and mobility.				marital status, health problems, cardiovascular risk, chronic pain and mobility). Being single was not associated with perceived cognitive impairment in the full model.
Fratiglioni, L., Wang, H. X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of Social Network on Occurrence of Dementia: A Community-Based Longitudinal Study. *The Lancet, 355*(9212), 1315-1319. **CATEGORIES: Social Isolation/Support and Depression Interaction or Moderation Models; Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1203 cognitively healthy adults, aged 75+. Longitudinal. Sweden.	Exposure: Social network (combined network factors: being married, living with someone, having frequent satisfying contacts), depression (dichotomous). Covariates: Age, sex, education, baseline cognition, baseline physical function, vascular disease. Stratification: Depression and cognitive impairment.	Outcome: Incident dementia.	Analysis: Cox proportional hazard and multivariable models.	Both men and women had similar results for all analyses.	Those with a poor/limited social network had a 60% higher risk of incident dementia compared to those with an extensive or moderate social network while holding depression and other covariates (age, sex, education, and baseline cognition) constant. The effect of depression was not reported on. The association between poor/limited social network and higher risk of dementia was apparent both in those with depressive symptoms and those without any depressive symptoms, and also among those with cognitive impairment and without cognitive impairment.
Fu, C., Li, Z., & Mao, Z. (2018). Association Between	8966 adults, aged 60+.	Exposure: Social activities (structural).	Outcome: Cognitive function	Analysis: Multiple linear regression.	Analyses were stratified by sex.	In both men and women, frequent interaction with friends, participation in hobby groups,

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| Social Activities and Cognitive Function Among the Elderly in China: A Cross-Sectional Study. *International Journal of Environmental Research and Public Health, 15*(2), 231.

CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable | Cross-sectional.

China. | Covariates: Depression, demographics, smoking, drinking, hypertension, diabetes, activities of daily living, self-rated health. | (domains: orientation, attention, episodic memory, visuospatial abilities). | | | and participation in sports groups were associated with better cognition when compared to no social participation. This association was significant after controlling for depression and all other covariates. There appeared to be differences in the magnitudes of the associations between the sexes for each category of social participation.

In the full model (controlling for depression and all other covariates), frequent participation (versus no participation) in volunteer activities was associated with cognition in women but not men.

There was some evidence for a protective impact on cognition at lower frequencies of select types of social activity in women. Infrequent participation in volunteer work and sports predicted better cognition with reference to no participation in volunteer work and sports. In contrast, frequent participation in volunteer and sports activities had no association with cognition when compared to no participation.

The effect of depression was not reported. |

Fuhrer, R., Antonucci, T. C., & Dartigues, J. F. (1992). The Co-Occurrence of Depressive Symptoms and Cognitive Impairment in a French Community: Are There Gender Differences? *European Archives of Psychiatry and Clinical Neuroscience, 242*(2-3), 161-171. **CATEGORIES: Social Isolation/Support Predicting Co-occurrence of Depression and Cognitive Outcomes**	2792 adults aged 65+. Cross-sectional. France.	Exposure: Dissatisfaction with social support (functional). Covariates: Education, age, marital status, place of residence, activities of daily living.	Outcome: Co-occurring depression and cognitive impairment.	Analysis: Multivariate polytomous logistic regression.	Analyses were stratified by sex.	Those who were dissatisfied with their level of social support were at higher odds of co-occurring* depression and cognitive impairment in both men and women, when compared to those who were satisfied. The magnitude of association was higher in men. Not being married was associated with depression-cognitive impairment co-occurrence* in men but not women. *Reference group: All subjects who did not have any one of the following: depression alone, cognitive impairment alone, or co-occurring depression and cognitive impairment.
Gow, A. J., Corley, J., Starr, J. M., & Deary, I. J. (2013). Which Social Network or Support Factors Are Associated with Cognitive Abilities in Old Age? *Gerontology, 59*(5), 454-463. **CATEGORIES: Depression and**	1091 adults aged 70+. Cross-sectional. United Kingdom.	Exposure: Functional social support. Covariates: Depression, age, sex, IQ at age 11, social class, marital status, living alone, social contact, loneliness.	Outcome: Cognition (general cognitive ability, processing speed, memory).	Analysis: General linear models (ANCOVA).	Moderation by age or gender was not considered or reported on.	Of all the social variables, loneliness, living arrangement and social support were most consistently associated with cognition, where increasing support was associated with increasing cognition. Depressive symptoms score resulted in a reduction in effect sizes for loneliness and social support on cognition, thus confounding the associations. Once depression was added to the

Social Isolation/Support in the Same Model with Cognition as Dependent Variable						final models, the association between social support and processing speed as well as loneliness and general cognition, were no longer significant. The association between living alone and processing speed remained significant after adding depression. The effect of depression controlling for social support factors was not reported on. Marital status and number of social contacts were not associated with cognition.
Guo, L., Luo, F., Gao, N., & Yu, B. (2021). Social Isolation and Cognitive Decline Among Older Adults with Depressive Symptoms: Prospective Findings from the China Health and Retirement Longitudinal Study. Archives of Gerontology and Geriatrics, 95, 104390. **CATEGORIES:** **Social Isolation Predicting Cognition**	2,507 middle-aged to older adults (aged 50+). Longitudinal. China.	<u>Exposure:</u> Structural social isolation. <u>Covariates:</u> Age, gender, education, chronic diseases, body mass index, health behaviours.	<u>Outcomes:</u> Memory, global cognition.	<u>Analysis:</u> Linear regression.	Moderation by gender was considered.	Fully adjusted results: The association between structural social isolation and global cognition was nonsignificant for both men and women with depression; however, the association was stronger (i.e., more negative) in women. The negative association between structural social isolation and memory was significant in women but not men.

in Populations with Depression						
Han, R., Tang, Z., & Ma, L. (2019). **Related Factors of Cognitive Impairment in Community-Dwelling Older Adults in Beijing Longitudinal Study of Aging.** *Aging Clinical and Experimental Research, 31*(1), 95-100. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	2017 adults aged 60+. Cross-sectional. Beijing, China.	Exposures: Depression, social participation (structural), marital status, sex, age, rural/urban, socioeconomic variables, health behaviours and risk factors, various diseases, disability.	Outcome: Cognitive impairment.	Analysis: Multivariable logistic regression.	Moderation by age or gender was not considered or reported on.	In the full model controlling for all independent variables, social participation and depression were associated with cognitive impairment, where those with more frequent social interactions had lower odds of cognitive impairment, and those with depression had higher odds of cognitive impairment. Marital status was non-significant.
Hatch, D. J., Schwartz, S., & Norton, M. C. (2015). **Depression and Antidepressant Use Moderate Association Between Widowhood and Alzheimer's Disease.** *International Journal of Geriatric Psychiatry, 30*(3), 292-299.	2419 adults age 65+. 218 with Alzheimer's disease and 2201 without dementia. Longitudinal - 4 waves over 13 years.	Exposure: Widowhood Covariates: Age, gender, occupation, and presence of ε4 allele. Stratified by: Depression history, anti-depressant use history. Positive history was defined as depressive	Outcome: Alzheimer's disease (AD).	Analysis: Cox regression (proportional hazards).	Age of widowhood was considered.	The association between widowhood and AD was moderated by history of depression and history of antidepressant use. Widowhood decreased risk for Alzheimer's disease in those with no history of depression, but increased risk in those with a history of depression. The models described above controlled for age, gender, occupation, and presence of ε4 allele. The reference category for

CATEGORIES: Social Isolation/Support and Depression Interaction or Moderation Models; Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable	Utah, Unites States.	episodes/antidepressant use at least one year before the onset of dementia. Major or minor depression was considered.				widowhood was the absence of widowhood. Moderation by age: Results suggest that widowhood experienced later in life compared to earlier in life may enhance the impact of depression on risk for AD.
Holwerda, T. J., Deeg, D. J., Beekman, A. T., van Tilburg, T. G., Stek, M. L., Jonker, C., & Schoevers, R. A. (2014). Feelings of Loneliness, but Not Social Isolation, Predict Dementia Onset: Results from the Amsterdam Study of the Elderly (AMSTEL). *Journal of Neurology, Neurosurgery & Psychiatry, 85*(2), 135-142. **CATEGORIES: Social Isolation/Support and Depression Interaction or Moderation Models; Depression and Social**	2173 community-dwelling older adults aged 65+ (no dementia). Longitudinal, with one follow-up period at 3 years post-baseline. Netherlands.	Exposure: Social isolation (either living alone, or being unmarried, or having no tangible social support), loneliness. Covariates: Depression, sociodemographic factors, medical conditions, cognition, functional status.	Outcome: Incident dementia diagnosis.	Analysis: Logistic regression.	The following interactions were tested with dementia as the outcome. All were non-significant: sex*loneliness sex*living alone sex*not married sex*social support	Loneliness, but not social isolation, was associated with 64% higher odds of dementia relative to those without loneliness. This was after controlling for all covariates including depression and social isolation. There was no interaction between social support and depression on incident dementia in multivariable analyses. Depression was associated with increased odds of incident dementia in the model adjusting for loneliness, social support and other covariates. The bivariate association between loneliness and incident dementia was significant in those living alone (OR=2.52; CI:1.63,3.89), but not in those living with others (OR=1.67, CI:0.74,3.80).

Isolation/Support in the Same Model with Cognition as Dependent Variable						Conclusion: The results suggest that loneliness is an independent predictor of incident dementia, and that this association may not necessarily be due to vascular pathology, Alzheimer pathology, or depression-related (stress overactivation) mechanisms. Feeling lonely (perception) versus the structural aspect of being alone may be more important in influencing risk of dementia.
Huntley, J., Corbett, A., Wesnes, K., Brooker, H., Stenton, R., Hampshire, A., & Ballard, C. (2018). Online Assessment of Risk Factors for Dementia and Cognitive Function in Healthy Adults. *International Journal of Geriatric Psychiatry, 33*(2), E286-E293. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	14,201 healthy adults aged 50+ without dementia. Cross-sectional. United Kingdom.	Exposures: Depression, perception of social isolation, education, smoking, physical activity, diabetes, hypertension, obesity.	Outcomes: Cognitive outcomes (spatial and verbal working memory, visual episodic memory, verbal reasoning).	Analysis: Hierarchical multivariate regression.	Moderation by age or gender was not considered or reported on.	In a model controlling for social support (availability of a confiding relationship) as well as other covariates, depression was negatively associated with paired-association learning task, digit span task, and spatial working memory, but not verbal reasoning. In a model controlling for depression as well as other covariates, higher social support (availability of a confiding relationship) was positively associated with all the measures of cognition (paired-association learning task, digit span task, spatial working memory, verbal reasoning) compared to no confiding relationship.

James, B. D., Wilson, R. S., Barnes, L. L., & Bennett, D. A. (2011). Late-Life Social Activity and Cognitive Decline in Old Age. *Journal of the International Neuropsychological Society, 17*(6), 998-1005. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1138 adults aged 65+, without dementia. Longitudinal – approximately 5-year average follow-up. Chicago metropolitan area, United States.	Exposure: Late life social activity (frequency). Covariates: Depression, age, sex, education, race, size of social network, chronic conditions, personality traits, disability, cognitive activity, physical activity, income.	Outcomes: Cognitive decline.	Analysis: Linear mixed effects model.	Moderation by age or gender was not considered or reported on.	In the full model adjusted for depression and all other covariates, higher social activity was associated with lower decline (rate of change) in all cognitive domains measured (episodic memory, semantic memory, working memory, perceptual speed, visuospatial ability) during follow-up. In bivariate analyses, those with higher social activity had lower depression scores. The effect of depression controlling for social support factors was not reported on.
Kim, D., Arai, H., & Kim, S. (2017). Social Activities Are Associated with Cognitive Decline in Older Koreans. *Geriatrics & Gerontology International, 17*(8), 1191-1196. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	2495 adults aged 65+, community-dwelling. Cross-sectional. Korea.	Exposure: Social activity (number of group social activities), social activity types, personal activity (frequency of meeting with close friends). Covariates: Depression, activities of daily living, weight loss, age, sex, education, employment.	Outcome: Cognitive impairment.	Analysis: Multiple logistic regression.	Moderation by age or gender was not considered or reported on.	In the full model controlling for depression and other covariates, the odds of cognitive impairment were higher in those with fewer group social activities. Frequency of personal social activities did not demonstrate a significant association with cognitive impairment. Depression was not associated with cognitive decline in the model controlling for age only. The effect of depression controlling for social support variables was not reported on.

Kim, J. H., Kim, Y., Kwon, J., & Park, E. C. (2019). **Association Between Changes in Depressive State and Cognitive Function.** *International Journal of Environmental Research and Public Health, 16*(24), 4944. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	6989 adults aged 45+. Longitudinal, population-based (5 time-points over 8 years). Korea.	Exposure: Change in depression states. Covariates: Age, employment, social participation, physical activity, number of chronic conditions.	Outcome: Global cognitive function.	Analysis: Generalized estimating equation (GEE).	Results were stratified by sex. Moderation by age was not considered or reported on.	Change to higher depression states were associated with worse cognition at similar magnitudes for both men and women after controlling for social participation and other covariates. Those with remitted depression had worse cognitive outcomes over time than those with no depression, but had better cognitive outcomes than those who transitioned from normal to depressed during the study. No participation in social activities was associated with worse cognitive outcomes compared to participation in social activities after controlling for depression and other covariates. This was evident for both sexes at similar magnitudes.
Kong, D., Davitt, J., & Dong, X. (2018). **Loneliness, Depressive Symptoms, and Cognitive Functioning Among US Chinese Older Adults.** *Gerontology and Geriatric Medicine.* **CATEGORIES: Social Isolation/Support and Depression**	3159 older adults. Cross-sectional. United States: Chinese older adults.	Exposure: Loneliness, depressive symptoms Covariates: Age, gender, education, marital status, living arrangements, children, chronic conditions, years in the United States. Interaction terms: loneliness*	Outcome: Global cognition and executive function.	Analysis: Linear regression.	Moderation by age or gender was not considered or reported on.	Loneliness predicted decreasing cognition and decreasing performance on tasks of executive function in the model controlling for health and sociodemographic covariates. These associations became non-significant after depression was added to the models. Both depression and loneliness were negatively related to cognition, but only depression was statistically significant in the full model.

Interaction or Moderation Models; Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable		depression				The interaction term between loneliness and depressive symptoms on global cognition was significant in the full model. Those with both loneliness and depressive symptoms are especially susceptible to poor cognitive function. Future directions: This study calls for longitudinal studies to assess casual relationships and underlying mechanisms linking depression, loneliness, and cognition.
Kuiper, J. S., Smidt, N., Zuidema, S. U., Comijs, H. C., Oude Voshaar, R. C., & Zuidersma, M. (2020). A Longitudinal Study of the Impact of Social Network Size and Loneliness on Cognitive Performance in Depressed Older Adults. *Aging & Mental Health,* **24(6) 889-897.** **CATEGORIES: Social Support Predicting Cognition in Populations with Depression**	378 older adults with a depressive disorder. Longitudinal – baseline and 2-year follow-up. Netherlands.	Exposure: Social network size, loneliness. Covariates: Depression severity (baseline and follow-up), age, sex, education, alcohol, physical activity.	Outcomes: Memory and executive function.	Analysis: Linear regression.	Moderation by age or gender was not considered or reported on.	In the full model controlling for sociodemographic variables, baseline cognition, and depression severity (at baseline and follow-up), neither loneliness nor social network size were associated with 2-year cognitive decline in any cognitive domain.

Lam, C. L., Yu, J., & Lee, T. M. (2017). Perceived Loneliness and General Cognitive Status in Community-Dwelling Older Adults: The Moderating Influence of Depression. *Aging, Neuropsychology, and Cognition, 24*(5), 471-480. **CATEGORIES: Social Isolation/Support and Depression Interaction or Moderation Models; Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	100 older adults, community-dwelling. Cross-sectional. Hong Kong.	Exposure: Perceived loneliness, depressed mood. Covariates: Age, marital status, non-verbal intelligence. Moderator: Depressive symptom scores.	Outcome: Global cognition.	Analysis: Bootstrapping moderation was conducted using PROCESS.	Moderation by age or gender was not considered or reported on.	In the full model, depressive symptoms and loneliness demonstrated a significant interaction for the outcome of global cognition. Loneliness and cognition were significant only in those with higher depression scores, with higher loneliness predicting lower cognition. Loneliness did not impact cognitive function for participants without high depression scores.
Lara, E., Caballero, F. F., Rico-Uribe, L. A., Olaya, B., Haro, J. M., Ayuso-Mateos, J. L., & Miret, M. (2019). Are Loneliness and Social Isolation Associated with Cognitive Decline? *International Journal of*	1691 community-dwelling adults 50+ years old Longitudinal, 2 waves over 3 years. Spain.	Exposure: Loneliness, social isolation. Covariates: Depression, age, sex, education, physical activity, alcohol, disability, stroke, diabetes.	Outcome: Tests for executive function, global cognition.	Analysis: Generalized linear models, clustered data, repeated measures.	Moderation by age or gender was not considered or reported on.	In the full model adjusting for all covariates, including depression and social isolation, loneliness was associated with lower scores on global cognition and tests of executive function. Similarly, in the full model adjusting for all covariates, including depression and loneliness, social isolation was also associated with lower scores

***Geriatric Psychiatry, 34*(11), 1613-1622.** **CATEGORIES: Social Support Predicting Cognition in Populations with No Depression; Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**						on global cognition and tests of executive function. The results for loneliness and social isolation remained similar after excluding those with depression. The effect of depression was not reported on.
Lee, S., Lee, S., Lee, E., Youm, Y., Cho, H. S., & Kim, W. J. (2020). Gender Differences in Social Network of Cognitive Function Among Community-Dwelling Older Adults. *Geriatrics & Gerontology International, 20*(5), 467-473. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	501 adults aged 60+, community-dwelling. Cross-sectional. Korea.	Exposure: Social networks. Covariates: Sociodemographic characteristics, depressive symptoms, instrumental ADLs, social activity, cognition.	Outcome: Cognitive function.	Analysis: Multiple linear regression and path analysis.	Sex was considered as a moderator. Age was not considered or reported on as a potential moderator.	Social activity and having a larger social network improved cognition only in women after accounting for depression and other covariates. Depression was not associated with cognition in either sex after accounting for social support variables among other covariates.

Leggett, A., Zarit, S. H., Hoang, C. N., & Nguyen, H. T. (2013). Correlates of Cognitive Impairment in Older Vietnamese. *Aging & Mental Health, 17*(8), 915-923. CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable	489 adults aged 55+. Cross-sectional. Vietnam.	Exposures: Depression, marital status, age, gender, material hardship, war injury, diseases (head trauma, diabetes, cardiovascular disease, cerebrovascular disease), urban/rural distinction.	Outcome: Global cognition score (continuous) and cognitive impairment (binary).	Analysis: Multiple linear and logistic regression.	Moderation by age or gender was not considered or reported on.	After controlling for marital status and other covariates, increasing depressive symptoms was associated with decreasing global cognition score but not cognitive impairment. After controlling for depression and other covariates, marital status was not associated with global cognition score or cognitive impairment.
Luchetti, M., Terracciano, A., Aschwanden, D., Lee, J. H., Stephan, Y., & Sutin, A. R. (2020). Loneliness is Associated with Risk of Cognitive Impairment in the Survey of Health, Ageing and Retirement in Europe. *International Journal of Geriatric Psychiatry. 35*(7), 794-801. CATEGORIES: Depression and Social Isolation/Support in	14,114 of middle- and older-aged adults (population-based). Longitudinal (11 years). Europe.	Exposure: Loneliness. Covariates: Age, sex, education, country, clinical and behavioural risk factors, health-related activity limitations, social isolation, social disengagement, depressive symptoms.	Outcome: Cognitive impairment.	Analysis: Cox regression hazard models.	There was no moderation by age or sex. Sensitivity analysis was conducted for those aged 65+ and results remained similar.	Loneliness was associated with increased risk of cognitive impairment even after accounting for depressive symptoms, social isolation, social disengagement, and other covariates. Depression increased risk for cognitive impairment after controlling for loneliness, social isolation, social disengagement, and other covariates. Depressive symptoms reduced the association between loneliness and cognitive impairment by 38%, although loneliness remained significant in the full model. This suggests that depression is a confounder and a potential mediator.

the Same Model with Cognition as Dependent; Depression as a Mediator Between Social Isolation/Support and Cognitive Outcomes						
Lyu, J., Lee, C. M., & Dugan, E. (2014). Risk Factors Related to Cognitive Functioning: A Cross-National Comparison of US and Korean Older Adults. *The International Journal of Aging and Human Development, 79*(1), 81-101. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	10,175 Americans and 3550 Koreans, analyzed separately. Middle-aged to older adults (community-dwelling). Cross-sectional. United States and Korea.	<u>Exposures:</u> Depression score, marital status (binary), age, sex, education, income, wealth, health behaviours, health factors, body mass index (BMI).	<u>Outcome:</u> Global cognition (including executive functions).	<u>Analysis:</u> Multivariable linear regression.	Stratification by gender was evident.	After controlling for structural social support (marital status) and other covariates, depression was associated with cognition in both American men and women, but not Korean men or women. In both American men and women, higher depression decreased cognition, with a greater effect size in women. After controlling for all covariates, in Korean men, marital status was associated with cognition, whereby being married was protective. Marital status showed no association with cognition in Americans.
McHugh Power, J., Tang, J., Kenny, R. A., Lawlor, B. A., & Kee, F. (2020). Mediating the Relationship Between Loneliness and Cognitive	7433 middle to older-aged adults. Individuals with neurological problems or psychiatric	<u>Exposure:</u> Loneliness. <u>Covariates:</u> Age, sex, education, physical health, comorbidities.	<u>Outcome:</u> Global cognition (including measures of executive function).	<u>Analysis:</u> Linear structural equation modelling.	Moderation by age or gender was not considered or reported on.	Loneliness at baseline predicted cognitive functioning at time-point 3. Depressive symptoms mediated this relationship, although this effect was small relative to the direct effect of loneliness on cognition.

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Function: The Role of Depressive and Anxiety Symptoms. *Aging & Mental Health, 24*(7), 1071-1078. **CATEGORIES: Depression as a Mediator Between Social Isolation/Support and Cognitive Outcomes**	problems were excluded. Longitudinal, 3 waves, 2 years apart. Ireland.	<u>Mediator</u>: Depressive symptoms, anxiety symptoms.				
Millán-Calenti, J. C., Sánchez, A., Lorenzo-López, L., Cao, R., & Maseda, A. (2013). Influence of Social Support on Older Adults with Cognitive Impairment, Depressive Symptoms, or Both Coexisting. *The International Journal of Aging and Human Development, 76*(3), 199-214. **CATEGORIES: Social Isolation/Support Predicting Co-occurrence of Depression and Cognitive Outcomes**	579 older adults aged 65+ with cognitive impairment (12.6%), depression (17.3%) or both coexisting (7.9%). Cross-sectional. Spain.	<u>Exposure</u>: Satisfaction with social contact (functional), extent of social contact (structural) <u>Covariates</u>: Sex, age, education, activities of daily living, comorbidity, medical history.	<u>Outcome</u>: Cognitive function; depression; cognitive function and depression coexisting.	<u>Analysis</u>: Multinomial logistic regression.	Moderation by age or gender was not considered or reported on.	After controlling for all covariates, the odds of coexisting depression and cognitive impairment were higher in those with lower satisfaction with social contact relative to those with high satisfaction with social contact. No relationship was found for the extent of contact.

Murata, C., Saito, T., Saito, M., & Kondo, K. (2019). The Association Between Social Support and Incident Dementia: A 10-Year Follow-Up Study in Japan. *International Journal of Environmental Research and Public Health, 16*(2), 239. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	14,088 older adults (functionally-independent). Longitudinal, 10 years. Japan.	Exposure: Social support (structural and functional aspects as separate measures). Covariates: Depression, age, health status, health behaviours, socioeconomic factors, subjective cognitive complaints.	Outcome: Dementia onset.	Analysis: Cox proportional hazard.	Moderation by gender was evident. Results were stratified by gender.	All results listed below were adjusted for all covariates, including depression. At least some social support aspects (functional or structural) were protective against incident dementia in men and women. For men, support from family members was protective against incident dementia, while no effect was found for women. Community engagement was protective for women but not men. Being married was protective for men and not women. The effect of depression controlling for social support factors was not reported on.
Nelson, L. A., Noonan, C. J., Goldberg, J., & Buchwald, D. S. (2013). Social Engagement and Physical and Cognitive Health Among American Indian Participants in the Health and Retirement Study. *Journal of Cross-Cultural Gerontology, 28*(4), 453-463.	203 American Indians and Alaska Natives, age 50+. Longitudinal, 12 years (7 waves). Unites States.	Exposure: Social engagement (structural). Covariates: Depression, sociodemographic factors, number of health conditions, vascular conditions, physical activity.	Outcome: Memory, mental status (composite of tests for executive function), self-reported health.	Analysis: Linear regression, random effects models.	Moderation by age or gender was not considered or reported on.	The association between higher social engagement and better mental status (composite measure including executive function tests) was significant after adjusting for all covariates as well as depression. The effect of depression controlling for social support factors was not reported on.

CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable						
Nguyen, H. T., Black, S. A., Ray, L. A., Espino, D. V., & Markides, K. S. (2002). Predictors of Decline in MMSE Scores Among Older Mexican Americans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 57*(3), M181-M185. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1759 older Mexican-American adults, aged 65+. Longitudinal, two time-points. United States.	Exposures: Marital status, household composition (number of people living in household), depression, sociodemographic characteristics, sensory impairment, chronic conditions.	Outcome: Global cognition - Mini Mental State Examination (MMSE).	Analysis: Multiple logistic regression.	An interaction effect between depression and age on cognition was insignificant.	Depression was associated with decline to moderate cognitive impairment after controlling for all covariates, including marital status and household composition. Being married vs unmarried was associated with lower odds of decline to severe cognitive impairment after controlling for depression and other covariates. Living with others had higher odds of decline compared to living alone, after controlling for all covariates including depression.
O'Luanaigh, C., O'Connell, H., Chin, A. V., Hamilton, F., Coen, R., Walsh, C., ... & Lawlor, B. A. (2012). Loneliness and Cognition in Older People: The	466 community-dwelling older adults. Cross-sectional. Ireland.	Exposure: Loneliness. Covariates: Depression, pre-morbid IQ, global cognition, demographic	Outcome: Cognition.	Analysis: Multiple linear regression.	Moderation by age or gender was not considered or reported on.	Loneliness was associated with impairments in global cognition and some aspects of executive function (processing speed, visual memory) after controlling for all covariates, including social networks and depression.

Dublin Healthy Ageing Study. *Aging & Mental Health, 16*(3), 347-352. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**		factors, social network (structural).				Social network, depression, and marital status were not associated with global cognition in the full model. Only loneliness was assessed with regard to specific executive function domains.
Raji, M. A., Reyes-Ortiz, C. A., Kuo, Y. F., Markides, K. S., & Ottenbacher, K. J. (2007). Depressive Symptoms and Cognitive Change in Older Mexican Americans. *Journal of Geriatric Psychiatry and Neurology, 20*(3), 145-152. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	2812 non-institutionalized Mexican-Americans aged 65+. Longitudinal, 7-years (4 time-points). United States.	Exposure: Depression Covariates: Sociodemographic variables (including marital status), medical conditions, vision, activities of daily living.	Outcome: Global cognitive change - Mini Mental State Examination (MMSE).	Analysis: General linear mixed modelling.	Moderation by age or gender was not considered or reported on.	In the full model, controlling for all covariates including marital status, depression was associated with greater cognitive decline over time. Being married was associated with increased cognition in the full model over time, controlling for depression. Marital status and depression had similar effect sizes.
Rawtaer, I., Gao, Q., Nyunt, M. S. Z., Feng, L., Chong, M. S., Lim, W. S., ... &	1601 cognitively normal adults aged 55+.	Exposures: Psychosocial variables including marital status,	Outcome: Incident mild cognitive impairment.	Analysis: Cox proportional hazards regression.	Interaction between marital status and gender	In the fully-adjusted model controlling for all covariates and psychosocial variables, being married was associated with a

					was tested and proven to be insignificant.	lower risk of developing mild cognitive impairment.
Ng, T. P. (2017). Psychosocial Risk and Protective Factors and Incident Mild Cognitive Impairment and Dementia in Community Dwelling Elderly: Findings from the Singapore Longitudinal Ageing Study. *Journal of Alzheimer's Disease, 57*(2), 603-611. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	Longitudinal, 8 years with 3 time-points. Singapore.	living alone, loneliness, life satisfaction. Covariates: Age, sex, education, ethnicity, smoking status, APOE4, cardiovascular disease and risk factors, physical activities, social activities, leisure activities.				Loneliness and depression were not associated with risk of cognitive impairment in the full model adjusting for all covariates and psychosocial variables.
Rej, S., Begley, A., Gildengers, A., Dew, M. A., Reynolds III, C. F., & Butters, M. A. (2015). Psychosocial Risk Factors for Cognitive Decline in Late-Life Depression: Findings from the MTLD-III Study. *Canadian Geriatrics Journal, 18*(2), 43.	130 adults aged 65+ with remitted depression. Exploratory analysis, nested within an RCT drug trial comparing donepezil to placebo. Longitudinal.	Exposure: Perceived social support. Covariates: Marital status, lifetime depression duration, depressive symptoms, age, race, education, sex, comorbidity, treatment allocation, baseline	Outcome: Time to conversion to mild cognitive impairment or dementia.	Analysis: Cox proportional hazards models.	Moderation by age or gender was not considered or reported on.	In a population of people with remitted depression, perceived social support (sense of belonging) was not associated with conversion to mild cognitive impairment or dementia after controlling for comorbidity and baseline global neuropsychological score. Depressive symptoms were not associated with cognition.

CATEGORIES: Social Support Predicting Cognition in Populations with Depression	Canada.	neuropsychological score.				*Note: Only significant predictors were controlled for in multivariable analysis.*
Roystonn, K., Abdin, E., Shahwan, S., Zhang, Y., Sambasivam, R., Vaingankar, J. A., ... & Subramaniam, M. (2020). Living Arrangements and Cognitive Abilities of Community-Dwelling Older Adults in Singapore. *Psychogeriatrics*. **DOI: 10.1111/psyg.12532.** **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	2548 adults aged 60+. Cross-sectional. Singapore.	Exposure: Living arrangements Covariates: Depression, marital status, age, education, gender, ethnicity, education, employment, disability, chronic conditions, self-reported health.	Outcome: Cognitive function.	Analysis: Multivariable linear regression.	Moderation by age or gender was not considered or reported on.	Living alone was not associated with cognitive function compared to living in a multigenerational household after controlling for depression and other covariates. Being widowed or never married was associated with worse cognition compared to being married after controlling for depression along with other covariates in a full model. Depression was associated with worse cognition after controlling for social support variables along with other covariates in a full model.
Riddle, M., McQuoid, D. R., Potter, G. G., Steffens, D. C., & Taylor, W. D. (2015). Disability but Not Social Support Predicts Cognitive Deterioration in	299 adults with depression, aged 60+. Longitudinal. United States.	Exposure: Change in social support (structural and functional). Covariates: Age sex, education, baseline depression.	Outcomes: Cognitive diagnosis (normal, cognitive impairment no dementia, dementia).	Analysis: Logistic regression.	Moderation by age or gender was not considered or reported on.	Increased baseline depression severity was associated with later cognitive impairment after controlling for all covariates, including social support. Neither structural nor functional social support variables were associated with cognitive conversion in the fully-adjusted

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Late-Life Depression. *International Psychogeriatrics, 27(5), 707-714.* **CATEGORIES: Social Support Predicting Cognition in Populations with Depression; Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**						model (including adjustment for depression). The same conclusions above persist for one-year change in social support (baseline depression remains significant, change in social support is still not significant).
Ryan, M. C. (1996). Loneliness, Social Support and Depression as Interactive Variables with Cognitive Status: Testing Roy's Model. *Nursing Science Quarterly, 9*(3), 107-114. **CATEGORIES: Social Isolation/Support and Depression Interaction or Moderation Models; Depression and Social Isolation/Support in the Same Model with**	74 older adults aged 60+, living in senior housing. Cross-sectional descriptive correlational study. United States.	Exposures: Loneliness, depression, social support (functional). Covariates: None.	Outcome: Global cognition - Mini Mental State Examination (MMSE).	Analysis: Pearson correlation coefficient; hierarchical entry multiple regression.	Moderation by age or gender was not considered or reported on.	There were no significant relationships between loneliness, depression, or social support on global cognition. The interaction effects between depression, loneliness and social support were non-significant for the global cognition outcome.

Cognition as Dependent Variable						
Schwartz, E., Khalaila, R., & Litwin, H. (2019). Contact Frequency and Cognitive Health Among Older Adults in Israel. *Aging & Mental Health, 23*(8), 1008-1016. **CATEGORIES: Depression as a Mediator Between Social Isolation/Support and Cognitive Outcomes**	1718 cognitively healthy adults aged 50+. Cross-sectional with supplemental longitudinal component. Israel.	Exposure: Contact frequency within the social network (structural). Covariates: Age, education, gender, marital status, social activities, physical health. Moderator: Ethnic group. Mediator: Depressive symptoms.	Outcome: Cognitive function.	Analysis: Moderated mediation using PROCESS macro model 10.	Moderation by age or gender was not considered or reported on.	Cross-sectional component: After controlling for all covariates, increased contact frequency was associated with increased cognitive function, and this association was mediated by reduced depressive symptoms. This mediated path differed according to ethnic group after controlling for all covariates. Both the direct and indirect effects were significant. Longitudinal component – controlling for cognition two years prior: Mediation by depression was reasonable after additionally controlling for past cognition using the piecemeal approach to mediation (i.e., both paths were highly significant). The indirect and direct effects were not reported on in the longitudinal analysis.
Semino, L., Marksteiner, J., Brauchle, G., & Danay, E. (2017). Networks of Depression and Cognition in Elderly Psychiatric Patients. *GeroPsych: The Journal of Gerontopsychology*	264 patients aged 60+ with cognitive impairment and/or depressive symptoms from a geriatric psychiatry ward. Cross-sectional.	Exposure: Several components of depression modelled simultaneously in a network analysis: social withdrawal, life satisfaction, feeling empty, feeling bored, having good spirit,	Outcome: Cognition. Cognitive scores were normalized for age, sex, education	Analysis: Network analysis, stratified into non-cognitively impaired and cognitively impaired groups.	Moderation by age or gender was not considered or reported on.	In the non-cognitively impaired group, social withdrawal (including dropping activities) connected depression and cognitive function. Out of all the depression components considered, social withdrawal was the strongest hub connecting depression to cognitive function in the non-

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and Geriatric Psychiatry, 30(3), 89–96. **CATEGORIES: Social Isolation/Support as a Mediator Between Depression and Cognitive Outcomes; Social Support Predicting Cognition in Populations with Depression**	Austria.	feeling happy, feeling helpless, having memory problems, loving life, feeling worthless, feeling full of energy, feeling hopeless, feeling worse than others.				cognitively impaired group, with reference to the other variables considered (i.e., life satisfaction, feeling empty, feeling bored, having good spirit, feeling happy, feeling helpless, having memory problems, loving life, feeling worthless, feeling full of energy, feeling hopeless, feeling worse than others).
Sharifi, F., Fakhrzadeh, H., Vannaghani, M., Arzaghi, S. M., Khoei, M. A., Farzadfar, F., & Tanjani, P. T. (2016). Prevalence of Dementia and Associated Factors among Older Adults in Iran: National Elderly Health Survey (NEHS). *Archives of Iranian Medicine (AIM), 19*(12). **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1257 community-dwelling adults aged 60+. Cross-sectional. Iran.	Exposures: Depression, marital status, living alone, age, gender, literacy, urban/rural, smoking, chronic conditions, body mass index (BMI).	Outcome: Dementia.	Analysis: Multivariable logistic regression.	Moderation by age or gender was not considered or reported on.	Depression was associated with higher odds of dementia (OR=4.3) after controlling for marital status, age, gender, literacy, urban/rural status, hypertension, and BMI. Marital status and living alone were non-significant after controlling for depression and other covariates. *Note: Only covariates with significant effects in the univariate analysis were included in the full model.*

Sims, R. C., Hosey, M., Levy, S. A., Whitfield, K. E., Katzel, L. I., & Waldstein, S. R. (2014). Distinct Functions of Social Support and Cognitive Function Among Older Adults. *Experimental Aging Research, 40*(1), 40-59. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	175 community-dwelling older adults. Cross-sectional. United States.	<u>Exposures:</u> Perceived social support (total), belonging support, self-esteem support. <u>Covariates:</u> Depressive symptoms, age, education, gender, blood pressure, body mass index (BMI), cholesterol, glucose.	<u>Outcome:</u> Memory and executive function (Stroop).	<u>Analysis:</u> Linear regression.	Moderation by age or gender was not considered or reported on.	After controlling for depression and other covariates, greater perceived social support was negatively associated with executive function. The same conclusions were evident for separate models for belonging support and self-esteem support. After controlling for perceived social support and other covariates, depression was not associated with executive function.
Stenfors, C. U., Hanson, L. M., Oxenstierna, G., Theorell, T., & Nilsson, L. G. (2013). Psychosocial Working Conditions and Cognitive Complaints Among Swedish Employees. *PLoS ONE, 8*(4): e60637. **CATEGORIES: Depression and**	3644 working adults. Longitudinal (2 time-points, 2 years apart) and cross-sectional. Sweden.	<u>Exposures:</u> Various psychosocial work conditions including a variable for social support (functional) and work-related relational conflicts (functional). <u>Covariates:</u> Age, sex, education, income, alcohol, cardiovascular	<u>Outcome:</u> Cognitive complaints frequency scale (i.e., difficulties with memory, concentration, decision-making, ability to think clearly).	<u>Analysis:</u> Multiple linear regression.	Interaction between gender and psychosocial work factors was tested in the cross-sectional and longitudinal models, but was not reported on. Interaction between work-	When depression was added to the model including baseline cognition and covariates, the association between social support and future cognitive complaints became non-significant, indicating that depression confounds the relationship between social support and future cognitive complaints. In the full model adjusting for all covariates (including baseline cognition, social support and

Social Isolation/Support in the Same Model with Cognition as Dependent Variable		disease, serious psychiatric illness, baseline cognitive complaints. Depressive symptoms were added, followed by sleeping problems.			related relational conflicts and gender was evident. Including depression as a variable eradicates the gender differences.	sleep problems), baseline depression was highly associated with future cognitive complaints at time-point 2. Work-related relational conflicts were not included in the longitudinal component of the study. They were, however, included in the cross-sectional component and were highly associated with cognitive complaints in both men and women after adjusting for all covariates including depression.
Stinchcombe, A., & Hammond, N. G. (2021). Correlates of Memory and Executive Function in Middle-Aged and Older Adults in the CLSA: A Minority Stress Approach. *The Journals of Gerontology: Series B.* **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	36,266 middle-aged and older adults. Cross-sectional. Canada.	Exposures: Age, marital status, gender, income, health measures (including mood disorders), education, retirement, social support availability, minority stress, cohort membership.	Outcome: Executive function and memory.	Analysis: Linear regression.	Moderation by age or gender was not considered or reported on.	Social support availability was positively associated with executive function even after controlling for structural social support (marital status), history of a mood disorder and other covariates. Being married/common-law was associated with lower executive function compared to being single/never married in a fully adjusted model. Contrary to expectations, having a mood disorder was associated with better executive function in fully adjusted models.
Tomioka, K., Kurumatani, N., & Hosoi, H. (2018). Social Participation	Cognitively normal community-	Exposure: Social participation (structural).	Outcome: Cognitive decline defined by a change	Analysis: Multiple logistic regression.	The association between social participation	Higher baseline social participation was associated with lower odds of cognitive decline three years later only in women in

and Cognitive Decline Among Community-Dwelling Older Adults: A Community-Based Longitudinal Study. *The Journals of Gerontology: Series B, 73*(5), 799-806. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	dwelling adults aged 65+. Longitudinal – 3 years, 2 time-points. Japan.	<u>Covariates</u>: Depression, age, body mass index (BMI), pension, comorbidities, medication, alcohol, smoking, activities of daily living, self-rated health, family structure.	from a baseline cognitive score of 0 to ≥1. A score of 0 indicates normal cognition, while scores ≥1 signify at least borderline intact.		and cognitive decline was stratified by gender.	the full model controlling for depression and other covariates. The effect of depression controlling for social support factors was not reported on.
Tsuji, T., Kanamori, S., Miyaguni, Y., Hanazato, M., & Kondo, K. (2019). Community-Level Sports Group Participation and the Risk of Cognitive Impairment. *Medicine and Science in Sports and Exercise, 51*(11), 2217. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with**	40,308 older adults (functionally independent). Longitudinal, six years. Japan.	<u>Exposure</u>: Frequency of sports group participation. <u>Covariates</u>: Sex, age, individual-level sports group participation, disease, obesity, social isolation, alcohol smoking, education, income, depression, daily walking time, population density, sunlight hours.	<u>Outcome</u>: Cognitive impairment.	<u>Analysis</u>: Multilevel survival analysis.	Moderation by age or gender was not considered or reported on.	More community-level group participation in sports was associated with lower risk of cognitive impairment in the full model controlling for depression among other covariates. The effect of depression and other covariates were not reported on.

Cognition as Dependent Variable						
van Gelder, B. M., Tijhuis, M., Kalmijn, S., Giampaoli, S., Nissinen, A., & Kromhout, D. (2006). Marital Status and Living Situation During a 5-Year Period Are Associated with a Subsequent 10-Year Cognitive Decline in Older Men: The FINE Study. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 61*(4), P213-P219. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	Community-dwelling older men aged 65+. Longitudinal, 10 years. Finland, Italy, Netherlands.	Exposures: Marital status, living alone. Covariates: Depression, marital status or living alone, baseline cognition, age, education, country, smoking, alcohol, chronic conditions, hypertension, physical activity.	Outcome: Cognition - Mini Mental State Examination (MMSE).	Analysis: Multiple linear regression (mixed).	Only men were included.	Full model: Compared to men who were married at baseline and five years later, men who were unmarried either at baseline or five years later (or both) had additional cognitive decline over ten years time*. Full model: Compared to men who lived with others at baseline and five years later, men who lived alone either at baseline or five years later (or both) had additional cognitive decline over ten years time*. *Adding depression to the models did not change any of the results. The effect of depression controlling for social support factors was not reported on.
Vilalta-Franch, J., López-Pousa, S., Llinàs-Reglà, J., Calvó-Perxas, L., Merino-Aguado, J., & Garre-Olmo, J. (2013). Depression Subtypes and 5-Year	451 cognitively healthy older adults aged 70+ (population-based). Longitudinal, 5 years.	Exposures: Subtypes of depressive disorders (major and minor depression, early and late onset depression,	Outcome: Incident dementia and Alzheimer disease.	Analysis: Cox proportional hazards regression	Moderation by gender was not considered or reported on.	After controlling for all covariates, including marital status, late-onset depression with depression-executive function syndrome was associated with increased dementia and Alzheimer disease. Early onset depression and late-onset

Risk of Dementia and Alzheimer Disease in Patients Aged 70 Years. *International Journal of Geriatric Psychiatry, 28*(4), 341-350. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	Spain.	depression-executive dysfunction syndrome). Covariates: Marital status, age, gender, education, cognitive impairment, executive function, stroke history.				depression without depression-executive dysfunction syndrome were not associated with dementia or Alzheimer disease risk. Being unmarried versus married was associated with increased dementia risk but not Alzheimer disease risk while controlling for other covariates, including depression variables.
Wang, H. X., Karp, A., Winblad, B., & Fratiglioni, L. (2002). Late-Life Engagement in Social and Leisure Activities is Associated with a Decreased Risk of Dementia: A Longitudinal Study from the Kungsholmen Project. *American Journal of Epidemiology, 155*(12), 1081-1087. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with**	776 cognitively healthy, non-institutionalized adults aged 75+. Longitudinal, 9 years. Kungsholmen district of Stockholm, Sweden.	Exposures: Frequency of engagement in social, mental and productive activities. Covariates: Depressive symptoms, education, sex, age, baseline cognition, comorbidity, physical functioning. Mental, social or productive activities were also included in the models.	Outcome: Dementia incidence.	Analysis: Cox proportional hazards model.	Moderation by age or gender was not considered or reported on.	After controlling for all covariates, including depression and mental and productive activities, frequent engagement in social activities was negatively associated with dementia incidence. This suggest an independent effect of social activities that cannot be explained by mental or productive activities, or depression. The effect was significant for less-than-weekly participation but not daily-weekly participation (with reference to no social activity participation). The results were not altered when the analysis was repeated for those without depressive symptoms. This may suggest that depression is not the cause of low social participation.

Cognition as Dependent Variable; Social Support Predicting Cognition in Populations with No Depression						The effect of depression controlling for social support factors was not reported on.
Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., ... & Bennett, D. A. (2007). Loneliness and Risk of Alzheimer Disease. *Archives of General Psychiatry, 64*(2), 234-240. CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable	823 older adults in older adult facilities (no dementia). Longitudinal, up to four years of follow-up. Chicago, IL, United States.	Exposure: Loneliness. Covariates: Depression (CES-D10 minus loneliness measure), objective measures of social isolation, participation in cognitively stimulating activities, physical activity, vascular burden, income, disability.	Main Outcome: Alzheimer disease (AD) diagnosis. Other outcome: Change in loneliness.	Analysis: Cox proportional hazards model, generalized estimating equation models.	Moderation by age or gender was not considered or reported on.	Even after controlling for objective measures of social isolation and depression, those with cumulative loneliness were at greater risk of developing dementia than those without loneliness. Loneliness was not associated with Alzheimer disease brain pathology post-mortem. Loneliness reduced the association between depression (CES-D10 minus loneliness) and risk for AD by half, thus making depression non-significant. Depression reduced the association between loneliness and risk for AD by only 16%. These results may suggest that loneliness impacts dementia independently of depressive symptoms, and that loneliness could explain the association between depression and dementia.
Wilson, R. S., Boyle, P. A., James, B. D., Leurgans, S. E., Buchman, A. S., & Bennett, D. A.	529 cognitively healthy older adults.	Exposure: Negative social interactions.	Outcome: Risk of mild cognitive impairment.	Analysis: Cox proportional hazards model.	Only moderation by age was considered.	More negative social interactions at baseline was associated with a higher risk of developing mild cognitive impairment after controlling for all covariates

(2015). Negative Social Interactions and Risk of Mild Cognitive Impairment in Old Age. *Neuropsycholog y, 29*(4), 561. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	Longitudinal, 4.8 years mean follow-up. United States.	<u>Covariates</u>: Depressive symptoms, social network size, social activity, loneliness, age, education, sex.				including depressive symptoms, social network size, social activity, and loneliness. There was a significant interaction between age and negative social interaction, whereby the association between more negative social interactions and risk of developing mild cognitive impairment was stronger in older ages versus younger ages. Only age, education and sex were controlled for in this model. The effect of depressive symptoms controlling for social support factors was not reported on.
Windsor, T. D., Gerstorf, D., Pearson, E., Ryan, L. H., & Anstey, K. J. (2014). Positive and Negative Social Exchanges and Cognitive Aging in Young-Old Adults: Differential Associations Across Family, Friend, and Spouse Domains. *Psychology and Aging, 29*(1), 28. **CATEGORIES: Depression and Social Isolation/Support in**	1618 cognitively healthy adults aged 60-64 years old. Longitudinal, 8 years (3 follow-ups). United States.	<u>Exposure</u>: Positive or negative social exchanges (functional). <u>Covariates</u>: Depressive symptoms, physical function, gender, age, education.	<u>Outcome</u>: episodic memory, executive function (working memory, perceptual speed).	<u>Analysis</u>: Bivariate latent growth curve models.	Moderation by age or gender was not considered or reported on.	Positive social interactions with friends/family was associated with lower decline in perceptual speed; however, this association decreased when depressive symptoms were added to the model. Negative spousal social interactions were associated with low baseline perceptual speed and working memory; however, the association between negative spousal social interactions and speed became non-significant after adding depression to the model. In terms of cognitive outcomes, the quality of social exchanges

the Same Model with Cognition as Dependent Variable						may be less important than other psychosocial variables. This is attributed to inconsistent results across domains of social exchange and cognition. The effect of depressive symptoms controlling for social support factors was not reported on.
Yen, C. H., Yeh, C. J., Wang, C. C., Liao, W. C., Chen, S. C., Chen, C. C., ... & Lee, M. C. (2010). Determinants of Cognitive Impairment Over Time Among the Elderly in Taiwan: Results of the National Longitudinal Study. *Archives of Gerontology and Geriatrics, 50*, S53-S57. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1626 cognitively healthy adults aged 60+ (population-based). Longitudinal, 10 years. Taiwan.	Exposures (Model 3): Depression, whether the participant was joining an organized group activity, age, sex, education, chronic diseases, disability, functional limitations, self-perceived health.	Outcome: Cognitive impairment.	Analysis: Logistic regression.	Moderation by age or gender was not considered or reported on.	In the full model controlling for all independent variables specified, neither depression nor joining a group activity were associated with cognitive impairment.
Yu, B., Steptoe, A., Chen, Y., & Jia, X. (2020). Social Isolation, Rather Than Loneliness, is	7761 adults aged 50+. Longitudinal (4 years, 2 waves).	Exposure: Loneliness (CES-D10 loneliness item), social	Outcome: Cognitive decline.	Analysis: Lagged dependant variable regression model.	Moderation by sex was tested for loneliness and social isolation. Sex	Loneliness was not associated with cognitive decline in the full model adjusting for all covariates. Adding depression (CES-D10 minus loneliness) eradicated the

Associated with Cognitive Decline in Older Adults: The China Health and Retirement Longitudinal Study. *Psychological Medicine*, 1-8. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable; Depression as a Mediator Between Social Isolation/Support and Cognitive Outcomes**	China.	isolation (structural). Covariates: Age, gender, education, urban/rural residence, health habits, functional limitations, chronic diseases, depressive symptoms (modified CES-D10 which excluded the loneliness measure).			did not interact with either isolation or loneliness. Moderation by age was not considered or reported on.	association between loneliness and cognitive decline. Social isolation (structural) was associated with cognitive decline in the full model controlling for loneliness, depression, and all other covariates. Depression was associated with cognitive decline in the full model controlling for loneliness, isolation and all other covariates.
Zahodne, L. B., Sharifian, N., Kraal, A. Z., Sol, K., Zaheed, A. B., Manly, J. J., & Brickman, A. M. (2021). Positive Psychosocial Factors and Cognitive Decline in Ethnically Diverse Older Adults. *Journal of the International Neuropsychological Society*, 27(1), 69-78.	578 adults aged 65 and over. Longitudinal. United States.	Exposure: Positive psychosocial factors (functional social support). Covariates: Age, sex/gender, race/ethnicity, education, depressive symptoms, chronic diseases.	Outcome: Executive function and memory.	Analysis: Latent difference scores.	Moderation by age or gender was not considered or reported on.	No domains of functional social support were associated with executive function in a fully adjusted model (including depressive symptoms). The effect of depressive symptoms in a fully adjusted model was not reported.

CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable						
Zahodne, L. B., Watson, C. W. M., Seehra, S., & Martinez, M. N. (2018). **Positive Psychosocial Factors and Cognition in Ethnically Diverse Older Adults.** *Journal of the International Neuropsychological Society, 24*(3), 294-304. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	548 ethnically diverse older adults aged 65+. Cross-sectional. United States.	Exposure: Positive psychosocial factors (including social support variables - emotional support, friendship, instrumental support, loneliness). Covariates: Depression, sex, age, education, language, health status.	Outcome: Global cognition.	Analysis: Multiple-group regression (allows comparison between positive psychosocial variables and cognition across race and ethnicity).	Moderation by age or gender was not considered or reported on.	After controlling for depression and other covariates, there were inconsistent associations between social support and cognition across different racial/ethnic groups, different social support subtypes, and different cognitive domains. Some associations were positive, some were negative, and some were non-significant. Above results did not change when depression and health status were removed from the model – this suggests that depression may not be a confounder. The effect of depression controlling for social support factors was not reported on.
Zahodne, L. B., Nowinski, C. J., Gershon, R. C., & Manly, J. J. (2014). **Which Psychosocial Factors Best Predict Cognitive Performance in Older**	482 adults aged 55+, community-dwelling and non-institutionalized. Cross-sectional. United States.	Exposure: Psychosocial factors. Covariates: Negative affect (anger hostility, anger affect, physical	Outcome: Global cognition and measures of executive function.	Analysis: Structural equation modelling and path analysis.	Analyses for those aged 65+ were conducted separately with similar findings.	After controlling for negative affect (e.g., depression) and other covariates, emotional support was associated with some executive functions. Negative affect was not associated with cognition after controlling for emotional support and other covariates. Negative affect was negatively

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Adults? *Journal of The International Neuropsychological Society, 20*(5), 487-495. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**		aggression, fear affect, fear somatic arousal, sadness), education, illness burden.			Moderation by gender/sex was not considered or reported on.	correlated with all positive psychosocial variables, and was positively correlated with loneliness. In a path analysis model including all negative affect and positive psychosocial variables, higher emotional support was associated with higher executive function on some tests. The only negative affect variable that was significantly associated with executive function was fear affect (negative association). Sadness, the closest negative affect variable to depression, was not associated with cognition. Results were unchanged when only considering those aged 65+. These results suggest that emotional support may have more of a role to play on cognition than negative affect.
Zhang, Z., Li, L. W., Xu, H., & Liu, J. (2019). Does Widowhood Affect Cognitive Function Among Chinese Older Adults? *SSM-Population Health*, 7, 100329. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with**	9203 adults aged 55+ (community-dwelling). Longitudinal (2 waves over two 2). China.	<u>Exposure:</u> Widowhood. <u>Covariates:</u> Depressive symptoms, economic resources, functional limitation, social engagement, age, sex, education, rural/urban residence, living arrangements.	<u>Outcome:</u> Change in executive function (mental intactness) and change in episodic memory.	<u>Analysis:</u> Lagged dependant variable approach, multivariable linear regression.	Moderation by age or sex was not considered for the executive function (mental intactness) outcome.	Widowhood was not associated with change in executive function (mental intactness) after controlling for covariates. Results were not shown for the mental intactness outcome. The effect of depression on executive function (mental intactness) was not reported on.

Cognition as Dependent Variable						
Zullo, L., Clark, C., Gholam, M., Castelao, E., von Gunten, A., Preisig, M., & Popp, J. (2021). Factors Associated with Subjective Cognitive Decline in Dementia-Free Older Adults—A Population-Based Study. *International Journal of Geriatric Psychiatry, 36*(8), 1188-1196. CATEGORIES: **Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**	1567 dementia-free community-dwelling older adults aged 65+ (urban). Cross-sectional. Switzerland.	Exposures: Age, sex, living alone, professionally active, education, current major depressive disorder, remitted major depressive disorder, current anxiety, neuroticism, extraversion., diabetes, body mass index, socioeconomic status, perceived social support, cardiovascular risk.	Outcome: Subjective cognitive decline	Analysis: Logistic regression	Moderation by age or gender was not considered or reported on.	Living alone and perceived social support were not associated with subjective cognitive decline in a fully adjusted model including depression. Current depression but not remitted depression was associated with subjective cognitive decline in a fully adjusted model.
Zunzunegui, M. V., Alvarado, B. E., Del Ser, T., & Otero, A. (2003). Social Networks, Social Integration, and Social Engagement Determine Cognitive Decline in Community-Dwelling Spanish Older Adults. *The*	964 community-dwelling adults over age 65. Longitudinal – 4 years, 2 time-points Spain.	Exposure: Social networks, social integration, social engagement. Covariates: Depressive symptoms, sex, age, education, blood pressure, functional status.	Outcome: Cognition (orientation and memory) and cognitive decline (absent, mild, severe). Decline was determined by using change scores (standardized).	Analysis: Multiple linear and logistic regression.	Moderation by sex (but not age) was considered by testing interaction terms.	Poor social connections, infrequent social participation, and social disengagement were associated with cognitive decline after controlling for depression and all other covariates. Gender/sex: High frequency of contact with relatives and community social integration was associated with lower cognitive decline in both men and women.

Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 58(2), S93-S100. **CATEGORIES: Depression and Social Isolation/Support in the Same Model with Cognition as Dependent Variable**					Engagement with friends was only protective against cognitive decline in women. Depression was associated with cognitive decline only in men. All models adjusted for depression, social support and other covariates.

Appendix C

Derivation of Analytical Sample
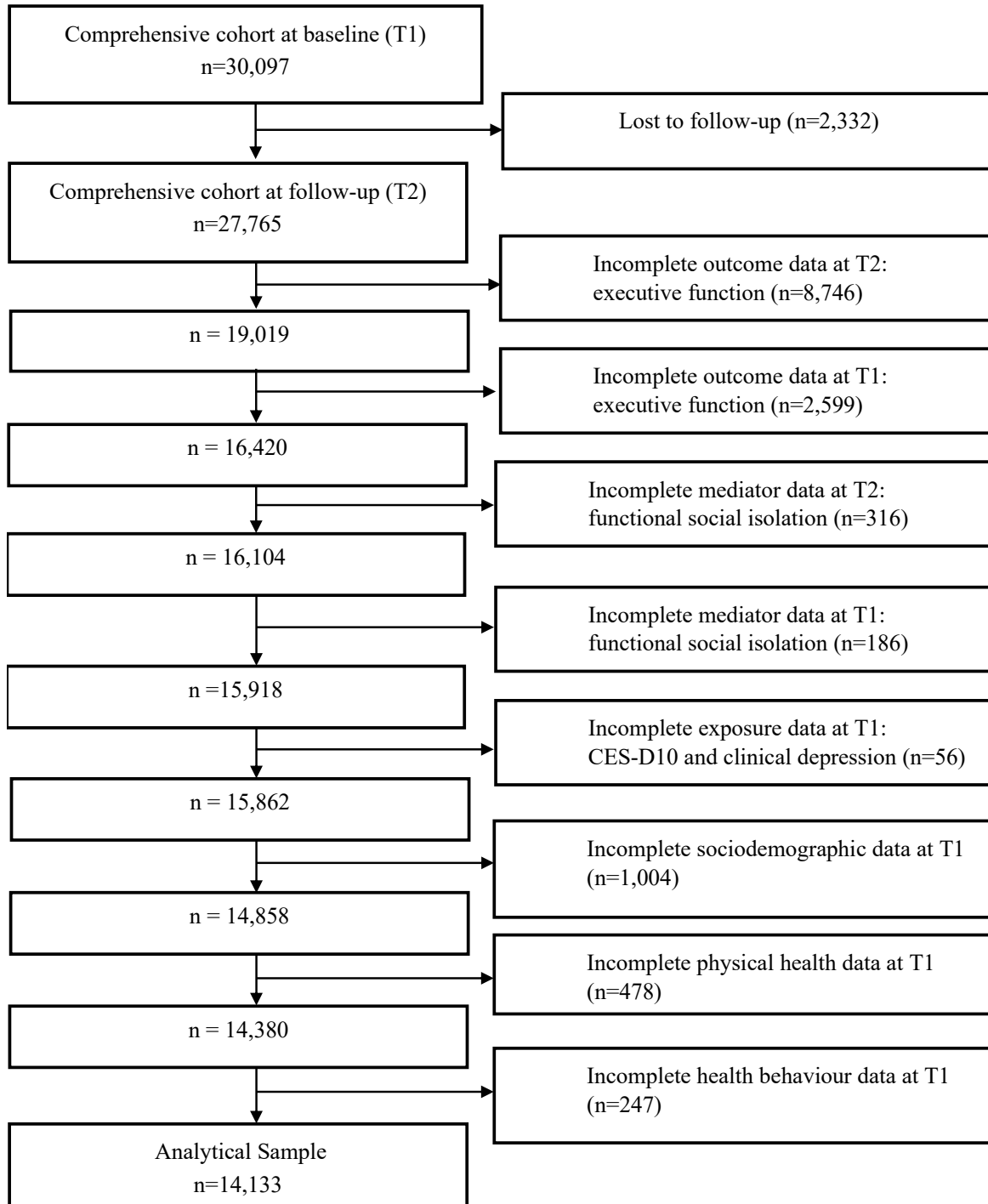
Figure C1. **Analytical Sample Flowchart**

Table C1: Incomplete Data on Executive Function Tests in the Follow-up (T2) Sample (n=27,765)

Executive Function Test	Missing at T1 (n=4,481)	Missing at T2 (n=8,746)
Animal Fluency Test (AFT)	1,121	3,946
Controlled Oral Word Association Test (COWAT)	2,095	2,865
Mental Alteration Test (MAT)	1,823	5,012
Stroop Neuropsychological Screening Test-Victoria Version (SNST-VV)	421	3,045
Time-Based Prospective Memory Test (TiMT)	396	2,644

Table C2: Incomplete Data on Baseline (T1) Covariates in the Follow-up (T2) Sample (n=27,765)

Covariates (T1)	Missing (n)
Sociodemographic	
Age group	0
Sex	0
Marital status	8
Living arrangements	17
Province	0
Education	43
Income	1,724
Urban/rural residence	344
Physical Health	
Self-rated health	19
Number of chronic conditions	1,069
Functional impairment	83
Health Behaviours	
Smoking use	1
Alcohol use	639

Appendix D

Measurement Instruments

Depressive Symptoms

The ten items of the Center for Epidemiological Studies Short Depression Scale (CES-D10) (Andresen et al., 1994) are available below. These questions reflect symptoms experienced in the past week.

1. How often were you bothered by things that usually don't bother you?
2. How often did you have trouble keeping your mind on what you were doing?
3. How often do you feel depressed?
4. How often did you feel that everything you did was an effort?
5. How often did you feel hopeful about the future?
6. Remember, we are asking about how you have felt in the past week. How often did you feel fearful or tearful?
7. How often was your sleep restless?
8. How often were you happy?
9. How often did you feel lonely?
10. How often did you feel that you could not "get going"?

Possible Responses for Each Item:

- Rarely or none of the time (less than 1 day)
- Some or a little of the time (1-2 days)
- Occasionally or a moderate amount of time (3-4 days)
- All of the time (5-7 days)

Scoring:

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)
Questions 5 and 8	3	2	1	0
Questions 1,2,3,4,6,7,9,10	0	1	2	3

The total score is derived from summing the item responses based on the scoring chart.

Functional Social Isolation

Below is a list of items used to construct the Medical Outcomes Survey – Social Support Survey (MOS-SSS) (Sherbourne & Stewart, 1991). Items were in response to the following question: "How often is each of the following kinds of support available to you if you need it?". Items were summed, transformed to a scale from 0 to 100, and then reverse coded to create the functional social isolation variable.

Items:

1. Someone to help you if you were confined to bed.
2. Someone you can count on to listen to you when you need to talk.
3. Someone to give you good advice about a crisis.
4. Someone to take you to the doctor if you needed it.
5. Someone who shows you love and affection.
6. Someone to have a good time with.
7. Someone to give you information to help you understand a situation.
8. Someone to confide in or talk to about yourself or your problems.
9. Someone who hugs you.
10. Someone to get together with for relaxation.
11. Someone to prepare your meals if you were unable to do it yourself.
12. Someone whose advice you really want.
13. Someone to do things with to help you get your mind off things.
14. Someone to help with daily chores if you were sick.
15. Someone to share your most private worries and fears with.
16. Someone to turn to for suggestions about how to deal with a personal problem.
17. Someone to do something enjoyable with.
18. Someone who understands your problems.
19. Someone to love and make you feel wanted.

Possible Responses for Each Item:
- None of the time (1)
- A little of the time (2)
- Some of the time (3)
- Most of the time (4)
- All of the time (5)

Executive Function

The table below describes the tests used to assess executive function in the CLSA (Raina et al., n.d.). Z-scores were created for each test based on language of administration (English and French), and then summed to create a composite score.

Executive Function Tests	Description
Animal Fluency Test (AFT)	Test of verbal fluency that asks participants to name as many animals as they can think of in 60 seconds.
Controlled Oral Word Association Test (COWAT)	Test of phonological fluency or knowledge that asks the participants to name words that begin with a specific letter.
Mental Alteration Test (MAT)	Participant is asked to alternate between numbers and letters as quickly as they can for 30 seconds.
Stroop Neuropsychological Screening Test-Victoria Version (SNST-VV)	Test of inhibition, attention, mental speed, and mental control. This test asks the participant to name the ink colour of a printed word. The word itself names a colour that is inconsistent with the ink colour to which it is printed.
Time-Based Prospective Memory Test (TiMT)	Test of prospective memory that contains event and time-based prospective memory tasks cued after delays of 15 or 30 minutes.

Covariates

Covariates	Classification	Details
Sociodemographic		
Age group	• 45-54 (ref) • 55-64 • 65-74 • 75+	Age (years)
Sex	• Male (ref) • Female	"Are you male or female?"
Marital status	• Married/living with a partner in a common-law relationship • Widowed • Divorced • Separated • Single, never married or never lived with a partner	
Living arrangements	• Living alone • Living with others	Derived from number of people living in the household
Province	• Alberta • British Columbia • Manitoba • Newfoundland and Labrador • Nova Scotia • Ontario (ref) • Quebec	Province at recruitment
Education	• Post-secondary education (university) (ref) • Post-secondary education (not university) • Some post-secondary • Secondary school graduation (no post-secondary) • Less than high school	Highest level of education obtained
Income	• $150,000 or more (ref) • $100,000 - $150,000 • $50,000-$100,000 • $20,000-$50,000 • <$20,000	Total household income
Urban/rural residence	• Urban (ref) • Rural	CLSA derived variable based on Statistics Canada's Postal Code Conversion File
Physical Health		
Self-rated health	• Excellent (ref) • Very good • Good • Fair • Poor	CLSA derived variable
Number of chronic conditions	• None (ref) • One • Two • Three	Self-reported diagnosis of high blood pressure/hypertension; diabetes/borderline high blood sugar; kidney disease/failure;

	• Four or more	cancer; under-active thyroid/hypothyroidism/myxedema; over-active thyroid/hyperthyroidism/Grave's disease; asthma; chronic obstructive pulmonary disease (COPD)/emphysema/chronic bronchitis; chronic cardiac conditions; stroke; or peripheral vascular disease.
Functional impairment	• No assistance required for any activity (ref) • Assistance required for at least one activity	Modified Older Americans Resources and Services – Multidimensional Assessment Questionnaire (OARS)
Health Behaviours		
Smoking use	• Never user (ref) – never smoked • Former user ("I don't smoke now but I have in the past") • Current user ("I currently smoke")	Smoking status self-report measure
Alcohol use	• Non-user (ref) – no alcohol consumed in the last year • Occasional user – alcohol consumed less than once per month • Regular user – alcohol consumed at least once per month for the last year	CLSA derived self-report measure

Appendix E

Post Hoc Analyses of Significant Mean Differences in Functional Social Isolation and Executive Function Across Sample Characteristics

See below for significant mean differences in T2 functional social isolation and executive function across categorical variables, corresponding to Section 5.1, Table 2.

Table E1: Post Hoc Analyses of Significant Mean Differences in T2 Functional Social Isolation and Executive Function Across Sample Characteristics – Analytical Sample in the Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Mediator (T2): Functional social isolation		Outcome (T2): Executive function	
Significant mean difference		*Significant mean difference*	
Age group (years)			
75+ vs. 45-54	5.98	75+ vs. 45-54	-3.58
75+ vs. 55-64	4.61	75+ vs. 55-64	-2.82
75+ vs. 65-74	4.19	65-74 vs. 45-54	-2.09
65-74 vs. 45-54	1.80	75+ vs. 65-74	-1.49
55-64 vs. 45-54	1.37	65-74 vs. 55-64	-1.33
		55-64 vs. 45-54	-0.76
Marital status			
Single/never married vs. partnered	15.59	Widowed vs. separated	-2.06
Separated vs. partnered	12.57	Widowed vs. partnered	-1.92
Divorced vs. partnered	12.51	Widowed vs. single	-1.76
Widowed vs. partnered	10.52	Widowed vs. divorced	-1.40
Single/never married vs. widowed	5.07	Divorced vs. separated	-0.65
Single/never married vs. divorced	3.08	Divorced vs. partnered	-0.52
Single/never married vs. separated	3.03	Divorced vs. single	-0.35
Divorced vs. widowed	1.99		
Province			
Nova Scotia vs. Quebec	3.66	Newfoundland and Labrador vs. British Columbia	-1.03
Newfoundland and Labrador vs. Quebec	3.34	Nova Scotia vs. British Columbia	-0.83
Manitoba vs. Nova Scotia	3.24	Quebec vs. British Columbia	-0.76
Alberta vs. Nova Scotia	3.16	Newfoundland and Labrador vs. Alberta	-0.73
Manitoba vs. Newfoundland and Labrador	2.93	Newfoundland and Labrador vs. Ontario	-0.61
Alberta vs. Newfoundland and Labrador	2.85	Newfoundland and Labrador vs. Manitoba	-0.60
British Columbia vs. Nova Scotia	2.33	Nova Scotia vs. Alberta	-0.53
Nova Scotia vs. Ontario	2.06	Quebec vs. Alberta	-0.46
British Columbia vs. Newfoundland and Labrador	2.02	Manitoba vs. British Columbia	-0.43
Newfoundland and Labrador vs. Ontario	1.75	Nova Scotia vs. Ontario	-0.42
Ontario vs. Quebec	1.60	Ontario vs. British Columbia	-0.42
British Columbia vs. Quebec	1.33	Nova Scotia vs. Manitoba	-0.40
		Quebec vs. Ontario	-0.34
		Quebec vs. Manitoba	-0.33
		Alberta vs. British Columbia	-0.30
Education, highest level obtained			
Less than secondary school vs. post-secondary education (university)	5.98	Less than secondary school vs. post-secondary education (university)	-3.75
Some post-secondary vs. post-secondary education (university)	3.92	Less than secondary school vs. post-secondary education (not university)	-2.38
Less than secondary school vs. secondary school graduation (no post-secondary)	3.84	Less than secondary school vs. some post-secondary	-2.35
Less than secondary school vs. post-secondary education (not university)	3.28	Less than secondary school vs. high school	-1.93
Post-secondary education (not university) vs. post-secondary education (university)	2.70	High school vs. post-secondary education (university)	-1.83

Mediator (T2): Functional social isolation		Outcome (T2): Executive function	
Significant mean difference		*Significant mean difference*	
Secondary school graduation (no post-secondary) vs. post-secondary education (university)	2.13	High school vs. post-secondary education (not university)	-1.46
		High school vs. some post-secondary	-1.42
		Some post-secondary vs. post-secondary education (university)	-1.40
		Post-secondary education (not university) vs. post-secondary education (university)	-1.37
Income			
<$20,000 vs. ≥$150,000	20.93	<$20,000 vs. ≥$150,000	-2.79
<$20,000 vs. ≥$100,000 and <$150,000	18.47	≥$20,000 and <$50,000 vs. ≥$150,000	-2.43
<$20,000 vs. ≥$50,000 and <$100,000	15.33	<$20,000 vs. ≥$100,000 and <$150,000	-2.24
≥$20,000 and <$50,000 vs. ≥$150,000	11.66	≥$20,000 and <$50,000 vs. ≥$100,000 and <$150,000	-1.89
<$20,000 vs. ≥$20,000 and <$50,000	9.28	<$20,000 vs. ≥$50,000 and <$100,000	-1.43
≥$20,000 and <$50,000 vs. ≥$100,000 and <$150,000	9.19	≥$50,000 and <$100,000 vs. $150,000 or more	-1.35
≥$20,000 and <$50,000 vs. ≥$50,000 and <$100,000	6.06	≥$20,000 and <$50,000 vs. ≥$50,000 and <$100,000	-1.07
≥$50,000 and <$100,000 vs. ≥$150,000	5.61	≥$50,000 and <$100,000 vs. ≥$100,000 and <$150,000	-0.81
≥$50,000 and <$100,000 vs. ≥$100,000 and <$150,000	3.13	≥$100,000 and <$150,000 vs. ≥$150,000	-0.54
≥$100,000 and <$150,000 vs. ≥$150,000	2.47	<$20,000 vs. ≥$20,000 and <$50,000	-0.35
Self-rated health			
Poor vs. excellent	16.07	Fair vs. excellent	-1.51
Poor vs. very good	13.17	Poor vs. excellent	-1.46
Fair vs. excellent	11.61	Fair vs. very good	-1.19
Poor vs. good	8.77	Poor vs. very good	-1.14
Fair vs. very good	8.70	Good vs. excellent	-0.86
Good vs. excellent	7.30	Fair vs. good	-0.65
Poor vs. fair	4.47	Good vs. very good	-0.55
Good vs. very good	4.40	Very good vs. excellent	-0.32
Fair vs. good	4.30		
Very good vs. excellent	2.90		
Number of chronic conditions			
4+ vs. 0	6.89	4+ vs. 0	-2.21
4+ vs. 1	5.57	4+ vs. 1	-1.67
4+ vs. 2	4.46	3 vs. 0	-1.63
3 vs. 0	4.14	4+ vs. 2	-1.18
3 vs. 1	2.82	3 vs. 1	-1.09
4+ vs. 3	2.75	2 vs. 0	-1.03
2 vs. 0	2.43	3 vs. 2	-0.60
1 vs. 0	1.32	4 vs. 3	-0.58
3 vs. 2	1.71	1 vs. 0	-0.54
2 vs. 1	1.11	2 vs. 1	-0.49

Mediator (T2): Functional social isolation		Outcome (T2): Executive function	
Significant mean difference		*Significant mean difference*	
Smoking status			
Current user vs. never user	6.43	Former user vs. never user	-0.49
Current user vs. former use	5.34	Current user vs. never user	-0.44
Former user vs. never user	1.09		
Alcohol use			
Occasional user vs. regular user	4.85	Non-user vs. regular user	-0.88
Non-user vs. regular user	4.59	Occasional user vs. regular user	-0.86

T1 = Baseline; T2 = Follow-up. Tests used: Tukey. Only significant mean differences (p < 0.05) are shown.

Appendix F

Sequential Models Adjusting for Covariates in Chunks (Models 0 to 3): Indirect, Pathway and Covariate Effects

The tables summarize a series of sequential models, with covariates added in chunks, including Models 1 and 2 as described under Section 5.2.1, Table 5. Tables F1a and F1b describe the indirect and pathway effects for the analytic sample (n=14,133) and subsample (women aged 75 and older, n=829), respectively, where depressive symptoms (CES-D10) are the exposure. Tables F2a and F2b include self-reported clinical depression as the exposure, but are otherwise similar to Tables F1a and F1b, respectively. Tables F3a-b (CES-D10) and F4a-b (self-reported clinical depression) include interaction and covariate effects for Path I (Tables F3a, F4a) and Path II (Tables F3b, F4b).

Table F1a: Sequential Models Adjusting for Covariates in Chunks: Indirect and Pathway Effects of Depressive Symptoms (CES-D10) on Executive Function through Functional Social Isolation by Age and Sex, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Independent Variables[†]	Moderators		Path I: X→M β (95% CI)	Path II: M→Y β (95% CI)	Indirect effect β (95% Bootstrap CI)
	Sex (Z)	Age (W)			
Base Model (Model 0)			**X*W*Z (ΔR^2= 0.0006)**	**M*W (ΔR^2 = 0.0005)**	
	Male		*X*W in Males (F=4.4009)*		
		45-54	**0.3237 (0.2091, 0.4383)**	-0.0015 (-0.0057, 0.0028)	-0.0005 (-0.0019, 0.0009)
		55-64	**0.2956 (0.1947, 0.3964)**	**-0.0051 (-0.0089, -0.0013)**	**-0.0015 (-0.0030, -0.0004)**
		65-74	**0.4355 (0.3013, 0.5697)**	-0.0043 (-0.0087, 0.0002)	-0.0019 (-0.0042, 0.0002)
		75+	0.0040 (-0.1899, 0.1978)	**-0.0141 (-0.0195, -0.0087)**	-0.0001 (-0.0034, 0.0035)
	Female		*X*W in Females (F=3.8662)*		
		45-54	**0.2171 (0.1187, 0.3155)**	-0.0015 (-0.0057, 0.0028)	-0.0003 (-0.0013, 0.0006)
		55-64	**0.3187 (0.2303, 0.4072)**	**-0.0051 (-0.0089, -0.0013)**	**-0.0016 (-0.0032, -0.0004)**
		65-74	0.0673 (-0.0505, 0.1850)	-0.0043 (-0.0087, 0.0002)	-0.0003 (-0.0012, 0.0003)
		75+	**0.2596 (0.0774, 0.4418)**	**-0.0141 (-0.0195, -0.0087)**	**-0.0037 (-0.0076, -0.0006)**
Model 1			**X*W*Z (ΔR^2= 0.0005)**	**M*W (ΔR^2 =0.0005)**	
	Male		*X*W in Males (F=3.7240)*		
		45-54	**0.2869 (0.1730, 0.4007)**	-0.0008 (-0.0050, 0.0035)	-0.0002 (-0.0015,0.0010)
		55-64	**0.2811 (0.1810, 0.3811)**	**-0.0043 (-0.0081, -0.0006)**	**-0.0012 (-0.0026, -0.0001)**
		65-74	**0.4189 (0.2859, 0.5520)**	-0.0035 (-0.0080, 0.0009)	-0.0015 (-0.0037, 0.0005)
		75+	0.0232 (-0.1690, 0.2154)	**-0.0135 (-0.0189, -0.0081)**	-0.0003 (-0.0035,0.0030)
	Female		*X*W in Females (F=3.4843)*		
		45-54	**0.1845 (0.0866, 0.2824)**	-0.0008 (-0.0050, 0.0035)	-0.0001 (-0.0010, 0.0007)
		55-64	**0.2925 (0.2046, 0.3804)**	**-0.0043 (-0.0081, -0.0006)**	**-0.0013 (-0.0026, -0.0002)**
		65-74	0.0643 (-0.0527, 0.1813)	-0.0035 (-0.0080, 0.0009)	-0.0002 (-0.0010,0.0003)
		75+	**0.2814 (0.1005, 0.4624)**	**-0.0135 (-0.0189, -0.0081)**	**-0.0038 (-0.0076, -0.0009)**

Independent Variables[†]	Moderators		Path I: X→M β (95% CI)	Path II: M→Y β (95% CI)	Indirect effect β (95% Bootstrap CI)
	Sex (Z)	Age (W)			
Model 2			X*W*Z (ΔR^2=0.0005)	M*W (ΔR^2=0.0005)	
	Male		*X*W in Males (F=3.5598)*		
		45-54	**0.2524 (0.1378, 0.3669)**	-0.0005 (-0.0048, 0.0037)	-0.0001 (-0.0012, 0.0010)
		55-64	**0.2478 (0.1469, 0.3486)**	**-0.0039 (-0.0077, -0.0002)**	**-0.0010 (-0.0022, -0.0000)**
		65-74	**0.3837 (0.2499, 0.5174)**	-0.0032 (-0.0076, 0.0012)	-0.0012 (-0.0032, 0.0006)
		75+	-0.0029 (-0.1953, 0.1895)	**-0.0131 (-0.0185, -0.0077)**	0.0000 (-0.0030, 0.0033)
	Female		*X*W in Females (F=3.2186)*		
		45-54	**0.1541 (0.0556, 0.2526)**	-0.0005 (-0.0048, 0.0037)	-0.0001 (-0.0008, 0.0006)
		55-64	**0.2555 (0.1665, 0.3445)**	**-0.0039 (-0.0077, -0.0002)**	**-0.0010 (-0.0022, -0.0000)**
		65-74	0.0355 (-0.0819, 0.1530)	-0.0032 (-0.0076, 0.0012)	-0.0001 (-0.0008, 0.0004)
		75+	**0.2436 (0.0623, 0.4250)**	**-0.0131 (-0.0185, -0.0077)**	**-0.0032 (-0.0069, -0.0004)**
Fully Adjusted (Model 3)			X*W*Z (ΔR^2=0.0005)	M*W (ΔR^2=0.0005)	
	Male		*X*W in Males (F=3.6500)*		
		45-54	**0.2484 (0.1339, 0.3629)**	-0.0005 (-0.0047, 0.0038)	-0.0001 (-0.0012,0.0010)
		55-64	**0.2459 (0.1450, 0.3468)**	**-0.0038 (-0.0076, -0.0001)**	-0.0009 (-0.0022, 0.0000)
		65-74	**0.3860 (0.2522, 0.5197)**	-0.0032 (-0.0076, 0.0012)	-0.0012 (-0.0032, 0.0006)
		75+	-0.0051 (-0.1975, 0.1873)	**-0.0130 (-0.0184, -0.0077)**	0.0001 (-0.0029, 0.0033)
	Female		*X*W in Females (F=3.2206)*		
		45-54	**0.1474 (0.0489, 0.2460)**	-0.0005 (-0.0047, 0.0038)	-0.0001 (-0.0008, 0.0006)
		55-64	**0.2550 (0.1660, 0.3440)**	**-0.0038 (-0.0076, -0.0001)**	-0.0010 (-0.0022, 0.0000)
		65-74	0.0376 (-0.0799, 0.1550)	-0.0032 (-0.0076, 0.0012)	-0.0001 (-0.0008, 0.0004)
		75+	**0.2477 (0.0664, 0.4291)**	**-0.0130 (-0.0184, -0.0077)**	**-0.0032 (-0.0069, -0.0005)**

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; ΔR^2 = R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex.

Path I: CES-D10 (T1) → Functional social isolation (T2); Path II: Functional social isolation (T2) → Executive function (T2)

Values where p<0.05 are in **bolded** font. Lower-order terms corresponding to interaction effects were automatically controlled for.

[†]Covariates:

  Model 0: Path I: M (T1), Y (T1); Path II: M (T1), Y (T1), X

  Model 1: Model 0 + sociodemographic factors at Path I and II (marital status, living arrangements, province, education, income, urban/rural residence).

  Model 2: Model 1 + physical health factors at Path I and II (self-rated health, number of chronic conditions, functional impairment).

  Model 3: Model 2 + health behaviour factors at Path I and II (smoking use, alcohol use).

Table F1b: Sequential Models Adjusting for Covariates in Chunks: Proportion of the Effect of Depressive Symptoms (CES-D10) on Executive Function Mediated by Functional Social Isolation in Women Aged 75 and Older, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=829)

Models[†]	Path I: X→M β (95% CI)	Path II: M→Y β (95% CI)	Indirect effect β (95% Bootstrap CI)	Direct effect β (95% CI)	Total effect β (95% CI)	Proportion Mediated (%)
Base Model (Model 0)	**0.3575 (0.1383, 0.5768)**	-0.0101 (-0.0230, 0.0028)	-0.0036 (-0.0094, 0.0008)	**-0.0481 (-0.0897, -0.0064)**	**-0.0517 (-0.0931, -0.0102)**	6.96
Model 1	**0.3598 (0.1376, 0.5821)**	-0.0097 (-0.0227, 0.0032)	-0.0035 (-0.0091, 0.0008)	-0.0376 (-0.0794, 0.0042)	-0.0411 (-0.0827, 0.0004)	8.52
Model 2	**0.2976 (0.0670, 0.5281)**	-0.0097 (-0.0228, 0.0033)	-0.0029 (-0.0080, 0.0008)	-0.0293 (-0.0727, 0.0140)	-0.0322 (-0.0755, 0.0110)	9.00
Fully Adjusted (Model 3)	**0.2795 (0.0474, 0.5115)**	-0.0098 (-0.0229, 0.0033)	-0.0027 (-0.0079, 0.0008)	-0.0310 (-0.0747, 0.0127)	-0.0337 (-0.0773, 0.0099)	8.01

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; T1 = Baseline; T2 = Follow-up; X = Exposure; Y = Outcome.

[†]Covariates:

  Model 0: Path I: M (T1), Y (T1); Path II: M (T1), Y (T1), X

  Model 1: Model 0 + sociodemographic factors at Path I and II (marital status, living arrangements, province, education, income, urban/rural residence).

  Model 2: Model 1 + physical health factors at Path I and II (self-rated health, number of chronic conditions, functional impairment).

  Model 3: Model 2 + health behaviour factors at Path I and II (smoking use, alcohol use).

Values where $p < 0.05$ are in **bolded** font.

Table F2a: Sequential Models Adjusting for Covariates in Chunks: Indirect and Pathway Effects of Self-Reported Clinical Depression on Executive Function through Functional Social Isolation by Age and Sex, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Independent Variables[†]	Moderators		Path I: X→M β (95% CI)	Path II: M→Y β (95% CI)	Indirect effect β (95% Bootstrap CI)
	Sex (Z)	Age (W)			
Base Model (Model 0)			**X*W*Z (ΔR^2=0.0004)**	**M*W (ΔR^2=0.0004)**	
			X*W in Males (F=2.2885)		
	Male	45-54	**3.2737 (1.7612, 4.7862)**	-0.0019 (-0.0061, 0.0023)	-0.0064 (-0.0219, 0.0072)
		55-64	**1.8110 (0.5624, 3.0596)**	**-0.0055 (-0.0092, -0.0017)**	**-0.0099 (-0.0225, -0.0013)**
		65-74	1.2454 (-0.4494, 2.9401)	**-0.0047 (-0.0091, -0.0002)**	-0.0058 (-0.0188, 0.0032)
		75+	-0.7211 (-3.6392, 2.1970)	**-0.0142 (-0.0196, -0.0088)**	0.0102 (-0.0401, 0.0673)
	Female		*X*W in Females (F=4.1508)*		
		45-54	**1.2139 (0.0806, 2.3472)**	-0.0019 (-0.0061, 0.0023)	-0.0024 (-0.0094, 0.0027)
		55-64	**1.4940 (0.4822, 2.5058)**	**-0.0055 (-0.0092, -0.0017)**	**-0.0082 (-0.0177, -0.0014)**
		65-74	0.0764 (-1.2925, 1.4453)	**-0.0047 (-0.0091, -0.0002)**	-0.0004 (-0.0081, 0.0073)
		75+	**5.3011 (2.7181, 7.8841)**	**-0.0142 (-0.0196, -0.0088)**	**-0.0753 (-0.1424, -0.0239)**
Model 1			**X*W*Z (ΔR^2=0.0005)**	**M*W (ΔR^2=0.0005)**	
			X*W in Males (F=2.2596)		
	Male	45-54	**2.9280 (1.4288, 4.4271)**	-0.0010 (-0.0052, 0.0032)	-0.0030 (-0.0163, 0.0095)
		55-64	**1.6372 (0.3991, 2.8753)**	**-0.0045 (-0.0083, -0.0008)**	**-0.0074 (-0.0184, -0.0002)**
		65-74	0.8521 (-0.8290, 2.5332)	-0.0038 (-0.0082, 0.0006)	-0.0032 (-0.0135, 0.0045)
		75+	-0.9537 (-3.8453, 1.9379)	**-0.0135 (-0.0189, -0.0082)**	0.0129 (-0.0353, 0.0676)
	Female		*X*W in Females (F=4.6960)*		
		45-54	0.6220 (-0.5037, 1.7477)	-0.0010 (-0.0052, 0.0032)	-0.0006 (-0.0051, 0.0028)
		55-64	**1.1112 (0.1064, 2.1161)**	**-0.0045 (-0.0083, -0.0008)**	**-0.0050 (-0.0127, -0.0000)**
		65-74	-0.3125 (-1.6727, 1.0476)	-0.0038 (-0.0082, 0.0006)	0.0012 (-0.0047, 0.0088)
		75+	**5.1522 (2.5909, 7.7136)**	**-0.0135 (-0.0189, -0.0082)**	**-0.0698 (-0.1352, -0.0197)**

Independent Variables[†]	Moderators		Path I: X→M β (95% CI)	Path II: M→Y β (95% CI)	Indirect effect β (95% Bootstrap CI)
	Sex (Z)	Age (W)			
Model 2			**X*W*Z (ΔR²=0.0004)**	**M*W (ΔR²=0.0004)**	
			X*W in Males (F=2.0360)		
	Male	45-54	**2.5974 (1.0975, 4.0974)**	-0.0007 (-0.0049, 0.0035)	-0.0017 (-0.0138, 0.0099)
		55-64	**1.3270 (0.0875, 2.5665)**	**-0.0040 (-0.0078, -0.0003)**	-0.0053 (-0.0151, 0.0008)
		65-74	0.5998 (-1.0806, 2.2801)	-0.0033 (-0.0078, 0.0011)	-0.0020 (-0.0110, 0.0052)
		75+	-1.0556 (-3.9442, 1.8329)	**-0.0131 (-0.0185, -0.0077)**	0.0138 (-0.0326, 0.0678)
	Female		*X*W in Female (F=4.7525**)*		
		45-54	0.2818 (-0.8457, 1.4092)	-0.0007 (-0.0049, 0.0035)	-0.0002 (-0.0035, 0.0026)
		55-64	0.7248 (-0.2833, 1.7328)	**-0.0040 (-0.0078, -0.0003)**	-0.0029 (-0.0092, 0.0012)
		65-74	-0.6163 (-1.9786, 0.7460)	-0.0033 (-0.0078, 0.0011)	0.0021 (-0.0030, 0.0101)
		75+	**4.8858 (2.3251, 7.4464)**	**-0.0131 (-0.0185, -0.0077)**	**-0.0641 (-0.1276, -0.0161)**
Fully Adjusted (Model 3)			**X*W*Z (ΔR²=0.0004)**	**M*W (ΔR²=0.0004)**	
			X*W in Males (F=1.9371)		
	Male	45-54	**2.5072 (1.0071, 4.0072)**	-0.0006 (-0.0048, 0.0037)	-0.0014 (-0.0130, 0.0099)
		55-64	**1.3061 (0.0665, 2.5457)**	**-0.0039 (-0.0077, -0.0002)**	-0.0051 (-0.0148, 0.0009)
		65-74	0.5585 (-1.1214, 2.2384)	-0.0033 (-0.0077, 0.0011)	-0.0019 (-0.0108, 0.0054)
		75+	-1.0551 (-3.9436, 1.8334)	**-0.0131 (-0.0185, -0.0077)**	0.0138 (-0.0330, 0.0677)
	Female		*X*W in Females (F=4.8156)*		
		45-54	0.2763 (-0.8508, 1.4034)	-0.0006 (-0.0048, 0.0037)	-0.0002 (-0.0033, 0.0026)
		55-64	0.7024 (-0.3053, 1.7101)	**-0.0039 (-0.0077, -0.0002)**	-0.0028 (-0.0090, 0.0012)
		65-74	-0.6071 (-1.9690, 0.7548)	-0.0033 (-0.0077, 0.0011)	0.0020 (-0.0031, 0.0100)
		75+	**4.9339 (2.3739, 7.4938)**	**-0.0131 (-0.0185, -0.0077)**	**-0.0644 (-0.1282, -0.0166)**

β = Regression coefficient value; CI = Confidence interval; M = Mediator; ΔR² = R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex. Values where $p<0.05$ are in **bolded** font.

Path I: Self-reported clinical depression (T1) → Functional social isolation (T2); Path II: Functional social isolation (T2) → Executive function (T2)

Lower-order terms corresponding to interaction effects were automatically controlled for.

[†]Covariates:

  Model 0: Path I: M (T1), Y (T1); Path II: M (T1), Y (T1), X

  Model 1: Model 0 + sociodemographic factors at Path I and II (marital status, living arrangements, province, education, income, urban/rural residence).

  Model 2: Model 1 + physical health factors at Path I and II (self-rated health, number of chronic conditions, functional impairment).

  Model 3: Model 2 + health behaviour factors at Path I and II (smoking use, alcohol use).

Table F2b: Sequential Models Adjusting for Covariates in Chunks: Proportion of the Effect of Self-Reported Clinical Depression on Executive Function Mediated by Functional Social Isolation in Women Aged 75 and Older Using an Unweighted Stratified Subsample, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=829)

Models[†]	Path I: X→M Effect of self-reported clinical depression (T1) on functional social isolation (T2) β (95% CI)	Path II: M→Y Effect of functional social isolation (T2) on executive function (T2) β (95% CI)	Indirect effect β (95% Bootstrap CI)	Direct effect β (95% CI)	Total effect β (95% CI)	Proportion Mediated (%)
Base Model (Model 0)	**5.5013 (2.5756, 8.4269)**	-0.0108 (-0.0238, 0.0021)	-0.0596 (-0.1490, 0.0077)	-0.3201 (-0.8798, 0.2396)	-0.3797 (-0.9354, 0.1760)	15.70
Model 1	**5.4528 (2.4697, 8.4358)**	-0.0102 (-0.0232, 0.0028)	-0.0556 (-0.1444, 0.0084)	-0.2907 (-0.8539, 0.2725)	-0.3463 (-0.9055, 0.2129)	16.06
Model 2	**5.1947 (2.1993, 8.1902)**	-0.0099 (-0.0230, 0.0032)	-0.0514 (-0.1405, 0.0108)	-0.2315 (-0.7993, 0.3363)	-0.2829 (-0.8470, 0.2812)	18.17
Fully Adjusted (Model 3)	**5.0316 (2.0289, 8.0343)**	-0.0099 (-0.0231, 0.0032)	-0.0500 (-0.1381, 0.0109)	-0.2351 (-0.8047, 0.3344)	-0.2852 (-0.8513, 0.2810)	17.53

β = Regression coefficient value; CI = Confidence interval; M = Mediator; T1 = Baseline; T2 = Follow-up; X = Exposure; Y = Outcome.
[†]Covariates:
   Model 0: Path I: M (T1), Y (T1); Path II: M (T1), Y (T1), X
   Model 1: Model 0 + sociodemographic factors at Path I and II (marital status, living arrangements, province, education, income, urban/rural residence).
   Model 2: Model 1 + physical health factors at Path I and II (self-rated health, number of chronic conditions, functional impairment).
   Model 3: Model 2 + health behaviour factors at Path I and II (smoking use, alcohol use).
Values where p<0.05 are in **bolded** font.

Table F3a: Covariate Effects: Sequential Models Adjusting for Covariates in Chunks, Depressive Symptoms (CES-D10) on Functional Social Isolation, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

	Path I: X→M Functional social isolation (T2) as the dependent variable			
Independent Variables	**Model 0 ($R^2 = 0.57$)** β (95% CI)	**Model 1 ($R^2 = 0.57$)** β (95% CI)	**Model 2 ($R^2 = 0.58$)** β (95% CI)	**Model 3 ($R^2 = 0.58$)** β (95% CI)
Exposure *(T1)*				
CES-D10	**0.3237 (0.2091, 0.4383)**	**0.2869 (0.1730, 0.4007)**	**0.2524 (0.1378, 0.3669)**	**0.2484 (0.1339, 0.3629)**
Age *(ref: 45-54)*				
55-64	0.7644 (-0.1963, 1.7250)	0.5350 (-0.4213, 1.4914)	0.4765 (-0.4822, 1.4353)	0.4627 (-0.4976, 1.4231)
65-75	0.7322 (-0.3166, 1.7810)	0.4069 (-0.6498, 1.4635)	0.3557 (-0.7104, 1.4217)	0.3565 (-0.7135, 1.4265)
75+	**3.7913 (2.4708, 5.1117)**	**3.3744 (2.0497, 4.6990)**	**3.2437 (1.9051, 4.5822)**	**3.3354 (1.9932, 4.6776)**
Sex *(ref: male)*				
Female	0.6073 (-0.4051, 1.6197)	0.2895 (-0.7156, 1.2946)	0.3066 (-0.6985, 1.3118)	0.3115 (-0.6937, 1.3167)
Interaction terms				
*CES-D10 * Age 55-64 * Sex*	0.1298 (-0.0697, 0.3293)	0.1138 (-0.0840, 0.3115)	0.1061 (-0.0916, 0.3037)	0.1101(-0.0875, 0.3077)
*CES-D10 * Age 65-74 * Sex*	**-0.2616 (-0.4932, -0.0300)**	**-0.2523 (-0.4819, -0.0226)**	**-0.2498 (-0.4794, -0.0203)**	**-0.2474 (-0.4769, -0.0179)**
*CES-D10 * Age 75+ * Sex*	**0.3623 (0.0581, 0.6664)**	**0.3606 (0.0592, 0.6620)**	**0.3448 (0.0435, 0.6462)**	**0.3538 (0.0525, 0.6551)**
*Age 55-64 * Sex*	-0.9890 (-2.3393, 0.3613)	-1.0883 (-2.4271, 0.2505)	-1.0105 (-2.3488, 0.3278)	-0.9923 (-2.3303, 0.3458)
*Age 65-74 * Sex*	0.7169 (-0.7842, 2.2180)	0.2263 (-1.2640. 1.7165)	0.2706 (-1.2191, 1.7603)	0.3299 (-1.1605, 1.8204)
*Age 75+ * Sex*	-1.2234 (-3.1595, 0.7126)	-1.7778 (-3.7088, 0.1533)	-1.6877 (-3.6194, 0.2440)	-1.6647 (-3.5979, 0.2686)
*CES-D10 * Sex*	-0.1066 (-0.2561, 0.0428)	-0.1024 (-0.2505, 0.0458)	-0.0983 (-0.2464, 0.0498)	-0.1010 (-0.2490, 0.0471)
*CES-D10 * Age 55-64*	-0.0282 (-0.1789, 0.1226)	-0.0058 (-0.1553, 0.1437)	-0.0046 (-0.1540, 0.1448)	-0.0025 (-0.1519, 0.1469)
*CES-D10 * Age 65-74*	0.1118 (-0.0629, 0.2865)	0.1321 (-0.0414, 0.3055)	0.1313 (-0.0421, 0.3047)	0.1376 (-0.0358, 0.3109)
*CES-D10 * Age 75+*	**-0.3198 (-0.5436, -0.0960)**	**-0.2636 (-0.4856, -0.0416)**	**-0.2553 (-0.4773, -0.0332)**	**-0.2535 (-0.4754, -0.0316)**
Baseline mediator and outcome *(T1)*				
Functional social isolation	**0.7196 (0.7078, 0.7314)**	**0.6827 (0.6701, 0.6954)**	**0.6805 (0.6679, 0.6932)**	**0.6792 (0.6665, 0.6919)**
Executive function	**-0.1472 (-0.2170, -0.0774)**	**-0.0852 (-0.1586, -0.0118)**	-0.0644 (-0.1380, 0.0093)	-0.0616 (-0.1355, 0.0122)
Sociodemographic characteristics				
Marital status (ref: partnered)				
Single/never married		**2.8418 (1.9572, 3.7265)**	**2.8696 (1.9855, 3.7537)**	**2.8432 (1.9591, 3.7274)**
Widowed		0.1666 (-0.7683, 1.1014)	0.2211 (-0.7135, 1.1558)	0.2122 (-0.7222, 1.1465)
Divorced		**1.7355 (0.9306, 2.5404)**	**1.7545 (0.9498, 2.5592)**	**1.7090 (0.9042, 2.5137)**
Separated		**1.3726 (0.1377, 2.6075)**	**1.4414 (0.2066, 2.6763)**	**1.4000 (0.1653, 2.6348)**
Lives alone (ref: lives with others)		0.0495 (-0.0239, 0.1229)	0.0511 (-0.0223, 0.1244)	0.0508 (-0.0226, 0.1242)
Province (ref: Ontario)				
Quebec		**-0.8362 (-1.4337, -0.2386)**	**-0.8928 (-1.4909, -0.2947)**	**-0.8954 (-1.4949, -0.2959)**
Newfoundland and Labrador		**-1.0275 (-1.7305, -0.3244)**	**-1.0319 (-1.7347, -0.3290)**	**-1.0483 (-1.7514, -0.3453)**

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Independent Variables	Path I: X→M Functional social isolation (T2) as the dependent variable			
	Model 0 ($R^2 = 0.57$) β (95% CI)	Model 1 ($R^2 = 0.57$) β (95% CI)	Model 2 ($R^2 = 0.58$) β (95% CI)	Model 3 ($R^2 = 0.58$) β (95% CI)
Nova Scotia		-0.6479 (-1.3315, 0.0358)	-0.6596 (-1.3428, 0.0235)	-0.6669 (-1.3501, 0.0163)
Manitoba		0.0151 (-0.6530, 0.6833)	0.0014 (-0.6665, 0.6694)	-0.0038 (-0.6715, 0.6639)
Alberta		0.5430 (-0.1637, 1.2498)	0.5466 (-0.1597, 1.2529)	0.5372 (-0.1691, 1.2434)
British Columbia		-0.0887 (-0.6103, 0.4329)	-0.1140 (-0.6356, 0.4075)	-0.0976 (-0.6202, 0.4250)
Education, highest level obtained (ref: university degree)				
Post-secondary diploma/ degree (not university)		0.4088 (-0.0235, 0.8412)	0.3373 (-0.0955, 0.7702)	0.2676 (-0.1687, 0.7038)
Some post-secondary		0.3676 (-0.3521, 1.0872)	0.2831 (-0.4369, 1.0030)	0.1661 (-0.5580, 0.8902)
Secondary school graduation (no post-secondary)		-0.0170 (-0.7084, 0.6744)	-0.0695 (-0.7606, 0.6217)	-0.1713 (-0.8664, 0.5238)
Less than secondary school		-0.4567 (-1.4515, 0.5381)	-0.6451 (-1.6417, 0.3515)	-0.8297 (-1.8325, 0.1731)
Income (ref: ≥ $150,000)				
≥$100,000 and <$150,000		**0.8067 (0.2500, 1.3634)**	**0.7808 (0.2242, 1.3373)**	**0.7484 (0.1916, 1.3051)**
≥$50,000 and <$100,000		**1.1000 (0.5552, 1.6447)**	**1.0247 (0.4795, 1.5698)**	**0.9794 (0.4329, 1.5258)**
≥$20,000 and <$50,000		**2.5280 (1.8321, 3.2239)**	**2.3654 (1.6673, 3.0636)**	**2.2750 (1.5727, 2.9773)**
<$20,000		**4.3520 (3.2096, 5.4945)**	**4.0779 (2.9294, 5.2265)**	**3.9291 (2.7730, 5.0853)**
Rural (ref: urban)		-0.1165 (-0.7873, 0.5543)	-0.0966 (-0.7669, 0.5737)	-0.0908 (-0.7610, 0.5794)
Physical health				
Self-rated health (ref: excellent)				
Very good			0.2639 (-0.2081, 0.7359)	0.2485 (-0.2234, 0.7204)
Good			**1.0868 (0.5437, 1.6299)**	**1.0304 (0.4866, 1.5741)**
Fair			**1.5158 (0.6324, 2.3993)**	**1.4328 (0.5481, 2.3176)**
Poor			1.2016 (-0.7623, 3.1656)	1.0400 (-0.9255, 3.0055)
Number of chronic conditions (ref: 0)				
1			0.2410 (-0.2003, 0.6823)	0.2519 (-0.1895, 0.6932)
2			0.1105 (-0.4181, 0.6392)	0.1215 (-0.4074, 0.6504)
3			**0.7443 (0.0504, 1.4381)**	**0.7469 (0.0517, 1.4420)**
4+			0.5511 (-0.3745, 1.4767)	0.5404 (-0.3868,1.4676)
Functional impairment (ref: no impairment)			0.1191 (-0.6139, 0.8521)	0.0783 (-0.6549, 0.8116)
Health behaviours				
Smoking status (ref: never used)				
Former user				0.1500 (-0.2324, 0.5324)
Current user				**1.3601 (0.6617, 2.0586)**

Independent Variables	Path I: X→M Functional social isolation (T2) as the dependent variable			
	Model 0 ($R^2 = 0.57$) β (95% CI)	Model 1 ($R^2 = 0.57$) β (95% CI)	Model 2 ($R^2 = 0.58$) β (95% CI)	Model 3 ($R^2 = 0.58$) β (95% CI)
Alcohol use (ref: non-user)				
Occasional user				-0.0144 (-0.7909, 0.7621)
Regular user				-0.2839 (-0.8986, 0.3308)

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; ΔR^2= R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex.

Values where $p<0.05$ are in **bolded** font.

Table F3b: Covariate Effects: Sequential Models Adjusting for Covariates in Chunks, Functional Social Isolation on Executive Function Controlling for Depressive Symptoms (CES-D10), Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Independent Variables	Path II: M→Y Executive function (T2) as the dependent variable			
	Model 0 (R^2 = 0.59) β (95% CI)	Model 1 (R^2 = 0.60) β (95% CI)	Model 2 (R^2 = 0.60) β (95% CI)	Model 3 (R^2 = 0.60) β (95% CI)
Exposure (T1)				
CES-D10	**-0.0146 (-0.0221, -0.0071)**	**-0.0095 (-0.0170, -0.0020)**	-0.0050 (-0.0128, 0.0028)	-0.0047 (-0.0125, 0.0031)
Mediator (T2)				
Functional social isolation	-0.0015 (-0.0057, 0.0028)	-0.0008 (-0.0050, 0.0035)	-0.0005 (-0.0048, 0.0037)	-0.0005 (-0.0047, 0.0038)
Age (ref: 45-54)				
55-64	**-0.1907 (-0.2990, -0.0824)**	**-0.1652 (-0.2736, -0.0568)**	**-0.1588 (-0.2677, -0.0498)**	**-0.1564 (-0.2656, -0.0472)**
65-75	**-0.7407 (-0.8654, -0.6161)**	**-0.6823 (-0.8105, -0.5542)**	**-0.6691 (-0.7990, -0.5391)**	**-0.6669 (-0.7975, -0.5363)**
75+	**-1.0717 (-1.2357, -0.9077)**	**-0.9910 (-1.1587, -0.8232)**	**-0.9539 (-1.1245, -0.7833)**	**-0.9562 (-1.1273, -0.7850)**
Sex (ref: male)				
Female	0.0151 (-0.0465, 0.0766)	**0.0743 (0.0113, 0.1372)**	**0.0814 (0.0176, 0.1451)**	**0.0793 (0.0152, 0.1435)**
Interaction terms				
*Functional social isolation * Age 55-64*	-0.0037 (-0.0084, 0.0011)	-0.0036 (-0.0083, 0.0012)	-0.0034 (-0.0081, 0.0014)	-0.0034 (-0.0081, 0.0013)
*Functional social isolation * Age 65-74*	-0.0028 (-0.0082, 0.0026)	-0.0028 (-0.0081, 0.0026)	-0.0027 (-0.0080, 0.0027)	-0.0028 (-0.0081, 0.0026)
Functional social isolation Age 75+*	**-0.0126 (-0.0189, -0.0064)**	**-0.0127 (-0.0189, -0.0065)**	**-0.0126 (-0.0188, -0.0063)**	**-0.0126 (-0.0188, -0.0064)**
Baseline Mediator and Outcome (T1)				
Functional social isolation	-0.0001 (-0.0030, 0.0027)	0.0001 (-0.0028, 0.0030)	0.0001 (-0.0028, 0.0030)	0.0002 (-0.0027, 0.0031)
Executive function	**0.7308 (0.7188, 0.7427)**	**0.6967 (0.6842, 0.7093)**	**0.6935 (0.6809, 0.7061)**	**0.6931 (0.6804, 0.7057)**
Sociodemographic Characteristics				
Marital status (ref: partnered)				
Single/never married		0.0625 (-0.0891, 0.2142)	0.0567 (-0.0949, 0.2082)	0.0584 (-0.0933, 0.2100)
Widowed		-0.0950 (-0.2539, 0.0639)	-0.0931 (-0.2520, 0.0658)	-0.0949 (-0.2538, 0.0640)
Divorced		0.0064 (-0.1314, 0.1441)	0.0062 (-0.1315, 0.1439)	0.0085 (-0.1293, 0.1462)
Separated		0.0847 (-0.1264, 0.2958)	0.0736 (-0.1375, 0.2847)	0.0739 (-0.1372, 0.2851)
Lives alone (ref: lives with others)		0.0038 (-0.0087, 0.0164)	0.0037 (-0.0088, 0.0162)	0.0036 (-0.0090, 0.0161)
Province (ref: Ontario)				
Quebec		0.0576 (-0.0446, 0.1598)	0.0637 (-0.0386, 0.1660)	0.0618 (-0.0408, 0.1644)
Newfoundland and Labrador		**-0.1770 (0.2972, -0.0567)**	**-0.1823 (-0.3025, -0.0621)**	**-0.1822 (-0.3025, -0.0619)**
Nova Scotia		**-0.1408 (-0.2578, -0.0239)**	**-0.1390 (-0.2558, -0.0221)**	**-0.1385 (-0.2553, -0.0216)**
Manitoba		**0.1416 (0.0274, 0.2558)**	**0.1369 (0.0227, 0.2510)**	**0.1369 (0.0228, 0.2511)**
Alberta		0.0630 (-0.0579, 0.1838)	0.0581 (-0.0627, 0.1789)	0.0574 (-0.0634, 0.1782)
British Columbia		**0.1099 (0.0207, 0.1991)**	**0.1098 (0.0206, 0.1990)**	**0.1137 (0.0243, 0.2031)**

Independent Variables	Path II: M→Y Executive function (T2) as the dependent variable			
	Model 0 ($R^2 = 0.59$) β (95% CI)	Model 1 ($R^2 = 0.60$) β (95% CI)	Model 2 ($R^2 = 0.60$) β (95% CI)	Model 3 ($R^2 = 0.60$) β (95% CI)
Education, highest level obtained (ref: university degree)				
Post-secondary diploma/ degree (not university)		**-0.3125 (-0.3863, -0.2386)**	**-0.3053 (-0.3792, -0.2313)**	**-0.2966 (-0.3711, -0.2221)**
Some post-secondary		**-0.3126 (-0.4356, -0.1897)**	**-0.3007 (-0.4237, -0.1777)**	**-0.2897 (-0.4135, -0.1660)**
Secondary school graduation (no post-secondary)		**-0.3736 (-0.4918, -0.2554)**	**-0.3697 (-0.4878, -0.2515)**	**-0.3562 (-0.4750, -0.2374)**
Less than secondary school		**-0.8777 (-1.0476, -0.7078)**	**-0.8433 (-1.0135, -0.6731)**	**-0.8248 (-0.9961, -0.6536)**
Income (ref: ≥ $150,000)				
≥$100,000 and <$150,000		-0.0394 (-0.1347, 0.0558)	-0.0381 (-0.1333, 0.0571)	-0.0346 (-0.1299, 0.0607)
≥$50,000 and <$100,000		**-0.1027 (-0.1960, -0.0093)**	**-0.0961 (-0.1895, -0.0027)**	-0.0912 (-0.1848, 0.0025)
≥$20,000 and <$50,000		**-0.2846 (-0.4039, -0.1653)**	**-0.2632 (-0.3828, -0.1435)**	**-0.2518 (-0.3722, -0.1314)**
<$20,000		**-0.3181 (-0.5139, -0.1222)**	**-0.2715 (-0.4683, -0.0747)**	**-0.2513 (-0.4494, -0.0531)**
Rural (ref: urban)		-0.0510 (-0.1657, 0.0637)	-0.0533 (-0.1679, 0.0613)	-0.0558 (-0.1704, 0.0589)
Physical health				
Self-rated health (ref: excellent)				
Very good			-0.0020 (-0.0826, 0.0787)	-0.0011 (-0.0818, 0.0796)
Good			-0.0688 (-0.1617, 0.0240)	-0.0651 (-0.1581, 0.0280)
Fair			**-0.2305 (-0.3815, -0.0794)**	**-0.2229 (-0.3742, -0.0715)**
Poor			0.1675 (-0.1681, 0.5031)	0.1839 (-0.1521, 0.5199)
Number of chronic conditions (ref: 0)				
1			-0.0255 (-0.1009, 0.0499)	-0.0250 (-0.1004, 0.0505)
2			-0.0284 (-0.1187, 0.0619)	-0.0269 (-0.1172, 0.0635)
3			-0.0786 (-0.1972, 0.0399)	-0.0708 (-0.1897, 0.0480)
4+			-0.1374 (-0.2956, 0.0208)	-0.1281 (-0.2866, 0.0305)
Functional impairment (ref: no impairment)			**-0.2245 (-0.3494, -0.0996)**	**-0.2198 (-0.3448, -0.0948)**
Health behaviours				
Smoking status (ref: never used)				
Former user				-0.0479 (-0.1130, 0.0173)
Current user				-0.0660 (-0.1853, 0.0534)
Alcohol use (ref: non-user)				
Occasional user				0.0781 (-0.0547, 0.2109)
Regular user				0.1050 (-0.0001, 0.2101)

β = Regression coefficient value; CES-D10 = Center for Epidemiologic Studies Short Depression Scale; CI = Confidence interval; M = Mediator; ΔR² = R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex. Values where p<0.05 are in **bolded** font.

Table F4a: Covariate Effects: Sequential Models Adjusting for Covariates in Chunks, Self-Reported Clinical Depression on Functional Social Isolation, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

Independent Variables	Path I: X→M Functional social isolation (T2) as the dependent variable			
	Model 0 ($R^2 = 0.56$) β (95% CI)	Model 1 ($R^2 = 0.57$) β (95% CI)	Model 2 ($R^2 = 0.57$) β (95% CI)	Model 3 ($R^2 = 0.58$) β (95% CI)
Exposure (T1)				
Clinical depression (self-reported)	**3.2737 (1.7612, 4.7862)**	**2.9280 (1.4288, 4.4271)**	**2.5974 (1.0975, 4.0974)**	**2.5072 (1.0071, 4.0072)**
Age (ref: 45-54)				
55-64	0.6671 (-0.0163, 1.3504)	0.5194 (-0.1623, 1.2011)	0.4930 (-0.1919, 1.1779)	0.4795 (-0.2071, 1.1662)
65-75	**1.1324 (0.3790, 1.8859)**	**0.8941 (0.1270, 1.6612)**	**0.9031 (0.1230, 1.6832)**	**0.9215 (0.1360, 1.7071)**
75+	**2.5192 (1.6097, 3.4287)**	**2.3096 (1.3836, 3.2356)**	**2.2740 (1.3272, 3.2207)**	**2.3598 (1.4068, 3.3128)**
Sex (ref: male)				
Female	0.3528 (-0.3759, 1.0816)	0.1151 (-0.6090, 0.8392)	0.1817 (-0.5427, 0.9061)	0.1606 (-0.5642, 0.8853)
Interaction terms				
*Clinical depression * Age 55-64 * Sex*	1.7428 (-0.7351, 4.2206)	1.7800 (-0.6759, 4.2360)	1.7134 (-0.7381, 4.1649)	1.6271 (-0.8239, 4.0781)
*Clinical depression * Age 65-74 * Sex*	0.8908 (-1.9912, 3.7728)	1.1414 (-1.7137, 3.9964)	1.0996 (-1.7512, 3.9504)	1.0652 (-1.7847, 3.9151)
*Clinical depression * Age 75+ * Sex*	**8.0820 (3.7515, 12.4125)**	**8.4119 (4.1201, 12.7038)**	**8.2571 (3.9726, 12.5416)**	**8.2198 (3.9358, 12.5038)**
*Age 55-64 * Sex*	-0.4908 (-1.4783, 0.4968)	-0.6871 (-1.6671, 0.2929)	-0.6360 (-1.6146, 0.3426)	-0.5820 (-1.5609, 0.3969)
*Age 65-74 * Sex*	-0.3815 (-1.4762, 0.7131)	-0.8782 (-1.9682, 0.2118)	-0.8304 (-1.9193, 0.2585)	-0.7462 (-1.8372, 0.3449)
*Age 75+ * Sex*	-0.1494 (-1.4397, 1.1409)	-0.7772 (-2.0766, 0.5222)	-0.8068 (-2.1074, 0.4939)	-0.7254 (-2.0293, 0.5785)
*Clinical depression * Sex*	**-2.0598 (-3.9485, -0.1711)**	**-2.3060 (-4.1777, -0.4343)**	**-2.3157 (-4.1841, -0.4473)**	**-2.2309 (-4.0989, -0.3628)**
*Clinical depression * Age 55-64*	-1.4627 (-3.4229, 0.4976)	-1.2908 (-3.2329, 0.6513)	-1.2704 (-3.2091, 0.6682)	-1.2010 (-3.1394, 0.7373)
*Clinical depression * Age 65-74*	-2.0283 (-4.2989, 0.2422)	-2.0759 (-4.3257, 0.1739)	-1.9977 (-4.2445, 0.2492)	-1.9487 (-4.1947, 0.2974)
*Clinical depression * Age 75+*	**-3.9948 (-7.2808, -0.7087)**	**-3.8817 (-7.1373, -0.6261)**	**-3.6531 (-6.9044, -0.4018)**	**-3.5623 (-6.8133, -0.3112)**
Baseline mediator and outcome (T1)				
Functional social isolation	**0.7413 (0.7301, 0.7525)**	**0.7035 (0.6914, 0.7156)**	**0.6967 (0.6845, 0.7089)**	**0.6953 (0.6831, 0.7075)**
Executive function	**-0.1751 (-0.2450, -0.1053)**	**-0.1019 (-0.1755, -0.0283)**	-0.0710 (-0.1449, 0.0029)	-0.0683 (-0.1424, 0.0057)
Sociodemographic characteristics				
Marital status (ref: partnered)				
Single/never married		**2.8184 (1.9312, 3.7056)**	**2.8717 (1.9859, 3.7575)**	**2.8441 (1.9582, 3.7300)**
Widowed		0.1977 (-0.7407, 1.1361)	0.2714 (-0.6659, 1.2087)	0.2631 (-0.6739, 1.2001)
Divorced		**1.6032 (0.7955, 2.4108)**	**1.6638 (0.8571, 2.4705)**	**1.6188 (0.8120, 2.4255)**
Separated		**1.3958 (0.1572, 2.6344)**	**1.4779 (0.2406, 2.7152)**	**1.4342 (0.1970, 2.6715)**
Lives alone (ref: lives with others)		0.0416 (-0.0320, 0.1152)	0.0456 (-0.0279, 0.1191)	0.0455 (-0.0280, 0.1190)

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Independent Variables	Model 0 (R^2 = 0.56) β (95% CI)	Model 1 (R^2 = 0.57) β (95% CI)	Model 2 (R^2 = 0.57) β (95% CI)	Model 3 (R^2 = 0.58) β (95% CI)
Province (ref: Ontario)				
Quebec		**-0.9674 (-1.5671, -0.3677)**	**-1.0073 (-1.6069, -0.4077)**	**-1.0095 (-1.6106, -0.4084)**
Newfoundland and Labrador		**-1.0773 (-1.7831, -0.3716)**	**-1.0836 (-1.7884, -0.3788)**	**-1.1002 (-1.8052, -0.3952)**
Nova Scotia		-0.6797 (-1.3659, 0.0065)	**-0.7045 (-1.3896, -0.0195)**	**-0.7119 (-1.3969, -0.0268)**
Manitoba		-0.0224 (-0.6929, 0.6480)	-0.0330 (-0.7026, 0.6366)	-0.0375 (-0.7069, 0.6319)
Alberta		0.4870 (-0.2221, 1.1961)	0.4984 (-0.2095, 1.2064)	0.4906 (-0.2173, 1.1985)
British Columbia		-0.1141 (-0.6375, 0.4093)	-0.1454 (-0.6682, 0.3774)	-0.1306 (-0.6544, 0.3933)
Education, highest level obtained (ref: university degree)				
Post-secondary diploma /degree (not university)		**0.4527 (0.0187, 0.8867)**	0.3487 (-0.0854, 0.7828)	0.2758 (-0.1618, 0.7133)
Some post-secondary		0.4303 (-0.2916, 1.1522)	0.3067 (-0.4149, 1.0282)	0.1858 (-0.5400, 0.9115)
Secondary school graduation (no post-secondary)		0.0950 (-0.5992, 0.7892)	-0.0026 (-0.6960, 0.6908)	-0.1099 (-0.8073, 0.5876)
Less than secondary school		-0.2161 (-1.2128, 0.7806)	-0.5341 (-1.5328, 0.4645)	-0.7238 (-1.7288, 0.2812)
Income (ref: ≥ $150,000)				
≥$100,000 and <$150,000		**0.8368 (0.2787, 1.3949)**	**0.7935 (0.2361, 1.3510)**	**0.7597 (0.2020, 1.3174)**
≥$50,000 and <$100,000		**1.1961 (0.6503, 1.7419)**	**1.0805 (0.5347, 1.6263)**	**1.0342 (0.4870, 1.5813)**
≥$20,000 and <$50,000		**2.7053 (2.0079, 3.4027)**	**2.4559 (1.7565, 3.1553)**	**2.3647 (1.6611, 3.0683)**
<$20,000		**4.7256 (3.5810, 5.8702)**	**4.2707 (3.1200, 5.4214)**	**4.1191 (2.9607, 5.2775)**
Rural (ref: urban)		-0.1393 (-0.8128, 0.5341)	-0.1105 (-0.7828, 0.5618)	-0.1034 (-0.7757, 0.5688)
Physical health				
Self-rated health (ref: excellent)				
Very good			0.4020 (-0.0700, 0.8739)	0.3858 (-0.0860, 0.8577)
Good			**1.4367 (0.8981, 1.9752)**	**1.3790 (0.8397, 1.9183)**
Fair			**2.2359 (1.3647, 3.1072)**	**2.1503 (1.2777, 3.0229)**
Poor			**2.3900 (0.4388, 4.3411)**	**2.2251 (0.2723, 4.1778)**
Number of chronic conditions (ref:0)				
1			0.2453 (-0.1972, 0.6878)	0.2560 (-0.1865, 0.6985)
2			0.1009 (-0.4296, 0.6314)	0.1116 (-0.4192, 0.6424)
3			**0.7600 (0.0639, 1.4562)**	**0.7609 (0.0635, 1.4583)**
4+			0.5299 (-0.3989, 1.4588)	0.5209 (-0.4095, 1.4513)
Functional impairment (ref: no impairment)			0.1999 (-0.5362, 0.9360)	0.1587 (-0.5776, 0.8951)

Health behaviours	
Smoking status (ref: never used)	
Former user	0.1712 (-0.2120, 0.5544)
Current user	**1.3685 (0.6686, 2.0685)**
Alcohol use (ref: non-user)	
Occasional user	-0.0551 (-0.8333, 0.7232)
Regular user	-0.3052 (-0.9214, 0.3109)

β = Regression coefficient value; CI = Confidence interval; M = Mediator; ΔR^2= R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex.
Values where p<0.05 are in **bolded** font.

Table F4b. Covariate Effects: Sequential Models Adjusting for Covariates in Chunks, Functional Social Isolation on Executive Function Controlling for Self-Reported Clinical Depression, Canadian Longitudinal Study on Aging Comprehensive Cohort (n=14,133)

	Path II: M→Y			
	Executive function (T2) as the dependent variable			
Independent Variables	Model 0 ($R^2 = 0.59$) β (95% CI)	Model 1 ($R^2 = 0.60$) β (95% CI)	Model 2 ($R^2 = 0.60$) β (95% CI)	Model 3 ($R^2 = 0.60$) β (95% CI)
Exposure (T1)				
Clinical depression (self-reported)	**-0.0989 (-0.1849, -0.0129)**	**-0.0897 (-0.1755, -0.0039)**	-0.0508 (-0.1379, 0.0363)	-0.0467 (-0.1339, 0.0404)
Mediator (T2)				
Functional social isolation	-0.0019 (-0.0061, 0.0023)	-0.0010 (-0.0052, 0.0032)	-0.0007 (-0.0049, 0.0035)	-0.0006 (-0.0048, 0.0037)
Age (ref: 45-54)				
55-64	**-0.1863 (-0.2946, -0.0779)**	**-0.1615 (-0.2699, -0.0530)**	**-0.1573 (-0.2663, -0.0484)**	**-0.1550 (-0.2642, -0.0458)**
65-75	**-0.7316 (-0.8561, -0.6070)**	**-0.6753 (-0.8033, -0.5473)**	**-0.6666 (-0.7964, -0.5367)**	**-0.6645 (-0.7950, -0.5340)**
75+	**-1.0728 (-1.2369, -0.9087)**	**-0.9919 (-1.1597, -0.8240)**	**-0.9561 (-1.1269, -0.7854)**	**-0.9581 (-1.1293, -0.7868)**
Sex (ref: male)				
Female	0.0119 (-0.0499, 0.0736)	**0.0743 (0.0112, 0.1375)**	**0.0813 (0.0175, 0.1451)**	**0.0791 (0.0149, 0.1433)**
Interaction terms				
*Functional social isolation * Age 55-64*	-0.0035 (-0.0083, 0.0012)	-0.0035 (-0.0082, 0.0012)	-0.0033 (-0.0081, 0.0014)	-0.0034 (-0.0081, 0.0014)
*Functional social isolation * Age 65-74*	-0.0027 (-0.0081, 0.0027)	-0.0028 (-0.0081, 0.0026)	-0.0027 (-0.0080, 0.0027)	-0.0028 (-0.0081, 0.0026)
*Functional social isolation * Age 75+*	**-0.0123 (-0.0185, -0.0060)**	**-0.0125 (-0.0187, -0.0063)**	**-0.0125 (-0.0187, -0.0062)**	**-0.0125 (-0.0187, -0.0063)**
Baseline Mediator and Outcome (T1)				
Functional social isolation	-0.0010 (-0.0038, 0.0018)	-0.0004 (-0.0033, 0.0024)	-0.0001 (-0.0030, 0.0027)	-0.0001 (-0.0029, 0.0028)
Executive function	**0.7323 (0.7204, 0.7443)**	**0.6974 (0.6849, 0.7100)**	**0.6938 (0.6812, 0.7064)**	**0.6933 (0.6807, 0.7059)**
Sociodemographic Characteristics				
Marital status (ref: partnered)				
Single/never married		0.0654 (-0.0862, 0.2170)	0.0579 (-0.0937, 0.2094)	0.0594 (-0.0922, 0.2110)
Widowed		-0.0984 (-0.2574, 0.0606)	-0.0955 (-0.2545, 0.0634)	-0.0971 (-0.2561, 0.0618)
Divorced		0.0152 (-0.1226, 0.1529)	0.0107 (-0.1270, 0.1484)	0.0127 (-0.1251, 0.1504)
Separated		0.0845 (-0.1266, 0.2957)	0.0732 (-0.1379, 0.2843)	0.0736 (-0.1376, 0.2847)
Lives alone (ref: lives with others)		0.0041 (-0.0085, 0.0166)	0.0038 (-0.0087, 0.0164)	0.0037 (-0.0088, 0.0162)
Province (ref: Ontario)				
Quebec		0.0634 (-0.0389, 0.1657)	0.0670 (-0.0353, 0.1694)	0.0649 (-0.0378, 0.1675)
Newfoundland and Labrador		**-0.1780 (-0.2983, -0.0577)**	**-0.1829 (-0.3032, -0.0627)**	**-0.1828 (-0.3031, -0.0624)**
Nova Scotia		**-0.1427 (-0.2597, -0.0258)**	**-0.1399 (-0.2568, -0.0231)**	**-0.1394 (-0.2562, -0.0225)**
Manitoba		**0.1424 (0.0282, 0.2567)**	**0.1373 (0.0231, 0.2515)**	**0.1374 (0.0232, 0.2515)**
Alberta		0.0643 (-0.0566, 0.1851)	0.0587 (-0.0621, 0.1794)	0.0580 (-0.0628, 0.1787)
British Columbia		**0.1101 (0.0209, 0.1993)**	**0.1100 (0.0208, 0.1992)**	**0.1139 (0.0246, 0.2033)**

Independent Variables	Path II: M→Y Executive function (T2) as the dependent variable			
	Model 0 ($R^2 = 0.59$) β (95% CI)	Model 1 ($R^2 = 0.60$) β (95% CI)	Model 2 ($R^2 = 0.60$) β (95% CI)	Model 3 ($R^2 = 0.60$) β (95% CI)
Education, highest level obtained (ref: university degree)				
Post-secondary diploma/ degree (not university)		**-0.3143 (-0.3882, -0.2404)**	**-0.3059 (-0.3798, -0.2319)**	**-0.2972 (-0.3717, -0.2227)**
Some post-secondary		**-0.3154 (-0.4383, -0.1924)**	**-0.3018 (-0.4248, -0.1788)**	**-0.2907 (-0.4144, -0.1670)**
Secondary school graduation (no post-secondary)		**-0.3800 (-0.4982, -0.2617)**	**-0.3729 (-0.4911, -0.2546)**	**-0.3591 (-0.4780, -0.2402)**
Less than secondary school		**-0.8917 (-1.0614, -0.7220)**	**-0.8498 (-1.0200, -0.6796)**	**-0.8309 (-1.0023, -0.6596)**
Income (ref: ≥ $150,000)				
≥$100,000 and <$150,000		-0.0398 (-0.1351, 0.0555)	-0.0380 (-0.1333, 0.0572)	-0.0346 (-0.1299, 0.0607)
≥$50,000 and <$100,000		**-0.1042 (-0.1975, -0.0108)**	**-0.0963 (-0.1897, -0.0029)**	-0.0915 (-0.1851, 0.0022)
≥$20,000 and <$50,000		**-0.2867 (-0.4060, -0.1674)**	**-0.2631 (-0.3828, -0.1434)**	**-0.2519 (-0.3723, -0.1314)**
<$20,000		**-0.3236 (-0.5193, -0.1278)**	**-0.2719 (-0.4688, -0.0751)**	**-0.2519 (-0.4501, -0.0537)**
Rural (ref: urban)		-0.0509 (-0.1656, 0.0638)	-0.0533 (-0.1679, 0.0613)	-0.0558 (-0.1704, 0.0589)
Physical health				
Self-rated health (ref: excellent)				
Very good			-0.0045 (-0.0850, 0.0760)	-0.0035 (-0.0840, 0.0770)
Good			-0.0747 (-0.1666, 0.0172)	-0.0707 (-0.1627, 0.0214)
Fair			**-0.2421 (-0.3907, -0.0934)**	**-0.2340 (-0.3830, -0.0851)**
Poor			0.1496 (-0.1831, 0.4823)	0.1666 (-0.1665, 0.4997)
Number of chronic conditions (ref: 0)				
1			-0.0246 (-0.1001, 0.0508)	-0.0242 (-0.0997, 0.0512)
2			-0.0266 (-0.1170, 0.0638)	-0.0252 (-0.1157, 0.0652)
3			-0.0765 (-0.1951, 0.0422)	-0.0689 (-0.1878, 0.0500)
4+			-0.1341 (-0.2925, 0.0243)	-0.1251 (-0.2838, 0.0336)
Functional impairment (ref: no impairment)			**-0.2240 (-0.3490, -0.0990)**	**-0.2195 (-0.3446, -0.0944)**
Health behaviours				
Smoking status (ref: never used)				
Former user				-0.0479 (-0.1130, 0.0173)
Current user				-0.0659 (-0.1853, 0.0534)
Alcohol use (ref: non-user)				
Occasional user				0.0784 (-0.0544, 0.2112)
Regular user				0.1047 (-0.0004, 0.2098)

β = Regression coefficient value; CI = Confidence interval; M = Mediator; ΔR^2= R-square change; SE = Standard error; T1 = Baseline; T2 = Follow-up; W = Age; X = Exposure; Y = Outcome; Z= Sex. Values where $p<0.05$ are in **bolded** font.

Appendix G

Model Diagnostics

The figures below illustrate assessments of linearity (Figures G1-G3) and standard model diagnostic plots for linear regression (Figures G4-G7). See Section 5.2.6 for a summary of the model diagnostic figures included below.
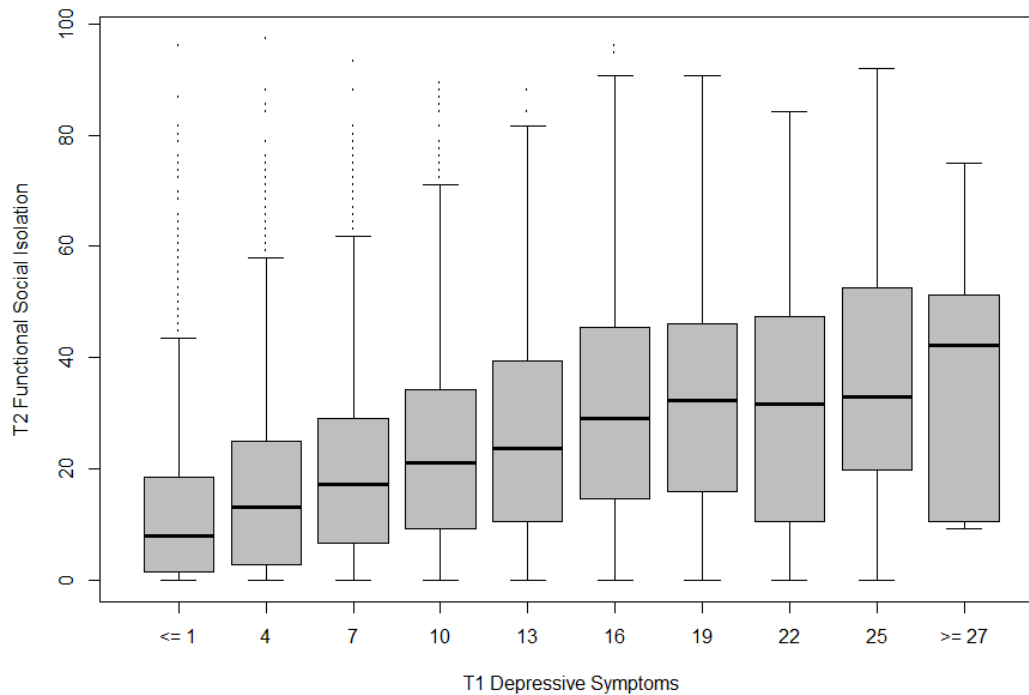

Figure G1: Visual Depiction of the Linear Relationship Between T1 Depressive Symptoms and T2 Functional Social Isolation
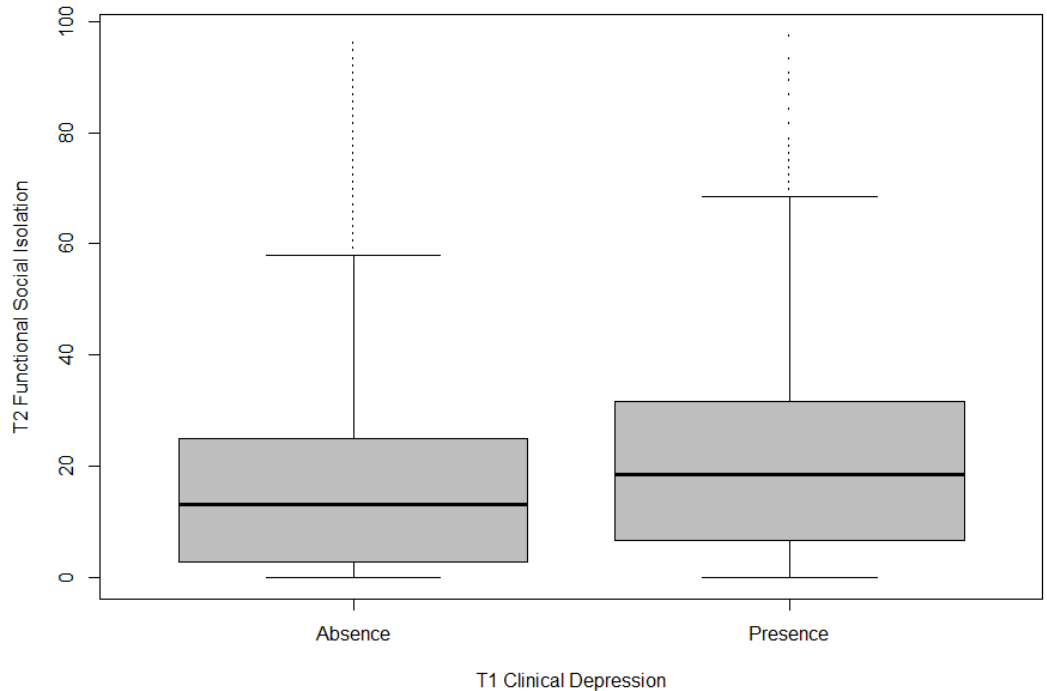
Figure G2: Visual Depiction of the Relationship Between T1 Self-Reported Clinical Depression and T2 Functional Social Isolation
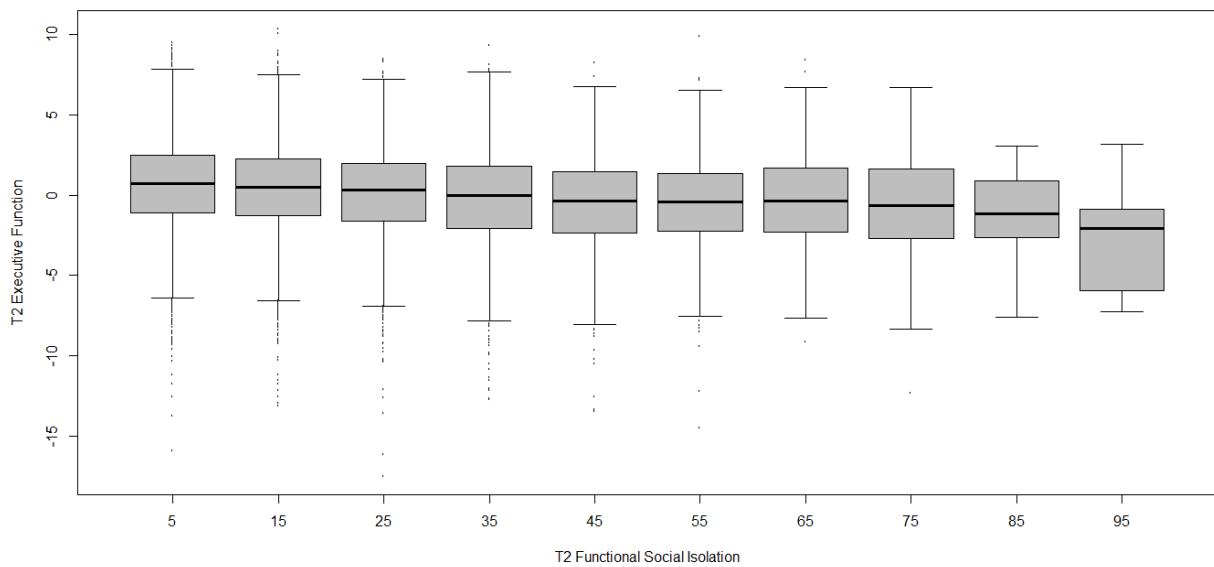

Figure G3: Visual Depiction of the Linear Relationship Between T2 Functional Social Isolation and T2 Executive Function
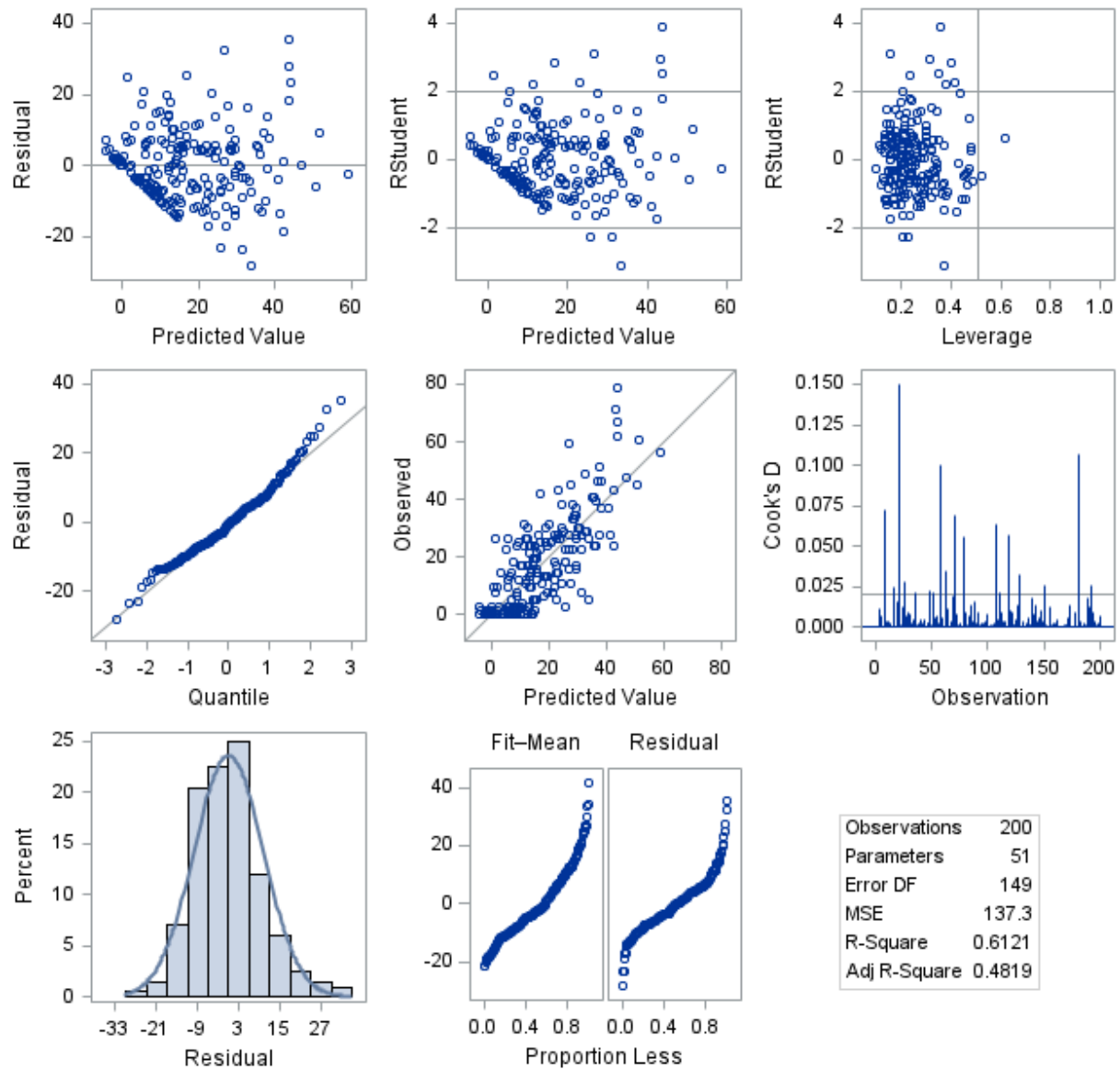
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Figure G4: Fit Diagnostics for a Fully Adjusted Path I Model (X=Depressive Symptoms) on a Random Sample of 200 Participants

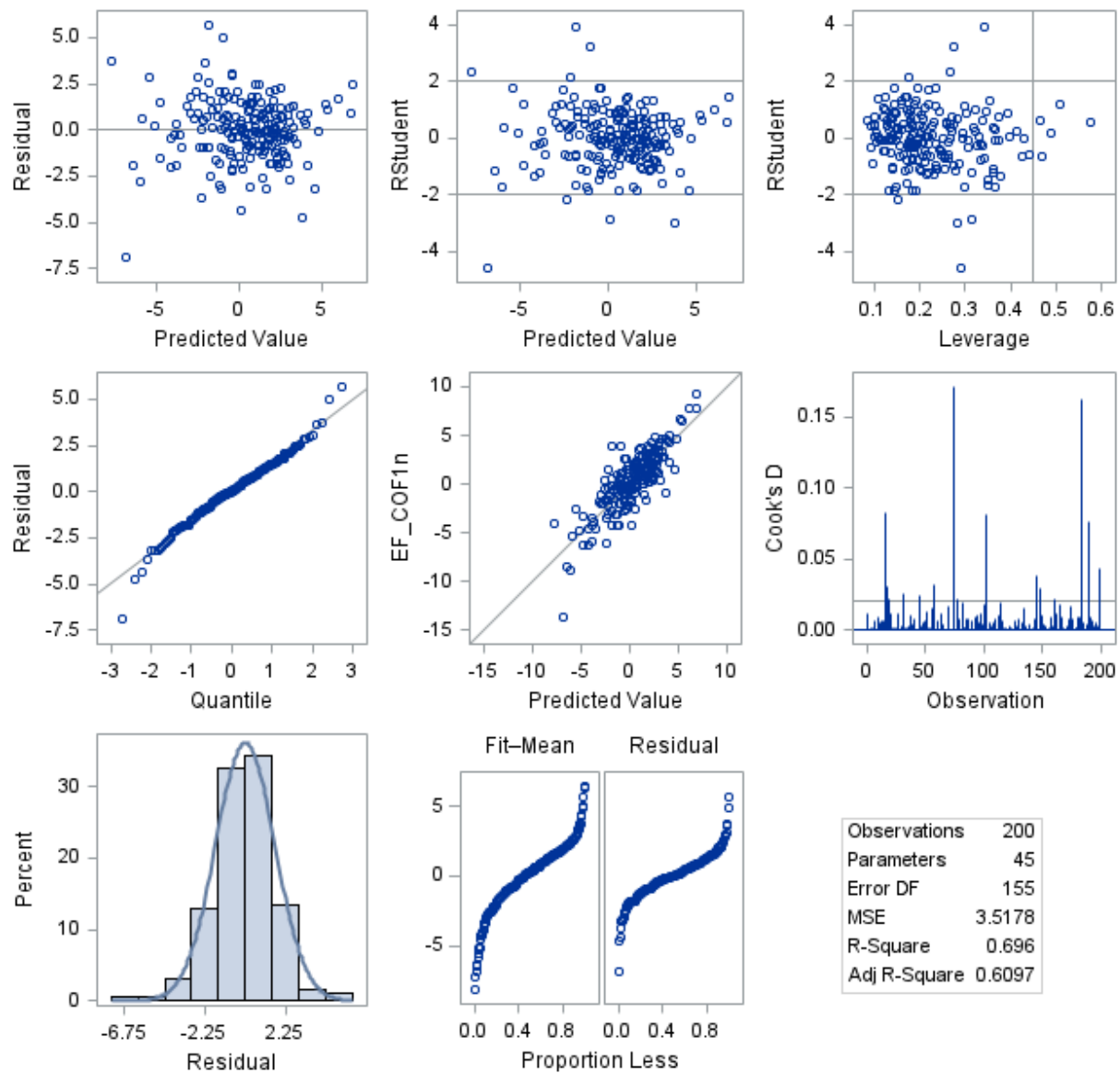**Figure G5: Fit Diagnostics for a Fully Adjusted Path II Model (X=Depressive Symptoms) on a Random Sample of 200 Participants**

Figure G6: Fit Diagnostics for a Fully Adjusted Path I Model (X=Self-Reported Clinical Depression) on a Random Sample of 200 Participants
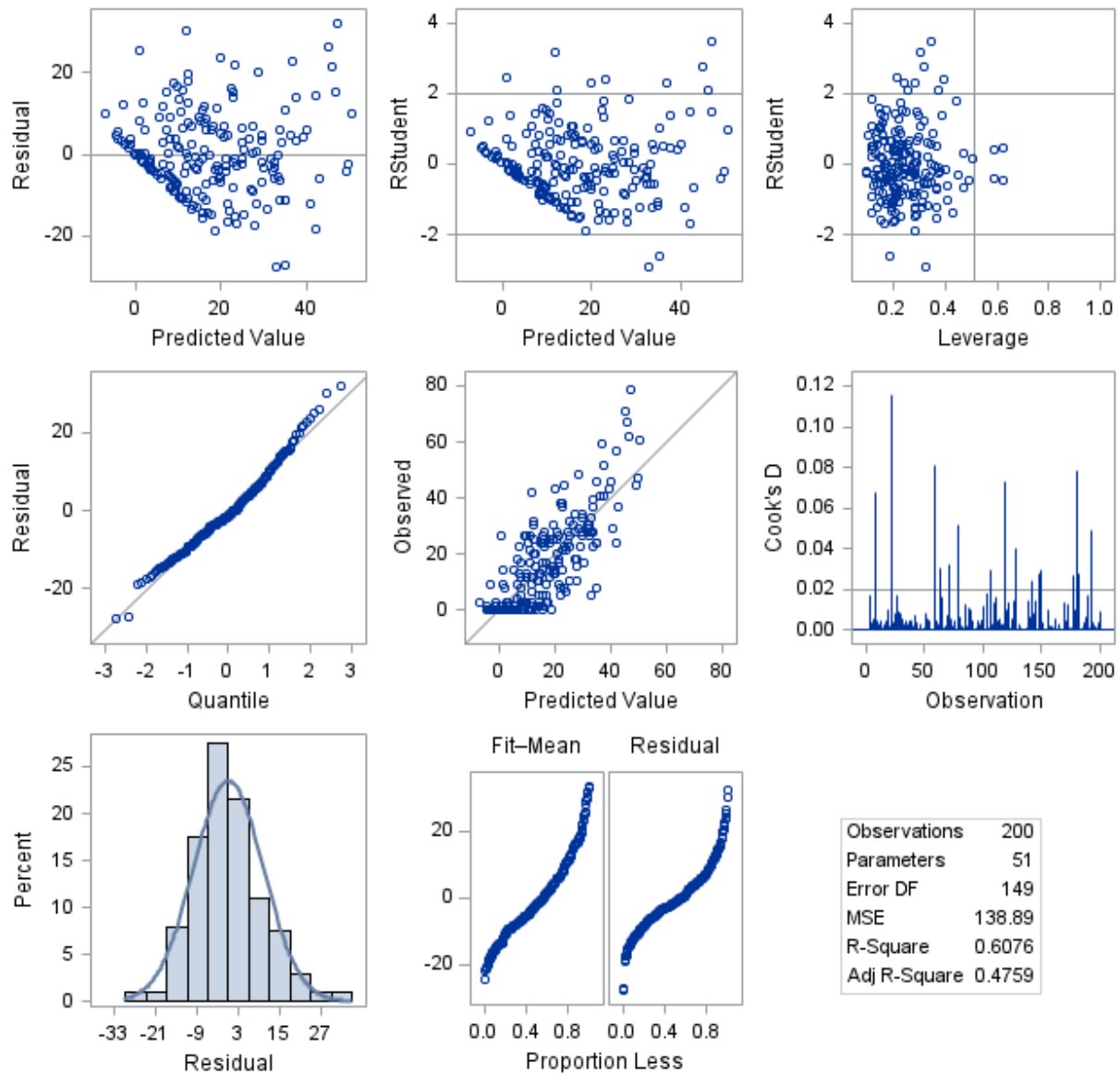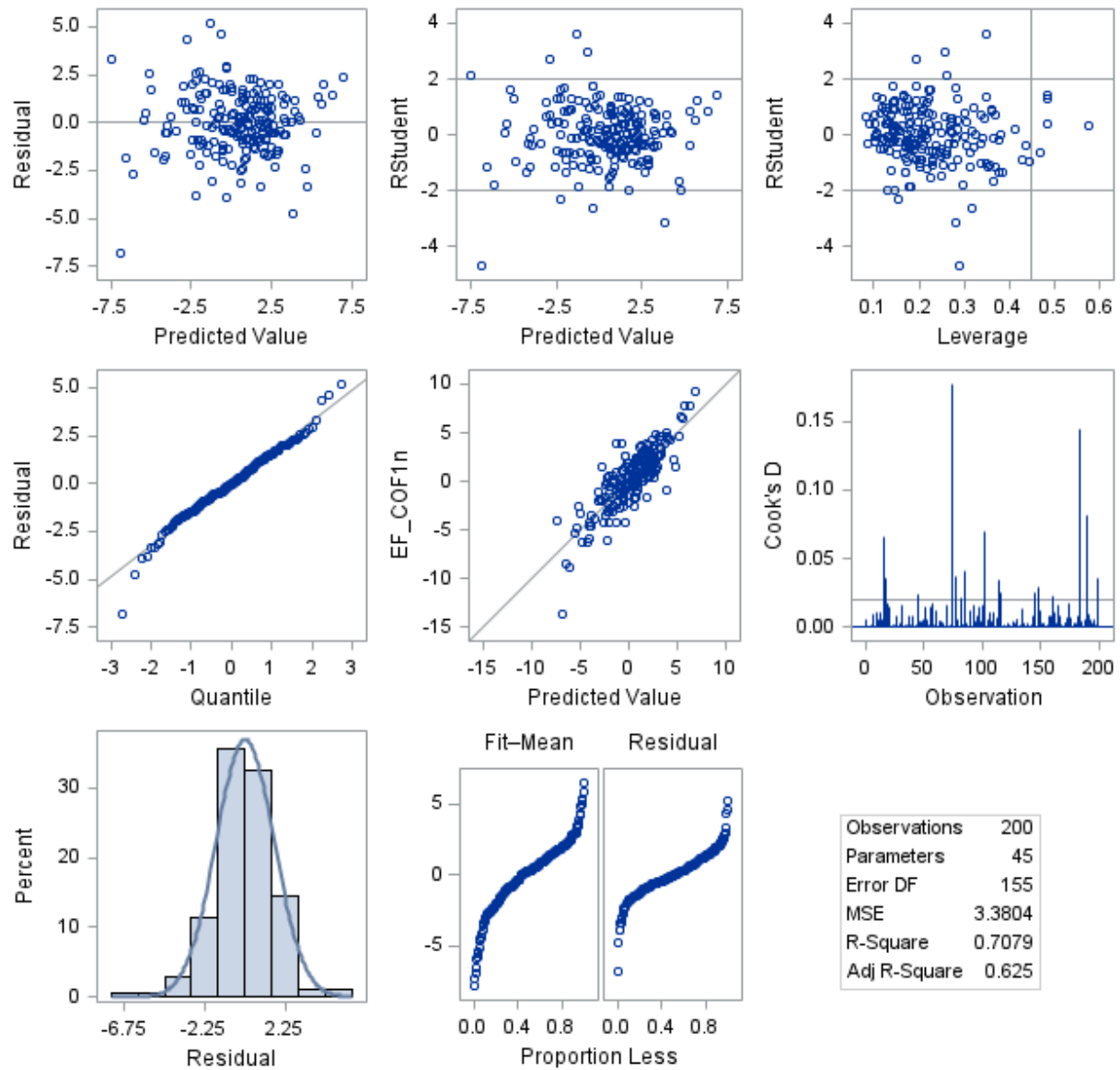
Figure G7: Fit Diagnostics for a Fully Adjusted Path II Model (X=Self-Reported Clinical Depression) on a Random Sample of 200 Participants

Appendix H
Analysis of Missing Data

Missing data on T2 executive function was associated with sample characteristics at T1, as shown in Table H1. See Section 5.2.7 for a summary of the table below.

Table H1: Predictors of Missing Data on Follow-Up Executive Function, Canadian Longitudinal Study on Aging (CLSA) Comprehensive Cohort (n=27,765)[‡‡]

Characteristics (T1)[†]	Executive function (T2)	
	Missing (n=8746)	Not missing (n=19,019)
Depression		
CES-D10		
$\bar{x}$ *(SD)*	**5.48 (4.81)**	**5.04 (4.50)**
Md (IQR)	4.00 (6.00)	4.00 (5.00)
Clinical depression (self-reported) (%)		
Presence	**33.91**	**66.09**
Absence	**30.95**	**69.05**
Functional social isolation		
$\bar{x}$ *(SD)*	**19.89 (17.99)**	**17.95 (16.70)**
Md (IQR)	15.79 (25.00)	14.47 (23.68)
Executive function		
$\bar{x}$ *(SD)*	**-0.17 (3.16)**	**0.33 (2.82)**
Md (IQR)	0.04 (4.03)	0.46 (3.63)
Sociodemographic (%)		
Age group		
45-54	**27.98**	**72.02**
55-64	**29.74**	**70.26**
65-74	**32.61**	**67.39**
75+	**38.94**	**61.06**
Sex		
Female	**32.58**	**67.42**
Male	**30.38**	**69.62**
Marital status		
Partnered	**29.64**	**70.36**
Single/never married	**34.00**	**66.00**
Widowed	**38.53**	**61.47**
Divorced	**35.23**	**64.77**
Separated	**33.95**	**66.05**
Living arrangements		
Lives alone	**36.16**	**63.84**
Lives with others	**30.18**	**69.82**
Province		
Alberta	**31.88**	**68.12**
British Columbia	**27.90**	**72.10**
Manitoba	**36.14**	**63.86**
Newfoundland and Labrador	**18.46**	**81.54**
Nova Scotia	**35.04**	**64.96**
Ontario	**25.22**	**74.78**
Quebec	**42.31**	**57.69**
Education, highest level obtained		
Less than secondary school	**42.46**	**57.54**
Secondary school (no post-secondary)	**35.17**	**64.83**
Some post-secondary	**30.86**	**69.14**
Post-secondary education (not university)	**32.52**	**67.48**

Post-secondary education (university)	**28.95**	**71.05**
Income		
<$20,000	**42.06**	**57.94**
≥$20,000 and <$50,000	**36.75**	**63.25**
≥$50,000 and <$100,000	**31.26**	**68.74**
≥$100,000 and <$150,000	**27.54**	**72.46**
≥$150,000	**25.36**	**74.64**
Rural/urban residence		
Rural	**33.42**	**66.58**
Urban	**31.26**	**68.74**
Physical health (%)		
Self-rated health		
Excellent	**28.94**	**71.06**
Very good	**30.06**	**69.94**
Good	**33.57**	**66.43**
Fair	**36.35**	**63.65**
Poor	**44.84**	**55.16**
Number of chronic conditions		
0	**28.70**	**71.30**
1	**30.89**	**69.11**
2	**32.65**	**67.35**
3	**33.32**	**66.68**
4+	**37.94**	**62.06**
Functional impairment		
Yes	**41.38**	**58.62**
No	**30.44**	**69.56**
Health behaviours (%)		
Smoking status		
Current user	**35.88**	**64.12**
Former user	**32.24**	**67.76**
Never user	**30.06**	**69.94**
Alcohol use		
Non-user	**34.77**	**65.23**
Occasional user	**34.17**	**65.83**
Regular user	**30.39**	**69.61**

CES-D10 = Center for Epidemiologic Studies Short Depression Scale; *IQR* = interquartile range; *Md* = median; *SD* = standard deviation; T1 = Baseline; T2 = Follow-up; $\bar{x}$ = mean.

Row denominators are used for proportions. Tests used: Chi-square, t-test. Values where p < 0.05 are **bolded.**