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Is My Loneliness Killing Me? Effects of Loneliness and Social Isolation on Transitions Between Cognitive Status Categories and Death

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Abstract

Loneliness and social isolation are associated with numerous adverse physical and psychological health outcomes in older adulthood, including cognitive impairment and mortality risk. Yet, how the individual and joint effects of loneliness and social isolation contribute to these outcomes remains unclear, particularly given the interplay between individual differences (loneliness) and environmental factors (social isolation) in shaping these important health outcomes in older adulthood (i.e., person-environment interactions). We used Cox regression, logistic regression, and multistate survival models to systematically investigate the *individual* and *adjusted* associations

among loneliness, social isolation, cognitive aging outcomes, and mortality risk. Further, extensive between-study variability in operational definitions, modelling approaches, and covariate adjustments may be contributing to mixed results in the existing literature. In this Registered Report, we applied a multi-study approach (i.e., coordinated data analysis) in which independent but identical models were fit across 11 longitudinal studies representing participants from 18 countries (N_{total}=175,070). Random effects meta-analyses synthesized results across studies, showing that loneliness was consistently associated with an elevated risk of cognitive impairment and mortality across statistical approaches, even after adjusting for social isolation. Conversely, social isolation was not consistently associated with cognitive impairment, and showed weaker associations with mortality risk. Together, our findings suggest that loneliness is a robust, proximal predictor of major aging outcomes and highlight avenues for theory development, strategies to strengthen cognitive resilience and independence in older adulthood, and more efficient resource allocation of public health resources.

Keywords

loneliness; social isolation; cognitive impairment; dementia; older adulthood; multi-state survival models; mortality

Introduction

Social connection and social contact are vital aspects of the human experience, undeniably essential for everything from development (Hartup, 1989; Orben et al., 2020) and brain function (Hari et al., 2015), to well-being (Diener, 2009) and health (Kaplan et al., 1977; Uchino, 2006). Thus, it is unsurprising that the absence of social connection and contact (i.e., loneliness and social isolation) is contributing to a major public health concern (Holt-Lunstad, 2022), posing problems across countries and cultures (Fakoya et al., 2020; Fokkema et al., 2012; Miyawaki, 2015; Surkalim et al., 2022). Indeed, the United States Surgeon General has declared loneliness and social isolation a public health epidemic (U.S. Department of Health and Human Services, 2023), highlighting the urgency of addressing these issues not only in the United States but also globally. This declaration aligns with growing international concerns, exemplified by initiatives such as the UK's appointment of a Minister for Loneliness in 2018 (UK Government, 2018).

Individuals across the entire lifespan report experiencing loneliness and social isolation (Cacioppo et al., 2011; Lee et al., 2019; Röhr et al., 2021; Twenge et al., 2021). While loneliness is most prevalent among adolescents under 25 years and adults 65+ years (Beam & Kim, 2020; Victor & Yang, 2012), both loneliness and social isolation are a substantial concern for some older adults (Courtin & Knapp, 2017; d'Hombres et al., 2021; Donovan & Blazer, 2020; Freedman & Nicolle, 2020; National Academies of Sciences, 2020; Victor & Yang, 2012). Notably, both loneliness and social isolation are associated with several adverse physical and psychological health outcomes for the aging demographic (Cornwell & Waite, 2009; Coyle & Dugan, 2012; Donovan & Blazer, 2020; Holt-Lunstad, 2017; Ong et al., 2016; Prohaska et al., 2020). For example, loneliness and social isolation are linked to cognitive decline (Boss et al., 2015; Samtani et al., 2022), depressive symptoms (Cacioppo

et al., 2006), poor sleep quality (Benson et al., 2021), heart disease (Hakulinen et al., 2018; Hu et al., 2021), and stroke (Hakulinen et al., 2018; Valtorta et al., 2016) in older adulthood (see also, Courtin & Knapp, 2017).

Given shifting aging demographics worldwide, there is a pressing need to describe and address the destructive impact of loneliness and social isolation. Cognitive impairment and mortality represent two of the most significant challenges to healthy aging, with profound implications for individual well-being and public health systems. Importantly, while there is not yet a cure for severe cognitive impairment (e.g., Alzheimer's disease and related dementias), extensive research suggests that adherence to a healthy lifestyle, including maintaining social connections and contact, may mitigate symptoms or slow progression to dementia (Di Marco et al., 2014; Litke et al., 2021; Zhang et al., 2022). Thus, understanding the roles of loneliness and social isolation in cognitive aging offers promising avenues for intervention. In the current study, we used a multi-study approach (i.e., coordinated data analysis) across 11 independent studies to investigate the individual and adjusted effects of loneliness and social isolation on the risk of cognitive impairment and mortality, indicators that are paramount to optimal aging and development.

Theoretical and Empirical Distinctions: Loneliness and Social Isolation

Conceptually, loneliness and social isolation are often considered in tandem or used interchangeably (Perissinotto et al., 2019), yet there are important distinctions between them. Loneliness is characterized by a feeling of distress arising from a discrepancy between desired and actual social connection (Smoyak, 1984), regardless of the size or density of an individual's social network. Conversely, social isolation is the tangible state of impoverished social contact with others (Ong et al., 2016). These distinctions have important implications for the pathways through which they may influence health outcomes, as well as important theoretical implications. In their seminal discussion of the social psychological theory of loneliness, Peplau and Perlman (1979) highlighted how loneliness and social isolation are not synonyms, but instead reflect the discrepancy between desired and achieved level of social interaction. Given individual differences in sociability between people (Soto & John, 2017), as well as differences in implications of objective versus subjective indicators of social well-being for health (Fiorillo & Sabatini, 2011), recognizing the distinction between subjective and objective social experiences is essential. That is, the distinction hinges on perception, wherein loneliness is a feeling of distress that arises alongside *perceived* social isolation (Cornwell & Waite, 2009) and social isolation is *objectively* being alone (Donovan & Blazer, 2020). Thus, akin to the transactional theory of stress and coping (Lazarus & Folkman, 1984), loneliness may be viewed as resulting from a transactional process between a person and their environment, whereas social isolation may be viewed as the objective, environmental state. Investigating the individual and adjusted effects of loneliness and social isolation provides opportunities to examine the relative importance and interplay between individual differences (loneliness) and environmental factors (social isolation) in shaping health outcomes (i.e., person-environment interactions).

Notably, loneliness has been conceptualized as a relatively stable individual difference: some individuals desire more social connections (Cacioppo & Patrick, 2008), and some

individuals are more likely to experience loneliness, regardless of the social environment (Marangoni & Ickes, 1989). Research focusing on daily life experiences of older adults has emphasized the moderating role of other individual differences in the experience of loneliness, as well as the importance of research differentiating loneliness and social isolation: although all participants who experienced social interactions subsequently reported lower momentary loneliness, older adults who were higher in trait loneliness benefited more (i.e., reported less momentary loneliness) following social interactions (Zhaoyang et al., 2022). This research is consistent with theories emphasizing that individuals scoring higher in trait loneliness have heightened hypersensitivity and reactivity to socially relevant stimuli (Cacioppo et al., 2009), as well as the positive feedback loop between loneliness and social isolation. Specifically, feelings of loneliness may elicit hypervigilance for social threats, and the perception of the world as a lonely, unsafe place may prompt lonely individuals to distance themselves socially, leading to further expectations of negative interactions accompanied by heightened emotional responses (Hawkley & Cacioppo, 2010). These dynamics reflect reactive person–environment transactions, in which individual differences in loneliness shape how social environments are interpreted and responded to, with downstream implications for social isolation. Yet, despite the intimate connection between loneliness and isolation, there are individual differences in the extent to which individuals perceive loneliness in the context of social isolation.

Thus, appropriately teasing apart the individual and adjusted effects[1] of loneliness and social isolation on health outcomes (i.e., incremental validity), including on the risk of cognitive impairment and mortality in older adulthood, across several longitudinal studies of aging may provide opportunities to inform theory and intervention strategies. For instance, interventions targeting loneliness may focus on management of emotion regulation and perceived stress, whereas interventions targeting social isolation may focus on lifestyle changes. However, several studies investigating social isolation have not accounted for loneliness (e.g., Chen et al., 2011; Crooks et al., 2008; James et al., 2011; Valenzuela et al., 2011; Zhang et al., 1999) and vice versa (e.g., Freak-Poli et al., 2022; Lobo et al., 2008; Sundström et al., 2020).

The Prevalence of Loneliness and Social Isolation

Loneliness and social isolation can affect individuals of all ages, genders, and cultural backgrounds. The prevalence of loneliness in older adults varies across cultures and measurement approaches, with estimates ranging from 10% to 40% (Dykstra, 2009; Ong et al., 2016; Victor et al., 2000). The prevalence of loneliness is higher among those who are widowed or never married (Cohen-Mansfield et al., 2016; Dahlberg et al., 2022; Fried et al., 2015) or experience poor health (Cohen-Mansfield et al., 2016; Dahlberg et al., 2022).

[1]To ensure clarity in our analyses and interpretations, we define our key terms as follows: a) Individual associations: These refer to the relationship between a single predictor (loneliness or social isolation) and an outcome, without adjusting for the other predictor. These associations represent the total effect of each social factor, which may include both direct effects and effects that operate through the other social factor. b) Adjusted associations: These refer to the relationship between a predictor and an outcome while statistically controlling for the other predictor. These associations represent the unique contribution of each social factor, over and above what is shared with the other factor. We chose these terms to avoid potential misconceptions: a) ‘Individual’ is preferred over ‘unique’ because the unadjusted associations are not necessarily unique to each predictor, as they may include shared variance. b) ‘Adjusted’ is preferred over ‘independent’ because even after statistical adjustment, the predictors may not be truly independent due to their conceptual and empirical overlap.

Similarly, the prevalence of social isolation is higher for individuals who are retired (Mullins et al., 1991), 65 years and older (Mullins et al., 1991), or experience chronic pain (Blyth & Noguchi, 2017). Research also finds that self-reported loneliness and social isolation are more common in older adults with unacknowledged hearing loss (Mick & Pichora-Fuller, 2016) and communication difficulties and disorders (Palmer et al., 2016). Thus, many of the factors associated with heightened prevalence of loneliness and social isolation highlight the importance of identifying, investigating, and delineating ways in which research can support older adults who are experiencing loneliness and/or social isolation. Given the established prevalence of loneliness and social isolation among older adults, understanding the extent to which loneliness and social isolation are predictive risk factors for adverse outcomes is essential from a public health perspective. In the current project we focus on the extent to which loneliness and social isolation are associated with cognitive aging processes and mortality risk.

Cognitive Outcomes and Mortality Risk in Older Adulthood

There are extensive individual differences in cognitive functioning in older adulthood, ranging from what is expected in normal aging to the more progressed state of severe cognitive impairment (e.g., dementia). Between these ends of the spectrum, mild cognitive impairment (MCI) is used to characterize or diagnose individuals who report cognitive complaints and decline that is not severe enough to interfere with day-to-day activities or warrant a dementia diagnosis (Petersen et al., 1999). In other words, older adults can be categorized as having 1) no cognitive impairment, 2) mildly impaired cognitive functioning (e.g., MCI), or 3) severely impaired cognitive functioning (e.g., dementia)[2] (see Supplementary Text 1 for a Glossary of cognitive terms and mapping of cognitive status categories to cognitive terms). Transitioning between these cognitive status categories is not necessarily a linear process. Specifically, MCI (i.e., mildly impaired cognitive functioning) increases the risk of dementia (i.e., severely impaired cognitive functioning) (*see* Bruscoli & Lovestone, 2004), but not all individuals with MCI will progress to dementia (Kaduszkiewicz et al., 2014; Visser et al., 2006). For instance, in a population-based cohort of older adults (N=2050), only 29% of individuals with prevalent or incident MCI progressed to dementia over a median follow-up of 5 years (Roberts et al., 2014). However, compared to individuals with no cognitive impairment, individuals with MCI had a substantially elevated risk of dementia (Hazard Ratio [*HR*]=23.2, 95% Confidence Interval [*CI*] [14.4, 37.2]) (Roberts et al., 2014).

Individuals with mildly impaired cognitive functioning may also revert to no cognitive impairment (Roberts et al., 2014). Based on older adults with MCI (N=567), 7% reverted

[2]Mildly impaired cognitive functioning is a primary symptom of MCI, while severely impaired cognitive functioning is a primary symptom of dementia. The terms MCI and dementia typically reflect clinical diagnoses, though some researchers will operationalize MCI or dementia based on performance on cognitive tests. When we refer to the current project (including research questions, hypotheses, and analytic approaches), we use the terms “mildly impaired cognitive functioning” and “severely impaired cognitive functioning” rather than “MCI” and “dementia”, as not all of the datasets meeting eligibility involved clinical MCI or dementia diagnoses. That is, although some datasets included clinical diagnoses based on clinical conferences (e.g., Rush MAP), we will conceptually harmonize cognitive status categories at the lowest possible denominator (i.e., mildly impaired and severely impaired cognitive functioning). When we refer to previous research investigating cognitive outcomes, we use the terminology that was originally used (e.g., when researchers investigated the “risk of MCI” or the “risk of dementia”) to more accurately reflect the outcomes reported in the literature.

to no cognitive impairment when assessed two years later (Welstead et al., 2021). Yet individuals who do revert to no cognitive impairment (i.e., transition backward) still remain at higher risk of incident dementia (Koepsell & Monsell, 2012). The increased risk of dementia is approximately 6.6-fold in individuals who were diagnosed with MCI and reverted back to no cognitive impairment compared to individuals who never received an MCI diagnosis, suggesting that mildly impaired cognitive functioning has critical prognostic implications for eventual dementia diagnosis (Koepsell & Monsell, 2012).

Finally, cognitive impairment also increases the risk of mortality (Rajan et al., 2014; Taniguchi et al., 2019; Wilson et al., 2006), *and* the risk of both cognitive impairment and mortality increase alongside older age. These age-related links between cognitive impairment and mortality emphasize the importance of simultaneously accounting for both cognitive outcomes and mortality risk when investigating the effect of predictive factors on any of these outcomes. That is, longitudinal panel datasets repeatedly assess participants across several years, while also tracking participant deaths during follow-up occasions (and sometimes beyond). Using these longitudinal datasets, the majority of the existing literature treats the risk of mildly impaired cognitive functioning (e.g., MCI), severely impaired cognitive functioning (e.g., dementia), and mortality as individual outcomes. However, cognitive aging processes and mortality are competing risks, especially in old age. To summarize: 1) individuals with mildly impaired cognitive functioning are at a greater risk of severely impaired cognitive functioning, 2) individuals with mildly or severely impaired cognitive functioning are at a greater risk of mortality, 3) individuals may die due to alternative causes prior to development of cognitive impairment, and 4) increasing age is a risk factor for cognitive impairment and mortality. Given this issue of heightened risk among cognitive outcomes and selective mortality, research investigating the impact of predictors (e.g., loneliness and social isolation) on any of these outcomes (e.g., mildly impaired cognitive functioning, severely impaired cognitive functioning, or death) in singularity is not properly accounting for the competing risks of the other outcome, which may lead to biased estimates.

Yet, most research does not consider or account for more than one outcome. For instance, out of 16 cohort studies examining loneliness and dementia systematically identified by Qiao et al. (2022), only one study statistically examined both cognitive decline and mortality; specifically, Tilvis et al. (2004) found that loneliness was not associated with the relative risk of mortality when adjusting for cognitive functioning at baseline and age-related cognitive decline. Thus, it is possible that the increased risk of mortality in individuals experiencing heightened loneliness may be accounted for, at least partially, by cognitive decline in older adulthood.

Empirical Research: Loneliness, Social Isolation, Cognitive Aging, and Mortality Risk

A rich body of empirical research has investigated whether loneliness and social isolation are associated with the risk of cognitive outcomes in older adulthood. Based on up to 65 reports, meta-analyses find consistent associations between higher loneliness or social isolation with impairment across several domains of cognitive functioning (*see* Boss et al., 2015; Evans et al., 2019; Kang & Oremus, 2022). Similarly, based on up to 77 independent

studies, meta-analyses revealed that social connectedness and social contact are inversely associated with cognitive decline (*see* Kuiper et al., 2015; Piolatto et al., 2022; Samtani et al., 2022). While most studies find an inverse association between social isolation and cognitive function (e.g., Evans et al., 2018), some research has failed to find this relationship (e.g., Wilson et al., 2007). These conflicting findings may be due to differences in measurement approaches or sample characteristics, which our multi-study approach aims to address. Further, although these associations are reliable, effect sizes are relatively small (e.g., the association between loneliness and global cognitive functioning, $r = -0.08$; 95% *CI* [−0.14, −0.02], $K=6$; Harrington et al., 2023). Findings between social isolation and risk of dementia are similarly consistent (*see also* Fratiglioni et al., 2004). Based on meta-analyses of longitudinal studies, poor social engagement ($k=17$, *see* Penninkilampi et al., 2018) and living alone (i.e., social isolation) ($k=12$, *see* Desai et al., 2020) were associated with an increased risk of incident dementia. Overall, these findings suggest that both loneliness and social isolation are reliable risk factors for cognitive impairment and cognitive decline, and that social isolation is reliably linked with the risk of dementia.

Despite the reliable associations between loneliness and cognitive functioning and decline, the association between loneliness and the risk of dementia, however, appears to be less congruent. For instance, Victor et al. (2021) concluded that there is insufficient evidence for loneliness as a risk factor for dementia, as earlier loneliness predicted incident dementia in only five out of eleven studies. In contrast, Qiao et al. (2022) ($k=16$) concluded that loneliness was consistently associated with an increased risk of dementia, but not risk of MCI (2022). Similarly, recent research based on a large sample of adults from the UK Biobank ($N=492{,}322$; $M_{age}=57$, $SD=8$) found that loneliness was associated with a 60% increased risk of several types of dementia, adjusting for social isolation (Sutin et al., 2022). However, two additional reports using the same dataset but with different operationalizations of loneliness and social isolation and shorter follow-up periods found that the increased risk of loneliness on dementia was no longer significant after adjusting for social isolation (Elovainio et al., 2022; Shen et al., 2022). Thus, consistent with theory emphasizing the importance of distinguishing between loneliness and social isolation (e.g., Peplau & Perlman, 1979), the extent to which loneliness is associated with risk of dementia when adjusting for social isolation appears to be less consistent compared to the effect of loneliness or social isolation on cognitive impairment or decline, or the effect of social isolation on risk of dementia. Moreover, these studies emphasize the challenge of delineating the extent to which mixed findings reflect true differences versus methodological differences.

Given the associations between loneliness and social isolation with detrimental cognitive and health outcomes, it is understandable that both loneliness and social isolation are also robustly and consistently associated with mortality risk (Crowe et al., 2021; Henriksen et al., 2019; Holt-Lunstad et al., 2010; Long et al., 2023; Luo et al., 2012; Steptoe et al., 2013). The landmark meta-analysis by Holt-Lunstad et al. (2015), which included data from 70 independent studies, found that social isolation is associated with a 29% increase in mortality risk, loneliness is associated with a 26% increase in mortality risk, and living alone is associated with a 32% increase in mortality risk. However, the authors emphasized that the vast majority of studies examined either loneliness, social isolation, or living alone,

thereby limiting direct comparisons between these predictors. Of the studies that did contrast loneliness and social isolation, results have been mixed, with some finding that loneliness (Holwerda et al., 2012) or social isolation (Steptoe et al., 2013) was a more important indicator of mortality risk.

Theoretical Pathways: Loneliness, Social Isolation, Cognitive Aging, and Mortality Risk

Theory and empirical research show that some of the pathways linking loneliness and social isolation to cognitive aging and mortality risk may be overlapping and bidirectional (del Pozo Cruz et al., 2021; Luo & Waite, 2014; Shankar, 2017). Specifically, cognitive decline may exacerbate loneliness and social isolation, as individuals experiencing cognitive impairment may feel lonelier and/or isolate themselves (Gibson & Springer, 2022; Yu et al., 2016). Similarly, both may accelerate aging and cognitive impairment (Berkman, 1988; Crowe et al., 2021; Hawkley & Cacioppo, 2010; Kuiper et al., 2015), as social activity and social relationships are important for maintaining cognitive functioning (Fratiglioni et al., 2004; Park et al., 2022; Penninkilampi et al., 2018). Additionally, both loneliness and social isolation may adversely affect health status, which can subsequently influence the risk of cognitive decline, dementia, and mortality. For instance, having a limited social network (i.e., social isolation) may adversely influence macrosocial forces important for healthy cognitive aging, including access to resources and social support (Holwerda et al., 2014). Individuals who are lonely or socially isolated are also more likely to engage in detrimental health behaviours (e.g., smoking, poor sleep quality, poor diet, low physical activity) (Christiansen et al., 2016; Kobayashi & Steptoe, 2018), leading to the increased risk of dementia (*see* Lee et al., 2010) and mortality (*see* Loef & Walach, 2012).

Extensive research also documents unique pathways linking loneliness and social isolation with cognitive outcomes and mortality risk in older adulthood. Specifically, loneliness may impact cognitive health and mortality via: a) Heightened stress reactivity: Lonely individuals often experience chronic activation of stress response systems, leading to elevated cortisol levels and inflammatory markers (Hackett et al., 2012). b) Altered cognitive processes: Loneliness is associated with heightened attention to social threats and negative social information, which may contribute to cognitive load and reduced cognitive resources for other tasks (Cacioppo et al., 2009). c) Sleep disruption: Loneliness is linked to poor sleep quality (Hawkley et al., 2010), which is a risk factor for cognitive decline and mortality. d) Health behaviors: Lonely individuals may be less likely to engage in health-promoting behaviors, such as physical activity or seeking medical care (Shankar et al., 2011). Longitudinal studies also show a bidirectional link between loneliness and cognitive decline in older adults, with loneliness predicting faster cognitive decline and cognitive impairment increasing feelings of loneliness over time (Boss et al., 2015; Lara et al., 2019).

On the other hand, social isolation may influence cognitive health and mortality via: a) Reduced cognitive stimulation: a lack of social interaction may lead to decreased cognitive engagement and lower cognitive reserve (Fratiglioni et al., 2004). b) Limited access to resources: Socially isolated individuals may have reduced access to health information, healthcare services, and practical support for daily living (Berkman & Glass, 2000). c) Physiological effects: Social isolation has been linked to increased blood pressure and

poorer immune function, which may contribute to cognitive decline and mortality risk (Courtin & Knapp, 2017). d) Lack of social control: Without regular social contact, there may be less external motivation to maintain healthy behaviors or adhere to medical treatments (Umberson, 1987). These pathways align with the cognitive reserve hypothesis (Stern, 2009), which posits that engaging in social activities may build cognitive resilience, potentially delaying the onset of dementia symptoms.

Together, this extensive literature highlights the crucial need to examine the individual and adjusted links between loneliness and social isolation with cognitive outcomes and mortality risk. It's also important to note that loneliness and social isolation may interact in their effects on health outcomes. For instance, the impact of social isolation on cognition might be exacerbated by feelings of loneliness, or conversely, the stress-related effects of loneliness might be buffered by maintaining some level of social contact. By examining the individual and adjusted effects of loneliness and social isolation on cognitive status and mortality, our study aims to disentangle these potentially distinct pathways. This approach permits opportunities to clarify whether interventions should focus on addressing subjective feelings of loneliness, improving objective social connections, or both, to most effectively promote cognitive health and longevity in older adulthood.

The Current Project

Together, the literature suggests that: 1) higher loneliness and social isolation are linked to greater risk of cognitive impairment and decline; 2) higher social isolation is linked to an increased risk of dementia, but the impact of loneliness on the risk of dementia is less conclusive; 3) the links between loneliness or social isolation with the risk of mild cognitive impairment is less clear; and 4) higher loneliness and social isolation are associated with greater mortality risk. However, in many cases, conclusions are complicated as research focuses solely on either loneliness or social isolation. Specifically, a great deal of this work does not consider both loneliness and social isolation, does not model loneliness and social isolation together, does not distinguish the subjective versus objective aspects of social isolation, varies in the reliability of measures assessing loneliness and social isolation, and/or aggregates assessments of loneliness and social isolation. Studies that have considered both factors highlight the importance of delineating the relative contributions of each (Freak-Poli et al., 2022; Joyce et al., 2021; Shen et al., 2022; Yu et al., 2016). Furthermore, the vast majority of research investigating the effect of loneliness or social isolation on cognitive outcomes or mortality risk has not accounted for the competing risk of the other outcome(s), which may result in biased estimates. That is, cognitive outcomes are strongly associated with mortality risk (see subsection 'Cognitive Outcomes and Mortality Risk in Older Adulthood'). Importantly, omitting key confounds (e.g., ignoring death as a competing risk factor) when investigating correlates of cognitive aging processes can result in biased estimates and/or may obscure the individual associations. Our approach of examining both outcomes simultaneously provides a more comprehensive understanding of the aging process. Moreover, the timing of when loneliness and social isolation may have the most substantial effect on the progression through cognitive functioning states is unclear.

In the current project, we used Cox proportional hazard models, logistic regression, and multistate survival models to systematically delineate the individual and adjusted associations between loneliness, social isolation, cognitive outcomes, and mortality risk. Understanding the relative contributions of loneliness and social isolation to cognitive outcomes and mortality risk is crucial for several reasons: a) Theoretical advancement: By examining these constructs simultaneously, we can better understand whether the subjective experience of loneliness or the objective state of social isolation has a stronger impact on health outcomes in older adults; b) Intervention development: Clarifying the unique effects of loneliness and social isolation can inform more targeted and effective interventions. For instance, if loneliness shows stronger associations with cognitive decline, interventions might focus more on cognitive reframing and emotional support. Conversely, if social isolation is more impactful, interventions might prioritize increasing objective social contacts; and c) Resource allocation: In a context of limited public health resources, understanding which aspect of social disconnection most strongly predicts adverse outcomes can guide more efficient allocation. Our study's design, which examines both the individual and adjusted effects of loneliness and social isolation across multiple datasets, is specifically tailored to address these important questions about the relative contributions. See Table 1 for a 2×2 mapping of our first four research questions (RQs), analytic approach, hypotheses, and number of models and effects of interest.

Moreover, between-study and between-review variability in statistical approach and operational definitions of loneliness and social isolation has further complicated conclusions drawn from previous research, in addition to hindering theory development. In response, we applied a coordinated data analysis methodological framework (Graham et al., 2022; Hofer & Piccinin, 2010; Willroth et al., 2022; Yoneda, 2025). Using this approach, independent but identical models (to the extent possible) were fit to 11 longitudinal aging studies. Coordinated data analysis is particularly well positioned to address idiosyncrasies across a set of findings by ensuring that statistical models and adjustment of covariates are held constant, permitting opportunities to explore how differences in operational definitions (e.g., loneliness assessed via multi-item scales versus single items) may influence the magnitude and reliability of associations. Furthermore, this approach facilitates the evaluation of robustness and generalizability, while preserving significant heterogeneity across datasets. Notably, a common theme across the numerous systematic reviews is an emphasis on the extensive heterogeneity across study designs, analytic approaches, and operational definitions of key constructs, thereby complicating between-study comparisons. This between-study variability underscores the importance of research that harmonizes across as many critical study features as possible.

Method

The current study was completed via secondary analysis of existing datasets that were either public and de-identified prior to our access to them or we completed a data use agreement that provided access to the requisite data to complete the analyses (see Supplementary Table 1). Under the study title "Advancing the Study of Social Isolation, Loneliness, and Cognitive Functioning in Older Adults Through the Use of Integrative Data Analysis", the

Northwestern University Biomedical Institutional Review Board confirmed that this project constitutes non-human subject research and does not require a protocol.

Research Questions and Hypotheses

Our study addresses four primary research questions (RQs), and corresponding hypotheses[3], examining the relationships between loneliness, social isolation, cognitive status, and mortality risk (see Table 1 and Supplementary Text 2 for a full description). Across these RQs, we report the model estimates including sociodemographic covariates (age, sex, and education). Finally, in addition to these four primary research questions, we asked how depressive symptoms impact the associations between loneliness, social isolation, cognitive functioning, and death (RQ5). To address this question, we repeated all analyses from RQ's 1–4 further adjusting for depressive symptoms. Together, these research questions assist in addressing the theoretical and empirical question of whether loneliness and social isolation represent distinct constructs that are individually or incrementally important for health outcomes in older adulthood (*see also* Lawson & Robins, 2021). Given the conceptual similarities and differences between loneliness and social isolation (i.e., perceived isolation versus objective isolation), the individual effects of either (RQ's 1 & 3) represent the importance of poor social health in general for cognitive outcomes and mortality risk. That is, although loneliness and social isolation are conceptually distinct, we suspect that the investigation of loneliness not accounting for social isolation likely still includes some variability related to social isolation, and vice versa. Conversely, the adjusted effects of loneliness (i.e., adjusting for social isolation, RQ's 2 & 4) reflect the extent to which individual differences in perceived loneliness are associated with cognitive outcomes and/or mortality risk, considering the extent to which individuals report being objectively alone. Likewise, the adjusted effects of social isolation (i.e., adjusting for loneliness, RQ's 2 & 4) reflect the extent to which being objectively alone is associated with cognitive outcomes and mortality risk, accounting for the extent to which individuals are bothered by being alone.

As recommended by Lawson and Robins (2021), researchers should test the individual importance of a construct by including both sibling constructs in a prediction model and having them "compete" to explain variance in a wide range of outcomes. Here, we tested the links between loneliness and social isolation (sibling constructs) and several related outcomes relevant to older adult health, independence, and well-being (risk of mildly and severely impaired cognitive functioning; risk of death; seven transitions between no cognitive impairment, mildly impaired cognitive functioning, severely impaired cognitive functioning, and death). Further, we tested these associations across a wide range of datasets (K=11), which, in a similar vein, permitted the ability to evaluate the replicability and robustness across datasets. Given previous research, we expected that higher levels of loneliness and social isolation would be associated with a greater likelihood of severe cognitive impairment and of death, as well as transitioning forward through cognitive status categories and to death. Moreover, we expected that, compared to loneliness, higher social isolation would be a more robust indicator of severe cognitive impairment and of

[3]A full written explanation of the research questions and hypotheses are included in Supplementary Text 2. This content was originally included in the Registered Report that was accepted in principle, but to streamline the primary manuscript, was moved to the supplement as the content overlaps directly with the information reported in Table 1.

death, as well as transitioning forward through cognitive status categories and to death. As previous research has not yet investigated whether loneliness or social isolation are associated with the backward transition from mildly impaired cognitive functioning back to no impaired cognitive functioning, we did not make predictions for the impact of loneliness or social isolation on backward transitions (i.e., analyses examining these specific transitions were exploratory). We acknowledge that while the deleterious effects of loneliness and social isolation likely apply to many health outcomes in older adulthood, our focus on cognitive status and mortality allows for a manageable and interpretable multistate modelling approach; adding additional health states would significantly increase model complexity and potentially reduce our ability to draw clear conclusions.

Design

To address our research questions and hypotheses, we used several modelling approaches (Cox regression, logistic regression, and multi-state survival models). Multistate survival modelling not only accounts for the issue of selective mortality in longitudinal datasets, but our comprehensive approach (also using Cox and logistic model) provides opportunities to tease apart the extent to which associations are impacted by accounting for death. See Figure 1 for a visual depiction of the possible transitions between cognitive status categories and death modelled by the multistate survival models.

We used a coordinated data analysis framework, including meta-analysis as a final step to synthesize our findings. This approach permits evaluation of the replicability across many large longitudinal datasets with varying start times, countries of origin, design features, and measurement tools, while preserving important individual dataset variability. However, applying a coordinated data analysis approach, in combination with the complex nature of multistate survival models, required us to limit the covariates and mediators included in models. For instance, investigating the role of culture and race is important, particularly in light of research suggesting that cognitive aging processes may develop differently across Black and Mexican American populations in the US (Mehta & Yeo, 2017). Yet many of the samples meeting eligibility for the current project are racially homogenous. Thus, to maximize harmonization across analyses, we did not examine racial differences; however, we report prevalence of race within each dataset when race data were available (see Supplementary Table 3). The SHARE datasets do not have race data; instead, we report country of birth as the closest possible proxy (see Supplementary Table 4).

Datasets were identified using the Integrative Analysis of Longitudinal Studies of Aging and Dementia (maelstrom-research.org/network/ialsa) and the Gateway To Global Aging (g2aging.org) platforms. Across these two sites, we searched for long-term longitudinal studies that contained the minimum required data for inclusion in the proposed analyses. At a minimum, datasets were required to have 1) at least one measurement occasion of loneliness (e.g., "*how lonely do you feel*") prior to or at the same measurement occasion of assessments of cognitive function, 2) at least one measurement occasion of social isolation containing multiple items assessing quantity or frequencies of social contact (i.e., "*how often do you meet with friends/family?*", "*do you live alone?*", "*do you frequently attend social events?*") prior to or at the same measurement occasion of assessments of cognitive

function, 3) at least five measurement occasions of cognitive functioning performance or an evaluation of cognitive status (i.e., dementia, MCI), and 4) a measurement of mortality that includes death status and death date.

Sampling plan

We used data from 11 longitudinal studies[4] (detailed below). These datasets are either publicly available or access can be requested directly from the study sites, with the exception of ELSA death data (see Supplementary Table 1). Data were downloaded following in-principle acceptance of this Registered Report.

English Longitudinal Study of Aging (ELSA): ELSA is a nationally representative longitudinal sample of English adults aged 50 and older living in private households (Clemens et al., 2019). The study began in 2002–2003, with core interviews repeated every two years for a total of eight waves. We used data starting in wave 8 (2016) when cognitive assessments began (analytic N=14,086).

Health and Retirement Study (HRS): HRS is a representative panel study of United States retirees aged 51 and over. Data collection was initiated in 1992 and occurred approximately every two years (Sonnega et al., 2014). Data were used from the eight waves of measurement that occurred since 2002, when the relevant psychosocial data collection began (analytic N=37,826).

Origins of Variances in the Oldest-Old: Octogenarian Twins (OCTO-Twin): OCTO-Twin is a sample from the Swedish population-based twin registry (McClearn et al., 1997). At study initiation, twin pairs were enrolled if they were born in 1913 or earlier and both twins consented to participation. A total of 351 twin pairs were enrolled (N = 702) in 1991, and new waves of data collection occurred every two years until 2002 (when the majority of the sample was deceased) for a total of five measurement occasions included in analysis (analytic N=697).

The Swedish Adoption/Twin Study of Aging (SATSA): SATSA is a long-term longitudinal study aimed at investigating gerontological genetics (Pedersen et al., 1991). The original sample, first collected in 1984, consisted of pairs of twins reared apart, matched with control pairs of twins reared together (total N = 3,838). Data collection occurred approximately every three years, for a total of nine waves of data available for analysis (analytic N=1,836).

Survey of Health, Ageing, and Retirement in Europe (SHARE): SHARE is a panel survey of older adults aged 50 and over who live in private households, across all 26 countries of the EU, Switzerland, and Israel (Borsch-Supan et al., 2013). The survey began in 2004 with new data collection occurring every two years, for a total

[4]When we registered this report, we thought that The Household, Income, and Labour Dynamics in Australia (HILDA) Survey and The German Socio-Economic Panel (SOEP) met our eligibility criteria. Similarly, we believed that Luxembourg from SHARE met eligibility. While all three of these datasets measure hundreds of variables repeatedly, upon data access we found that they did not include the measurement of variables necessary for the current project (e.g., due to timing) and were therefore excluded. See Supplementary Table 2 for registration deviations.

of up to nine waves. Of the 26 countries, 16 met eligibility for the current project, as they included at least five waves of data. We executed analyses using SHARE datasets independently in four groups of countries, based on geopolitical grounds and by broad category of welfare state, consistent with previous research (Solé-Auró & Gumà, 2023): 1) Northern European (analytic N=13,898): Denmark and Sweden; 2) Central European (analytic N=42,423): Austria, Belgium, France, Germany, the Netherlands, and Switzerland; 3) Southern European (analytic N=25,776): Greece, Italy, and Spain; 4) Eastern European (analytic N=30,670): Czech Republic, Estonia, Poland, and Slovenia. Israel was analyzed independently, as it cannot be grouped within European regions (analytic N=4,653). Thus, SHARE represents independent analyses across five datasets (analytic N_{total}=117,420).

Rush Memory and Aging Project (MAP): MAP is a longitudinal epidemiological cohort study that began in 1997 focusing on common chronic conditions, decline in cognitive and motor function, and risk of AD and related dementias (Bennett et al., 2012). Participants were older adults recruited from retirement communities, subsidized senior housing facilities, church groups, and social service agencies in northeastern Illinois. All participants agreed to annual clinical evaluation and organ donation. It was approved by an Institutional Review Board of Rush University Medical Center and all participants signed informed and repository consents and an Anatomic Gift Act. Data were available for up to 20 measurement occasions (analytic N=2,356).

Minority Aging Research Study (MARS): MARS is a longitudinal epidemiologic cohort study of cognitive decline and risk of AD in older African Americans, beginning in 2004 (Barnes et al., 2012). Participants are African American adults aged 65+ years. At study enrollment, participants had no known dementia, agreed to annual clinical evaluation and blood draw, and (optionally) consented to brain donation after death. All participants signed an informed consent and consented to share data; a subset signed an Anatomic Gift Act. Data were available for up to 12 measurement occasions (analytic N=849).

Transparency and Openness

Each dataset used is cited in the text with appropriate marker papers and listed in the reference section. Analytic methods and program packages are appropriately cited in the text and listed in the reference section. Data Transparency: Data used for the current study are either publicly available to qualified users or available after completing data use agreements[5]. Specific information about accessibility for each dataset is included in the text and in Supplementary Table 1. All research materials, including analytic plan, instructions to analysts, deviations and justifications, and analytic code, are available on the OSF project page (URL: https://osf.io/vqyeu/overview?view_only=d67be59fefb94c269cb4f356fc0dd968). All data decisions were made prior to data access or analysis. See Supplementary Table 2 for all deviations and decisions that were made after seeing the data (Willroth & Atherton, 2024). After In Principle Acceptance, we posted the manuscript on the OSF as a pre-registration (https://osf.io/vqyeu/files/osfstorage).

[5]One exception to this is for ELSA death data. Although ELSA data are mostly publicly available, after in-principle acceptance of this Registered Report, death data in ELSA were no longer available (publicly or by request) due to new government privacy laws. Therefore, an internal ELSA analyst was invited to fit the models on site (co-author PQ).

Prior Exposure to Data

To increase transparency regarding prior exposure to these data, Supplementary Table 5 reports existing publications and manuscripts (K=103) that included co-authors of the current project using the same dataset(s). The table also provides details regarding primary differences between the current study and the existing report/publication. The existing projects include data from ELSA (k=8), HRS (k=17), OCTO (k=10), SATSA (k=5), SHARE (k=1), and Rush MAP (k=24). In addition, our group has (co)authored several coordinated data analyses (k=38) including the datasets that meet eligibility criteria. The table emphasizes that co-authors of the proposed project have been involved in several existing projects using the datasets that meet eligibility to investigate loneliness, social isolation, cognition, and mortality. However, none of these projects included investigation of all four of the current primary variables and none including loneliness or social isolation have used multistate survival models. Importantly, the researcher decisions regarding operational definitions of the primary independent and dependent variables are clearly justified based on previous research and the harmonization approach is consistent across datasets.

Variables

We aimed to conceptually harmonize all variables across studies. This approach allowed us to conduct comparable analyses across datasets while maintaining awareness of the underlying differences in assessment. In our results, we present both dataset-specific results and pooled, synthesized results to allow examination of potential systematic differences.

Cognitive Status Categories: We followed a decision tree for operational definitions of cognitive status categories in which we maximized available data and preserved the strength of studies. Specifically, the highest preference of cognitive status information was based on a clinical diagnosis of MCI and dementia, followed by the Clinical Dementia Rating scale, followed by traditional assessments used by medical professionals to screen for cognitive impairment (e.g., the Mini Mental State Examination), followed by composites of cognitive test scores (see Supplementary Text 3 for more details). Supplementary Table 6 provides a comprehensive overview of how cognitive status is assessed and harmonized across all included datasets, including operation definition of each cognitive status category. As shown, there is considerable variation in the original measures used, ranging from clinical diagnoses to specific cognitive test batteries. Our harmonization process aimed to create comparable categories across studies while respecting the integrity of each dataset's original assessment approach. We recognize that perfect equivalence across datasets is not achievable due to inherent differences in assessment methods. For instance, clinical diagnosis-based categorizations (e.g., in MAP) may not be directly comparable to categories based on cognitive test scores (e.g., in ELSA). We address this limitation by using language reflecting broad categories (no impairment, mild impairment, severe impairment) that can be reasonably applied across diverse assessment methods. Furthermore, we clearly document the original criteria and our harmonization decisions for each dataset.[6]

[6]We required that the summed cognitive tests can be clearly delineated into cognitive status categories. Specifically, previous research (Yoneda et al., 2020) found that the range of summed cognitive test scores were not normally distributed in two countries (Spain and

Loneliness: For each study, loneliness items were pulled from every available occasion of measurement. Multi-item scales were summed, where higher scores reflect more loneliness. Summed scores were then standardized using Percent of Maximum Possible (POMP) scoring (Cohen et al., 1999), scaled from 0 to 10 to aid in interpretation and convergence. Specifically,

$$POMP = [(observed\ score\ -\ min\ possible\ score)\ /\ (max\ possible\ score\ -\ min\ possible\ score)] \times 10$$

POMP scoring in this context is preferred over z-standardization, as it preserves differences in variation across samples. To improve comparability across datasets, we also POMP scored the response options for any study that only had a single item of loneliness. Notably, POMP scoring allows for optimal comparability across studies, regardless of whether they use multi-item scales or single items. See Supplementary Table 7 for available loneliness items and operational definition for each included dataset.

Social Isolation: For each study, social isolation items were pulled from every available occasion of measurement. We harmonized social isolation items to the extent possible across datasets using the approach reported by Shanker et al. (2011) as a guide. Notably, the operational definition of social isolation varies extensively across studies, even when studies use the same dataset. For example, across 32 existing publications using the ELSA dataset, social isolation has been operationalized 20 unique ways. The most common approach was originally reported by Shanker et al. (2011), in which participants were given one point for endorsing any of the following five items: 1) if they were not married/not cohabiting with a partner; 2) had less than monthly contact (including face-to-face, telephone, or written/email contact) with children; 3) had less than monthly contact other immediate family; 4) had less than monthly contact with friends; and 5) if they did not participate in any organizations, religious groups, or committees. Using this approach, scores ranged from 0 – 4, with higher scores indicating greater social isolation. This approach was used in 12/32 studies (38%) and a further 14 (44%) of the existing reports applied slight variations of Shanker et al.'s (2011) approach.

Given that this approach is most commonly applied across the existing literature using ELSA data, we aimed to use a similar approach across the datasets included in the current project. Specifically, we assigned participants higher social isolation scores based on whether or not they cohabitate with someone, participate in social activities at least monthly, and have at least monthly contact (either in person or via phone, email, or letter writing) with three groups of individuals: children, friends, and parents or other relatives. Although ELSA did not ask participants about neighbours, we condensed items from other studies that ask about contact with neighbors with items that ask about contact with friends. We made

Italy) from SHARE, such that the majority of individuals fell within a range too close to 0 (in raw scores) to distinguish cognitive states based on standard deviations. We did not expect this to be an issue for the majority of datasets (ELSA, HILDA, SOEP, and most countries in SHARE: Austria, Belgium, Denmark, France, Germany, the Netherlands, Sweden, and Switzerland); however, we acknowledged that this could be an issue in some of the countries from SHARE (Czech Republic, Poland, Estonia, and Slovenia). In the case that we could not clearly delineate the cognitive status categories in an individual dataset, we planned to exclude the dataset, but delineation of cognitive categories was possible in all datasets (possibly because countries were pooled to reflect regions in Europe).

one exception to this harmonization scheme: In OCTO-Twin and SATSA, we considered contact with one's twin as a distinct category from other relatives. This decision was based on research suggesting that twin relationships often have unique characteristics, including higher levels of intimacy and contact frequency compared to other sibling relationships (Neyer, 2002; Segal, 2012). Given the potential for heightened isolation when this unique relationship is absent, we believe including it as a separate indicator provides a more nuanced measure of social isolation in these specific populations.

We acknowledge the importance of contact frequency in assessing social isolation. Due to variations in how this is measured across datasets, we standardized to a monthly time frame where possible. In datasets with more granular measures, we aggregated to monthly contact. Where only broader categories were available, we used the closest approximation to monthly contact. To address the limitation of differing contact frequency measures, we report the specific contact frequency measure used for each dataset in our supplementary materials and include this as a limitation in our discussion, explicitly addressing how differences in contact frequency measurement may impact our findings and interpretations. See Supplementary Table 8 for available social isolation items for each included dataset, as well as explanations of our operational definition of social isolation. Across all datasets, the selected items were summed, where higher scores reflect more social isolation. To maintain consistency, we applied the same POMP scoring procedure to measures of social isolation to ensure comparability not only across studies, but also between our two key predictors.

Covariates: We tested whether parameter estimates in all models were robust to the inclusion of four covariates: Age (in years; mean-centered within study), sex (female as reference group), and education (in years[7]; mean-centered within study) in the primary models; as well as depressive symptoms in a follow-up series of models addressing RQ5. Depressive symptoms were assessed in most datasets (ELSA, HRS, SATSA, SHARE, MAP, MARS) using items from the Center for Epidemiologic Studies Depression Scale (CES-D, Radloff, 1977), whereas Octo-Twin has a single item assessing depression. Across all datasets, depression items were summed and POMP scored for the individual study analyses.

These four covariates were chosen based on a) Their consistent measurement across all samples, which facilitates harmonization. b) Their typical measurement at baseline, making their temporal alignment appropriate for testing as confounders rather than mediators (i.e., covariates are measured at the time of or preceding predictors). c) Prior empirical work linking them to loneliness, social isolation, cognitive function, and mortality. d) Prior theoretical and empirical work suggesting they are more likely to be confounders rather than colliders, which could bias estimates (Rohrer, 2018; Wysocki et al., 2022). We recognize that other sociodemographic markers, such as marital status, income, and occupational status, could also act as confounders. We did not include these due to conceptual overlap with core variables (e.g., social isolation and marital status) and the necessity of using proximate variables due to lack of availability across studies (e.g., education acting as an

[7]There was one exception: In ELSA, education was measured in categories (No high-school, high-school graduate, some college, college and above) rather than in years. Therefore, we *z* scored the ordinal education categories. Also see Deviations Table (Supplementary Table 2).

indicator of SES in the absence of harmonizable income and occupational status indicators across samples).

First, age is associated with loneliness (e.g., Graham et al., 2024; Mullins et al., 1991), social isolation (*see* Wen et al., 2023), cognitive function (Graham et al., 2021; Salthouse, 2009; Yang et al., 2023), and mortality (Kesteloot & Huang, 2003). Herein, we used age as a proximate variable for a variety of biological aging processes that likely jointly impact all predictors and outcomes, making it a likely confounder. Causality in the opposite direction is implausible, as we treat age as a time-invariant variable at baseline. Second, sex may influence both social experiences and cognitive outcomes through biological and social pathways. By controlling for sex, we aimed to account for these systematic differences. Notably, female participants tend to report higher levels of loneliness (e.g., Cohen-Mansfield et al., 2016; Graham et al., 2024), are slightly more at risk for dementia (Li & Singh, 2014), and tend to live substantially longer (Newman & Murabito, 2013) compared to male participants, on average (associations with other variables are less clear). In particular, causality in the opposite direction is implausible (as we treat sex as a time-invariant binary variable, given original assessments of sex), making sex a likely confounder of observed associations. Third, early-life education is temporally prior to our predictors and outcomes, and may influence cognition both through cognitive reserve and socioeconomic pathways. Including education also helps isolate the effects of later-life social experiences. Importantly, education is associated with all predictors (e.g., Cohen-Mansfield et al., 2016) and outcomes (*see* Balaj et al., 2024; Lövdén et al., 2020). Education is thought to impact all measures via the resources associated with higher levels of education, including healthcare access, fiscal resources, cognitive engagement and employment, diet, and more (e.g., *see* Majoka & Schimming, 2021; Roehr et al., 2020). Thus, we used education as a proximate measure of the confounding influence of socioeconomic resources that impact loneliness, isolation, cognitive impairment, dementia, and death.

Finally, the relationship between depressive symptoms and our predictors/outcomes is complex and potentially bidirectional. We included it as a covariate to conservatively estimate the effects of loneliness and social isolation, acknowledging the potential for overcontrol. Previous research suggests that individuals who report more depressive symptoms also tend to report higher levels of loneliness and social isolation (e.g., Cacioppo et al., 2006). Likewise, individuals who report more depressive symptoms are also at greater risk of cognitive impairment (*see* Rock et al., 2014), dementia (*see* Cherbuin et al., 2015), and mortality (*see* Zhang et al., 2023), suggesting that depression may act as a confounder of any unique causal association among them. That is, this research suggests that depressive symptoms may be a common cause (i.e., confounder) of the associations between loneliness, social isolation, adverse cognitive outcomes, and mortality risk in older adulthood; therefore, it is important to systematically investigate whether and how depressive symptoms impact these associations (see Rohrer, 2018; Wysocki et al., 2022). While depressive symptoms could potentially mediate the relationship between loneliness/social isolation and cognitive outcomes, we treated it as a covariate in this study for several reasons: a) The temporal precedence necessary to establish mediation is not consistently available across all datasets. b) Depressive symptoms may also act as a confounder, influencing both social experiences and cognitive outcomes. c) Treating depression as a mediator would require a different

analytical approach (e.g., structural equation modelling) that is beyond the scope of our current study d) Our primary aim is to establish the direct effects of loneliness and social isolation on cognitive outcomes and mortality. By controlling for depressive symptoms, we provided a conservative estimate of the direct effects of loneliness and social isolation.

We expected that the impact of social isolation on cognitive outcomes and death would be robust to adjustment for covariates, whereas the impact of loneliness on cognitive outcomes and death may be attenuated by adjustment for depressive symptoms. Although previous research finds that associations between loneliness and cognitive outcomes (e.g., Sutin et al., 2022) or mortality (e.g., Holt-Lunstad et al., 2015) are robust to adjustment for depressive symptoms, other research finds that adding depressive symptoms to the models diminished these associations (e.g., Boss et al., 2015; Harrington et al., 2023). Notably, because loneliness and depressive symptoms are psychological processes including aspects of thinking and feeling in comparison to social isolation (which is an objective, contextual construct), we expected that loneliness and depressive symptoms would account for some shared variance in outcomes.

As a result of including these four covariates, all inferences in these models rested on several causal assumptions, including that covariates are confounders, not mediators or colliders; that there are no open back-door paths (e.g., controlling for education closes a possible back door path due to occupational success); and that all relevant variables have been included.

Measurement of Key Predictors: Our study employs slightly different approaches depending on the RQ. For Cox and logistic regression models (addressing RQs 1 and 2), we used baseline measurements of loneliness and social isolation. These models estimated the risk of an outcome over time based on initial levels of a predictor. For multistate survival models (addressing RQs 3 and 4), we treated loneliness and social isolation as time-varying processes, utilizing all available waves of assessment. The use of baseline measurements in Cox and logistic regression models allows us to examine how initial levels of loneliness and social isolation predict long-term outcomes, consistent with much of the existing literature. In contrast, the use of time-varying measurements in multistate survival models enables us to capture how proximal measures of loneliness and social isolation may influence transitions between cognitive states and mortality risk. This approach provides a more dynamic understanding of these relationships. It’s important to note that not all studies have the same number of measurement occasions for loneliness and social isolation, and further, results from baseline models and time-varying models may differ. Baseline models capture the long-term predictive power of initial loneliness and social isolation, while time-varying models capture more proximal effects of these factors on cognitive status and mortality risk.

Analysis Plan

For both individual study analyses and meta-analytic analyses, we developed our code using random subsamples of ELSA data, prior to distributing the scripts to data analysts for each study that met eligibility criteria.

Individual Study Analysis: All analyses were executed in R statistical software (R. Core Team, 2013), using the following packages: Survival (Therneau & Lumley, 2015),

Multistate Survival Models (Jackson, 2011), and metafor (Viechtbauer, 2010). We first computed the zero-order correlations between loneliness, social isolation, and each cognitive functioning status category, as well as age, years of education, and depressive symptoms (see Supplementary Table 9). Next, to tease apart the inconsistencies in the field, we used Cox Proportional Hazard models, logistic regression models, and multi-state survival models to examine the *individual* (i.e., independent; not adjusting for competing risks) and *adjusted* (i.e., adjusting for competing risks) associations among social disparities, cognitive aging, and mortality by addressing four primary research questions (see Footnote 1, Table 1, and Supplementary Text 2). We executed all analyses individually in each dataset (ELSA, HRS, OCTO-Twin, SATSA, MAP, and MARS), as well as individually in Israel and each European region (Northern European, Central European, Southern European, and Eastern European) from SHARE.

To address research questions **(RQs) 1 and 2**, we used Cox Proportional Hazards and logistic regression models. Cox regression offers the advantage of modelling time-to-event outcomes and properly handling censoring, whereas logistic regression (while more robust to coarsely spaced assessments) does not incorporate information about when an event occurs or distinguish between participants who experienced the event early in follow-up versus later. This limitation can lead to reduced sensitivity to timing effects and potential misclassification of event risk. Thus, to model survival time to severely impaired cognition, Cox regression is most appropriate for datasets with frequently spaced assessments that allow for finer-grained estimation of event timing and censoring. Two of our datasets had annual cognitive assessments (Rush MAP and ROS), while the remaining eight had follow-up intervals of two to three years, which may limit precision in identifying the timing of impairment onset. To balance the strengths and limitations of each approach, we conducted both Cox and logistic regression models in all datasets.[8] To address **RQ1**, we modelled the individual effect of each predictor (loneliness and social isolation) on each outcome (severely impaired cognitive functioning and mortality), such that the *individual* effects are represented by separate models for loneliness and social isolation. To address **RQ2**, we repeated the Cox Proportional Hazards and logistic regression models including both predictors (loneliness and social isolation) simultaneously to examine the adjusted risk of each predictor on each outcome (i.e., severely impaired cognitive functioning and death).

To address **RQ3**, we fit two multi-state survival models to examine the impact of loneliness, and then the impact of social isolation, on transitions between cognitive status categories (no cognitive impairment, mildly impaired cognitive functioning, and severely impaired cognitive functioning) and death. To address **RQ4**, we fit a final multistate survival model in which loneliness and social isolation are simultaneously included in the model. This approach estimated the adjusted effect of each predictor, above and beyond the other, on

[8]When we registered this project, the Individual Study Analysis and Meta-Analysis subsections were inconsistent –we registered that we would fit Cox models for datasets with annual assessment and logistic regression models for datasets with more than one year between occasions; however, we also registered that we would only meta-analyze the Cox models. As this would mean losing estimates for the majority of studies, we executed both Cox and logistic regression models in all datasets. We report the Cox model meta-analysis in the main manuscript and the logistic regression meta-analyses in the supplement, and discuss the limitations of each approach here. Also see Supplementary Table 2 for deviations.

each outcome, adjusting for all outcomes. Finally, to address **RQ5**, we repeated all analyses from RQs 1–4 further adjusting for depressive symptoms at baseline.

Power Analysis. At present, there are no widely accepted methods for a priori power analysis in MSMs, particularly when modelling multiple states and transitions simultaneously. This is due to the complexity of these models and the multiple parameters being estimated concurrently. Thus, we based our expectations on recent publications, such as Schaeffer et al. (2024), who successfully implemented these models with as few as 6 individual transitions between some states in a relatively small sample (N=378). Furthermore, research using multistate models in other fields have suggested a minimum of 5–10 events per predictor variable per transition (Peduzzi et al., 1995; Vittinghoff & McCulloch, 2007). Based on these guidelines and our preliminary data checks, we anticipated robust estimation in larger studies (e.g., HRS, ELSA, SHARE) with sample sizes >10,000, but potential challenges in smaller studies (e.g., OCTO-Twin, N=702) or for rare transitions. There is also variation across transitions, with more common transitions (e.g., no impairment to death) likely to have sufficient events in most datasets. However, we acknowledge that model convergence depends on multiple factors beyond sample size, including the number of transitions between states, covariates, and measurement occasions.

Interpretation of estimates. After rescaling, a POMP score of 0 represents the lowest possible loneliness (or social isolation or depressive symptoms), 5 represents the midpoint, and 10 represents the highest possible loneliness (or social isolation or depressive symptoms). In our results, we report effects in terms of a one-point increase on this 0–10 scale. While POMP scoring enhances comparability, we acknowledge that differences in the original scales may still influence results.

Missing Data. For multistate survival models, leaving missing states in the data improves piecewise-constant approximation, which is an interpolation method that locates the nearest data value, and assigns the same value. The reported analytic sample sizes may decrease in fully adjusted models due to missing covariate data.

Outliers. Outliers were not removed, as long as values fell within the possible range for a given scale/index.

Meta-Analyses: After analyzing each individual dataset, we used random effects meta-analysis to synthesize the effect of each predictor (loneliness and social isolation) on each transition (see Figure 1 for all possible transitions between states). This approach recognizes that each transition in the MSM represents a unique process that should be meta-analyzed independently (e.g., transitioning from no cognitive impairment to mild impairment is fundamentally different from transitioning from mild to severe impairment). Additionally, the effects of loneliness and social isolation may vary across different transitions, and combining these effects could obscure important nuances. This approach allowed us to examine the consistency of effects across different types of transitions, potentially revealing patterns that a single overall meta-analysis would miss. Specifically, we executed 36 individual meta-analyses that directly align with our RQs (see Table 1). For the Cox regression models, we executed four meta-analyses for RQ1 (individual predictors,

individual outcomes) and four meta-analyses for RQ2 (adjusted predictors, individual outcomes). We considered the hypothesis supported if the hazard ratios were significantly greater than 1, with smaller hazard ratios in the adjusted models (RQ2; H2) compared to the individual models (RQ1; H1). For the multistate survival models, we executed 14 meta-analyses for RQ3 (individual predictors, adjusted outcomes) and 14 meta-analyses for RQ4 (adjusted predictors, adjusted outcomes), with each meta-analysis representing each possible transition. We considered the hypothesis supported if the transition intensities for forward transitions and death were significantly higher with higher loneliness/social isolation, with smaller effects in the adjusted models (RQ4; H4), compared to the individual models (RQ3; H3).

We focus on effect sizes and confidence intervals rather than solely on p-values.[9] Across all meta-analyses, effect sizes were weighted based on standard error (i.e., more precise estimates are given more weight). For each meta-analysis, we report I^2 and the Q statistic, which provide information on between-study heterogeneity in results. I^2 is reported as a percentage and quantifies the proportion of total observed between-study variability that is inferred to be greater that sampling error, rather than a direct estimate of true heterogeneity; we interpret values according to rough guidelines (Higgins et al., 2003) (25%=low, 50%=moderate, 75%=high). The Q statistic is intended to test the null hypothesis that all studies share a common effect size (i.e., homogeneity). However, Q has well-documented limitations (Higgins & Thompson, 2002): it is underpowered when the number of studies is small and can be biased when there is extreme variability in sample sizes (both of which apply here).

Given our relatively low between-study power (K=11), we lacked the power for formal meta-regression. However, we calculated and reported I^2 statistics for each meta-analytic effect size to quantify the extent of heterogeneity, created forest plots for each key outcome to visually represent the distribution of effect sizes across studies, conducted sensitivity analyses excluding one study at a time to assess the impact of individual studies on overall effect sizes and heterogeneity, and qualitatively examined patterns in effect sizes, based on previous work. Specifically, existing meta-analyses (Buecker et al., 2020; Holt-Lunstad et al., 2010, 2015; Kuiper et al., 2015; Long et al., 2023; Piolatto et al., 2022; Surkalim et al., 2022) and coordinated data analyses (e.g., Graham et al., 2024) have aimed to account for heterogeneity based on various factors, including study-level differences in baseline age, country of data collection, measurement differences (in both outcome and predictor), and longitudinal follow-up time (Buecker et al., 2020). As such, we sorted effect sizes by mean baseline year of birth, geographic region (North America versus Europe), measurement approach for loneliness and social isolation (number of items, scale used), operational

[9] In response to a peer reviewer during the registered report stage, this study specified a Bonferroni-corrected significance threshold of $p < .0028$. This threshold was intended to account for multiple planned meta-analyses (36 total: 18 for loneliness and 18 for social isolation), but upon further consideration we determined that such a correction was overly conservative and not appropriate for the present design. Specifically, our hypotheses concerning the two primary predictors (loneliness and social isolation) and the outcomes (risk of cognitive impairment and death) are conceptually and inferentially independent; support for one hypothesis neither increases nor decreases the necessity of testing the others (Rubin, 2024). In such cases, adjustment for multiple testing is not warranted. Accordingly, we do not apply a multiple-comparison correction, but instead report exact p values for all individual study estimates and meta-analytic effects, allowing readers to evaluate the robustness of the findings.

definition of cognitive status categories (e.g., formal diagnosis versus cognitive test cut-offs), and length of follow-up.

Data availability

All datasets are publicly available for researchers, and access can be requested directly from the study sites (see Supplementary Table 1). The one exception is death data in ELSA, which are no longer available (publicly or by request) due to new government privacy laws.

Code availability

All analytic code is publicly available on OSF, including detailed cleaning scripts, inferential modelling, meta-analysis, and outputs from individual study analyses (as .rdata files) (https://osf.io/vqyeu/overview). These outputs do not contain individual participant data but allow readers to understand and reproduce the reported analyses and results.

Analytic Contingency Plans

It is important to note that model estimation for multistate survival models can become unstable with few individual transitions between cognitive status categories, particularly when backward transitions are modelled, when occasions are infrequent (e.g., every 3 years compared to every year) relative to the process being modelled, or when numerous covariates are included in the models. This can result in non-convergence, imprecise estimates, and/or large confidence intervals. Given that we did not access the data until after this registered report was accepted-in-principle, we were uncertain whether the selected datasets had sufficient individual transitions for multi-state model estimation. Therefore, we registered an extensive analytic contingency plan (see Supplementary Text 4).

Results

Given the number of datasets, single-page tables were not feasible. This report therefore includes two sets of supplementary results: a series of tables, figures, and text shared as a PDF document (see Supplementary Materials), and a series of tables based on the individual and meta-analytic results shared on OSF (titled HTML Supplement). Baseline descriptive statistics of loneliness, isolation, and depressive symptoms for each dataset and the overall total sample are reported in HTML Supplementary Table 1. Across datasets, baseline age ranged from 22 to 110 years (Total M_{age} = 64.5; SD = 10.4), just over half of the sample were female participants (57%), and education ranged from 0 to 30 years (Total $M_{education}$ = 10.5, SD = 4.7). Across datasets, 12% (SHARE Central) to 68% (OCTO) of the participants died (N_{total} = 32,239; 19%) during up to 26 years of follow-up ($M_{years\ of\ follow\ up}$ = 16.4; $M_{occasions}$ = 10.3, range = 5–26 across datasets). Correlation matrices of primary study variables for each study are reported in Supplementary Figure 1, while Table 2 summarizes the primary synthesized results across modelling techniques.

Cox Proportional Hazard Models and Logistic Regression Models

To examine the independent effects of loneliness and social isolation on the risk of severely impaired cognition or death (**RQ1**), we conducted both Cox and logistic regression analyses with loneliness or social isolation entered separately as predictors. To examine the adjusted

effects (**RQ2**), we repeated these analyses including both predictors within the same models. The following subsections focus on Cox model results adjusting for age, sex, and education (but not depressive symptoms). All individual study unconditional and conditional estimates for the Cox models (HTML Tables 2a1–3c3) and Logistic regression models (HTML Tables 4a1–5c3), as well as meta-analytic results (HTML Tables 6a/6b and 7a/7b, respectively) are reported in the HTML Supplement, while forest plots for logistic regression results are reported in Supplementary Figures 2 – 5. All effects are expressed per 1-unit increase in each predictor on the 0–10 POMP scale, corresponding to a 10% increase of the scale's full range.

Independent Effects on Severe Cognitive Impairment (RQ1): The left-side panel of Figure 2 displays individual study and meta-analytic estimates from the Cox models for the independent effects of loneliness on survival time to severe cognitive impairment. Higher loneliness was linked with an increased risk of severe cognitive impairment (*Hazard Ratio* [*HR*]=1.09, *95% Confidence Interval* [*95% CI*] [1.06, 1.11], $p<0.001$), though between-study heterogeneity was substantial (I^2=78.9%; Q=34.66, $p<0.001$; k=11). Results were consistent across studies: all eleven HRs exceeded 1.0, nine reaching significance at $p<0.05$).

The right-side panel of Figure 2 displays corresponding estimates for social isolation. The synthesized effect indicated that social isolation was significantly associated with risk of severe cognitive impairment (*HR*=1.03, *95% CI* [1.00, 1.05], p=0.009), with substantial between-study heterogeneity (I^2=76.4%; Q=45.37, $p<0.001$; k=11). Nine studies had point estimates above 1.0 (two with $p<0.05$), and two had point estimates below 1.0 (none with p<0.05).

Independent Effects on Death (RQ1): The left-side panel of Figure 3 displays individual study and meta-analytic estimates for the independent effects of loneliness on survival time to death. Higher loneliness was associated with increased risk of death (*HR*=1.05, *95% CI* [1.04, 1.07], $p<0.001$), with substantial between-study heterogeneity (I^2=89.6%; Q=95.10, $p<0.001$; k=11). The pattern of individual study results was consistent, with all eleven HRs above 1.0 (10 with $p<0.05$).

The right-side panel of Figure 3 displays corresponding estimates for social isolation. Social isolation was also associated with increased mortality risk (*HR*=1.04, *95% CI* [1.02, 1.05], $p<0.001$), with high between-study heterogeneity (I^2=84.9%; Q=100.1, $p<0.001$; k=11). All eleven HRs exceeded 1.0, with seven reaching significance at $p<0.05$.

Adjusted Effects on Severe Cognitive Impairment (RQ2): The left-side panel of Figure 4 displays individual study and meta-analytic estimates for the adjusted effect of loneliness on survival time to severe cognitive impairment, adjusting for social isolation. Higher loneliness remained associated with increased risk of severe cognitive impairment (*HR*=1.08, *95% CI* [1.06, 1.10], $p<0.001$), with moderate between-study heterogeneity (I^2=62.2%; Q=23.37, p=0.0095; k=11). All eleven HRs exceeded 1.0, with nine reaching significance at p<0.05).

The right-side panel of Figure 4 displays the effect of social isolation, adjusting for loneliness. Social isolation was not significantly associated with risk of severe cognitive impairment (*HR*=1.01, *95% CI* [0.98, 1.03], p=0.643; k=11), with substantial between-study heterogeneity (I^2=74.5%; Q=48.2, p<0.001). Results were variable: five point estimates exceeded 1.0 (one with p<0.05), and six below 1.0 (none significant).

Adjusted Effects on Death: The left-side panel of Figure 5 displays individual study and meta-analytic estimates for the adjusted effects of loneliness on survival time to death, controlling for social isolation. Higher loneliness remained associated with increased mortality risk (*HR*=1.05, *95% CI* [1.03, 1.06], p<0.001), with substantial heterogeneity (I^2=85.2%; Q=66.1, p<0.001; k=11). All eleven HRs exceeded 1.0, with eight reaching significance at p<0.05.

The right-side panel of Figure 5 displays the adjusted effect of social isolation, controlling for loneliness. Social isolation remained associated with mortality risk (*HR*=1.03, *95% CI* [1.02, 1.04], p<0.001; k=11), with moderate between-study heterogeneity (I^2=68.1%; Q=46.74, p<0.001). Ten HRs exceeded 1.0, with six reaching significance at p<0.05.

Cox and Logistic Models Summary: The Cox models indicated that loneliness was associated with a modest but robust increased risk of severely impaired cognitive functioning (9% increased risk per 10% higher loneliness), while social isolation was associated with a small increased risk (3% increased risk per 10% higher social isolation). Once these predictors were jointly modeled (i.e., adjusted for each other), the effect of loneliness was attenuated slightly (8% increased risk), while the effect of social isolation was no longer significant. Contrary to our hypothesis that social isolation would be the stronger predictor of cognitive impairment, loneliness showed more robust associations. Both loneliness and isolation were associated with higher mortality risk (5% and 4% higher risk, respectively). These associations were evident whether loneliness and isolation were modelled separately (individual effects) or simultaneously (adjusted/joint effects), though the social isolation effect was slightly attenuated in mutually adjusted models (3%). Overall, synthesized results from the logistic regression models were consistent with those from the Cox models (also see Supplementary Text 5), with one exception: social isolation was not associated with severely impaired cognitive functioning in the logistic regression model (when loneliness was not included in the model) but was in the Cox model.

Multistate Survival Models

To examine the independent effects of loneliness and social isolation on the risk of transitioning between cognitive status categories and death (**RQ3**), we used multistate survival models with either loneliness or isolation included as a predictor. To examine the adjusted effects, (**RQ4**), we repeated these models including both predictors. Both loneliness and isolation were treated as time-varying predictors. HTML Supplementary Table 12 displays the final model that converged for each dataset according to our contingency plan, and the total number of individual transitions between cognitive status categories and death. Figure 1 reports the total number of individual transitions across all datasets. All effects are

expressed per 1-unit increase in each predictor on the 0–10 POMP scale, corresponding to a 10% relative difference in the predictor.

When interpreting results from our multistate model, several features are important to note. First, the effects represent the impact of loneliness or social isolation on the *rate* of transitioning between states, not on being in a particular state. Second, each participant's contribution is based on every available measurement of loneliness and social isolation, not just their baseline assessment. Third, the model accounts for both cognitive decline and improvement, as well as the competing risk of death.

Independent Effects on Transitions Between Cognition and Death. Figure 6 displays individual study and meta-analytic estimates from the multistate survival models for the independent effects of loneliness on each transition (but adjusting for age, sex, and education). Synthesized results showed that higher loneliness was associated with increased risk of forward transitions: from no impairment to mildly impaired cognitive functioning (*HR*=1.08, *95% CI* [1.05, 1.10], $p<0.001$), from no impairment to death (*HR*=1.10, *95% CI* [1.09, 1.11], $p<0.001$), from mildly to severely impaired cognitive functioning (*HR*=1.02, *95% CI* [1.00, 1.04], $p=.027$), and from severely impaired cognitive functioning to death (*HR*=1.02, *95% CI* [1.00, 1.04, $p=.019$). As one exception, loneliness was not a significant predictor of the transition from mildly impaired cognitive functioning to death, with five individual studies showing HRs above 1.0 (1 with CI excluding 1.0) and six showed HRs below 1.0 (two with CI excluding 1.0). Additionally, higher loneliness was associated with decreased likelihood of transitioning from mildly impaired cognitive functioning to no cognitive impairment (*HR*=0.97, *95% CI* [0.94, 0.99], $p=.010$).

Results were relatively consistent across studies: all eleven studies showed HRs above 1.0 for the transition from no impairment to mildly impaired cognitive functioning (eight with CI excluding 1.0), nine showed HRs above 1.0 for the transition from no impairment to death (six with CI excluding 1.0), nine showed HRs above 1.0 for the transition from mildly to severely impaired cognitive functioning (one with CI excluding 1.0), and nine showed HRs above 1.0 for the transition from severely impaired cognitive functioning to death (two with CI excluding 1.0). Finally, seven showed HRs below 1.0 for the backward transition from mildly impaired cognitive functioning to no impairment (three with CI excluding 1.0).

Figure 7 displays the corresponding estimates for social isolation. Higher social isolation was associated with increased risk of transitioning from no impairment to death (*HR*=1.08, *95% CI* [1.06, 1.09], $p<0.001$), consistent with the individual study results: ten of eleven showed HRs above 1.0 (seven with CI excluding 1.0). Higher social isolation was also associated with a lower likelihood of transitioning backward from mildly impaired cognitive functioning to no cognitive impairment (*HR*=0.97, *95% CI* [0.96, 0.99], $p=.003$), relatively consistent with individual study results: eight of eleven showed HRs below 1.0 (two with CI excluding 1.0). Social isolation was not a significant predictor of other transitions at the meta-analytic level, though some individual studies showed that social isolation was a predictor of some transitions (see Figure 7).

Adjusted Effects on Transitions Between Cognition and Death. Figure 8 displays individual study and meta-analytic estimates for the adjusted effects of loneliness on each transition, controlling for social isolation (and age, sex, and education). One dataset (Central Europe from SHARE) did not converge. Higher loneliness remained associated with increased risk of transitioning from no impairment to mildly impaired cognitive functioning (*HR*=1.08, *95% CI* [1.05, 1.11], $p<0.001$) and from no impairment to death (*HR*=1.08, *95% CI* [1.06, 1.10], $p<0.001$). Results were consistent across studies: all ten studies showed HRs above 1.0 for the transition from no impairment to mildly impaired cognitive functioning (seven with CIs excluding 1.0), and seven of ten showed HRs above 1.0 for the transition from no impairment to death (five with CIs excluding 1.0). Loneliness was not associated with the other transitions once social isolation was included in the model.

Figure 9 displays the adjusted effect of social isolation, controlling for loneliness. Once loneliness was included in the model, higher social isolation was only associated with increased risk of transitioning from no cognitive impairment to death (*HR*=1.06, *95% CI* [1.01, 1.12], $p=0.024$). However, individual study results showed substantial variability: eight studies showed HRs above 1.0 (four with CIs excluding 1.0) and two studies showing an HR below 1.0 (one with CIs excluding 1.0).

Multistate Survival Models Summary: The multistate survival models indicated that loneliness, but not isolation, was associated with a modest but robust increased risk of transitioning from no cognitive impairment to mildly impaired cognitive functioning (8% higher risk per 10% increase in loneliness). This effect size remained consistent regardless of whether isolation was included in the model. Loneliness was also associated with increased risk of transitioning from no cognitive impairment to death (10% higher risk), though the effect was slightly diminished (to 8%) when isolation was included. Furthermore, higher loneliness was associated with increased risk of transitioning from mildly impaired cognitive functioning to severely impaired cognitive functioning (2% higher risk) and from severely impaired cognitive functioning to death (2% higher risk), and decreased likelihood of transitioning from mildly impaired cognitive functioning to no impairment (3% lower likelihood), though these associations became nonsignificant once adjusting for social isolation. Loneliness was not robustly associated with any other transitions. Social isolation was associated with increased risk of transitioning from no cognitive impairment to death (8% higher risk) and decreased likelihood of transitioning from mildly impaired cognitive functioning to no impairment (3% lower likelihood) when loneliness was not included in the model; however, once loneliness was included, social isolation was no longer associated with transitioning from mildly impaired cognitive functioning to no cognitive impairment. These findings indicate that loneliness is the more proximal predictor of both cognitive impairment transitions and mortality when both constructs are considered simultaneously.

Between-Study Moderators

We examined whether the heterogeneity in effects was accounted for by the following study-level factors: baseline age (younger vs. older samples), geographic region (North American vs. Europe), measurement approach for loneliness and social isolation (number of isolation items, loneliness scale used), operational definition of cognitive status categories

(e.g., formal dx vs. cognitive cut-offs), and length of follow up. Given that the current project was relatively underpowered for formal meta-regressions (k = ~3–4 per study-level category), the study team visually inspected whether the distribution of effects for each of our 12 key models (eight Cox models and four multistate survival models) clustered as a function of these study-level factors.

This process showed that, for the majority of our key results, none of the pre-registered study-level factors accounted for systematic variation in the point estimates, with a few exceptions. There was some evidence that studies that used the UCLA loneliness scale, had more isolation items, used cognitive cut-off scores, were based in Europe, had younger samples at baseline, and had follow up times between 10 and 20 years, tended to have the most consistent point estimates. This was only the case for one to four of our key models, suggesting that these patterns were not robust across outcomes or modeling approaches. Moreover, this consistency reflected convergence in the direction and relative magnitude of estimates and confidence intervals, rather than statistically distinguishable subgroup effects. As such, these observations should be interpreted as exploratory rather than confirmatory. Future coordinated analyses with a larger number of contributing studies will be necessary to more definitively evaluate whether these study-level factors systematically moderate associations between loneliness, social isolation, cognitive outcomes, and mortality.

Additional Adjustment for Depressive Symptoms

Beyond the four primary research questions, we examined whether associations between loneliness, social isolation, cognitive functioning, and death were robust to additional adjustment for depressive symptoms (**RQ5**). We repeated all analyses from RQ's 1–4 further adjusting for depressive symptoms in addition to age, sex, and education.

Although point estimates tended to be slightly smaller, the direction and significance of nearly all estimates across both the Cox models (see HTML Supplement 2a3, 2b3, 2c3, 3a3, 6b, 7b) and multistate survival models (see HTML Supplement 10a–10c) were consistent when additionally adjusting for depressive symptoms, with only four exceptions. First, the independent effect of social isolation on the risk of severe cognitive impairment (Cox) was no longer significant once adjusting for depressive symptoms (similarly to the "adjusted model"; i.e., when adjusting for loneliness). Across the multistate survival models, the effect of loneliness on severely impaired cognitive functioning to death in the adjusted model became significant once adjusting for depressive symptoms. Similarly, the effect of social isolation became significantly associated with increased risk of transitioning from severely impaired cognitive functioning to death in independent models and from mildly impaired cognitive functioning to severely impaired cognitive functioning in adjusted models. Thus, accounting for individual differences in depressive symptoms reduces the variability in loneliness/social isolation estimates, in some cases attenuating results (Cox) and in others revealing previously obscured associations (multistate survival models). Consistent with this interpretation, adjustment for depressive symptoms also reduced between-study heterogeneity according to the I^2 statistic in the Cox models examining loneliness by 10% to 15%. Conversely, adding depressive symptoms had an inconsistent effect on heterogeneity in the Cox models examining social isolation: between-study

variability increased slightly in the models predicting severe cognitive impairment and decreased slightly in models predicting death. See Supplementary Text 6 for the complete results from models additionally adjusting for depressive symptoms.

Discussion

Across 11 longitudinal studies representing over 175,000 individuals from 18 countries, this Registered Report used multiple modeling techniques to systematically investigate the *individual* and *adjusted* associations among loneliness, social isolation, cognitive aging outcomes, and mortality risk. The findings are consistent and clear: loneliness, rather than social isolation, is the more robust risk factor for cognitive impairment and mortality. These results provide comprehensive evidence regarding the relative importance of subjective and objective social disconnection for critical aging outcomes.

A substantial body of research has examined the influences of loneliness and social isolation on cognitive aging outcomes and mortality. Indeed, social isolation has been identified as a key modifiable risk factor for dementia by the Lancet Commissions on dementia prevention, with the 2024 update explicitly recognizing both social isolation and loneliness as distinct, modifiable contributors to dementia risk across the life course (Livingston et al., 2020; Livingston et al., 2024). Together, these reports underscore the public health relevance of social disconnection while also highlighting the need for greater conceptual and empirical clarity regarding its subjective and objective components. Notably, drawing firm conclusions about whether subjective loneliness or objective social isolation is the more robust predictor has been difficult because much prior work does not consider both constructs, does not model them together, does not distinguish subjective from objective aspects of social disconnection, or aggregates assessments. By carefully distinguishing between subjective and objective aspects of being alone and using measures harmonized across datasets, we replicated and extended the existing literature by examining each combination of predictors and outcomes individually and adjusted for each other, independently across eleven longitudinal datasets.

First, Cox Proportional hazard models and logistic regression models replicated existing studies by treating cognitive impairment and death as independent outcomes (RQ1), while also addressing uncertainty regarding the relative contributions of loneliness and social isolation (RQ2). Existing systematic reviews show that social isolation is reliably associated with increased incident dementia risk (Desai et al., 2020, k=12), whereas there is more uncertainty regarding loneliness (Penninkilampi et al., 2018, k=17; Qiao et al., 2022, k=16; Victor et al., 2021, k=11). Recent work concluded that the loneliness-dementia association was no longer significant after adjusting for social isolation (Elovainio et al., 2022; Shen et al., 2022). We therefore hypothesized that although both loneliness and isolation would be associated with increased risk of cognitive impairment and of death, social isolation would be a stronger predictor of severely impaired cognitive functioning when adjusting for loneliness. Contrary to this hypothesis, our systematic approach showed that loneliness was consistently and robustly associated with severely impaired cognitive functioning and with death, whereas social isolation was only associated with death (and to a lesser degree) when adjusting for loneliness. These findings help clarify discrepancies in the existing literature,

pointing to methodological differences as a key factor contributing to mixed findings. It is important to note that social isolation was associated with cognitive impairment in some individual studies, particularly when loneliness was not accounted for, which may explain why prior work concluded that social isolation increases risk of cognitive impairment (e.g., Desai et al., 2020).

Second, we extended the existing literature by using multistate survival models (Hougaard & Hougaard, 2000) to simultaneously investigate the impact of loneliness *or* social isolation (i.e., as independent predictors, RQ3), as well as loneliness *and* social isolation (i.e., as adjusted, or joint, predictors, RQ4), on transitions between cognitive status categories and death. Unlike Cox models, which examine the effect of a predictor on a single event (e.g., dementia risk or mortality), multistate survival models discriminate predictor effects at different stages of cognitive impairment while permitting backward transitions and multiple transitions per person, as well as accounting for death as a competing risk. This approach is crucial because cognitive impairment increases mortality risk, and both cognitive impairment and mortality risk increase with age. The multistate survival results showed that higher loneliness was associated with increased risk of transitioning from no cognitive impairment to death, as well as forward through the process to more severe cognitive impairment categories. Moreover, higher loneliness was associated with a lower likelihood of transitioning from mildly impaired cognitive functioning back to no impairment. Notably, higher loneliness remained associated with the transitions from no cognitive impairment to mildly impaired cognitive functioning and to death, regardless of whether social isolation was in the model. Consistent with the Cox models, higher social isolation was also associated with increased risk of the transitions from no cognitive impairment to death, regardless of adjustment for loneliness. Furthermore, social isolation was associated with reduced likelihood of transitioning from mildly impaired cognitive functioning to no impaired cognitive functioning; however, once loneliness was included in the multistate survival model, the association was no longer significant.

In sum, our results suggest that loneliness is a robust predictor of cognitive impairment and of death. The meta-analytic effects for increased risk of cognitive impairment were highly consistent across modelling approaches. Being 10% higher in loneliness was associated with an 8%–9% increased risk of severely impaired cognitive functioning (Cox models) and of transitioning from no impairment to mildly impaired cognitive functioning (multistate survival models). This effect was consistent regardless of adjustment for social isolation, and only slightly diminished with additional adjustment for depressive symptoms. Higher loneliness was also associated with an increased risk of death (Cox models) and of transitioning from no cognitive impairment to death (multistate survival models), though the estimated effect was slightly reduced when social isolation was included (from 4% to 3%, and from 10% to 8%, respectively).

On the other hand, social isolation was also associated with cognitive impairment, but only when loneliness was not included in the (Cox or multistate survival) models. Thus, social isolation is likely important for cognitive impairment risk, but its unique contribution diminishes when accounting for loneliness. Similarly, consistent with the landmark meta-analysis (Holt-Lunstad et al., 2019), our results also show that social isolation is a risk

factor for mortality, although the effect was attenuated once we adjusted for loneliness and depressive symptoms. Together, these findings suggest that social isolation and loneliness likely overlap to some extent (also see Supplementary Figure 1), but loneliness is the more proximal risk factor for death.

These findings also emphasize *when* social disparities matter most in cognitive aging. With the exception of the transition from mildly impaired cognitive functioning to death, synthesized results show that loneliness was associated with all forward transitions through cognitive status categories and death. First, the effect sizes provide some guidance for interpreting these findings; namely, loneliness appears most consequential for the transition from no impairment to mildly impaired cognitive functioning (8% increased risk per 10% higher loneliness). The effect was smaller at later stages (2% for both the transition from mildly impaired to severely impaired cognitive functioning and from severely impaired cognitive functioning to death). Higher loneliness was also associated with 3% lower likelihood of transitioning backward from mildly impaired cognitive functioning to no cognitive impairment. Second, loneliness was only associated with the transition from no impairment to mildly impaired cognitive functioning and to death once we included social isolation in the models. Together, these findings suggest that loneliness may be most prominent in early stages of cognitive impairment but is also a risk factor after impairment develops: lonelier individuals may be more likely to progress to more severe stages *and* less likely to recover, though its unique role emerges most clearly when distinguished from social isolation. Future research should investigate loneliness, social isolation, and transitions through cognitive impairment status categories at more frequent intervals, as it is also possible that we had less power to detect later, rarer transitions.

Theoretical Advancement

Across datasets and analytic techniques, our results provide strong evidence that the subjective experience of loneliness, rather than the objective state of social isolation, is a more consequential predictor of cognitive impairment and mortality risk in older adulthood. This distinction is central to longstanding theoretical arguments (e.g., Peplau & Perlman, 1979) emphasizing loneliness as an appraisal of one's social world rather than a direct reflection of one's objective social conditions. By harmonizing measures across 11 longitudinal studies and modelling loneliness and social isolation both independently and jointly, our results offer clear empirical support that the distressing emotional experience of loneliness may exert stronger influences on health than the degree to which someone is physically disconnected from social activities. Although loneliness and social isolation are linked in multifaceted ways, the importance of loneliness is particularly notable in this context.

These findings integrate and extend theories positioning loneliness as a construct with unique cognitive, affective, and motivational consequences. Prominent conceptual models highlight maladaptive social-cognitive processes (e.g., heightened threat sensitivity, biased expectations of rejection, and avoidance tendencies) that can initiate or contribute to reinforcing cycles of disengagement (Cacioppo et al., 2009; Hawkley & Cacioppo, 2010). Our findings are consistent with these accounts: even when accounting for objective social

isolation, loneliness remained a robust predictor of transitioning from no impairment to cognitive impairment and to death. Although not tested directly, our pattern of findings suggest that the internal, transactional processes posited by cognitive-motivational theories of loneliness may be more robustly linked to health trajectories than the structural characteristics of social networks. Our findings support a person-environment interaction perspective in which the meaning individuals assign to their social experiences is more tightly linked to health consequences than the objective environment alone.

Our findings also emphasize that social disparities may be most important at the early stages of cognitive impairment. Higher loneliness confers the most consistent risk in early stages, prior to impairment onset. These findings are consistent with previous work showing an association between loneliness and MCI (Lobo et al., 2008; Luchetti et al., 2020). Loneliness may shape early risk through multiple pathways (e.g., chronic stress, reduced social and cognitive stimulation, and diminished reserve), highlighting the need for theoretical models that account for when in the impairment process specific social disparities exert their greatest influence. However, our results also suggest that loneliness may be a risk factor for transitioning to more severe impairment stages and a barrier to recovery. Together, these patterns suggest that loneliness may serve both as an early vulnerability factor and as a barrier to later recovery, possibly pointing to different mechanisms that become salient at different stages and underscoring the need for theoretical models that conceptualize social disparities as dynamic across the cognitive impairment process.

Finally, studies assessing only social isolation or only loneliness may implicitly treat one construct as capturing both subjective and objective social experiences. Our findings demonstrate that these assumptions can mask distinct processes: social isolation contributes incrementally to mortality risk, but loneliness accounts for most of the variance in both cognitive and mortality outcomes. This differentiation advances theory by identifying the unique and overlapping pathways through which subjective and objective social conditions influence aging outcomes. Taken together, these findings refine theoretical models of social functioning in later life by demonstrating that the *perception* of one's social world, rather than the social world itself, reliably predicts cognitive and physical health.

Methodological Advancement

The methodological design of this work, combining Registered Report and coordinated data analysis frameworks, has important implications for transparency, replicability, and generalizability. Registered reports are proposed as a means of changing incentive structures by reporting results regardless of findings, which diminishes hindsight bias and publication bias (Chambers & Tzavella, 2022; Nosek & Lakens, 2016). Registered reports typically involve reviewing and accepting research proposals prior to data collection, ensuring that methodological decisions are not influenced by the data. Few Registered Reports using secondary data analysis exist, partly because ensuring that researcher decisions are not influenced by known data characteristics is challenging. However, a Registered Report is possible within a coordinated data analysis framework because the focus is on optimizing identical statistical models and variables across multiple datasets rather than a single dataset. Harmonization of identical models and operational definitions ensures that methodological

decisions are not influenced by known characteristics of existing data. By providing accessibility information about each dataset (see Supplementary Table 1) and detailed harmonization tables (see Supplementary Tables 6–8), this project contributes to ongoing efforts to develop more standardized methods for assessing cognitive status and social isolation across diverse longitudinal aging studies.

By executing analyses independently within 11 longitudinal datasets, this Registered Report also contributes to generalizability and cumulative science. Notably, coordinated data analysis protects against Type I and Type II errors, permits evaluation of cross-country replicability, and facilitates knowledge accumulation (Graham et al., 2022; Hofer & Piccinin, 2009; Yoneda, 2025). Furthermore, this project contributes to the emerging literature on sample size considerations in multistate survival models applied to cognitive aging. HTML Supplementary Table 11 shows the contingencies implemented for model convergence, while HTML Supplementary Table 12 shows the number of individual transitions between states. By transparently reporting our experiences across multiple datasets, we hope to inform future research on the practical application of these models.

Our systematic approach to modelling predictors and outcomes individually and jointly demonstrates the importance of considering the subjective and objective aspects of being alone. Our use of ‘individual’ and ‘adjusted’ associations aligns with recent recommendations (e.g., Lawson & Robins, 2021) for clarity in discussing effects of related constructs. This terminology allows us to contribute to discussions about the distinct versus overlapping effects of different aspects of social connection on health outcomes. Given major calls to address the harmful impacts of loneliness globally (UK Government, 2018; U.S. Department of Health and Human Services, 2023), research on loneliness and social isolation spans a wide range of disciplines. Given this multidisciplinary field, it is unsurprising that researchers have focused on various aspects of social disparities and have adopted different methodological approaches. A focus on delineating psychological distress (i.e., loneliness) from the objective environment (i.e., social isolation) may be particularly interesting to psychologists but has important real-world implications as well.

Implications

Beyond theoretical and methodological advancements, systematically investigating the *individual* and *adjusted* effects across 11 longitudinal datasets provides a clear conceptual rationale for clinical and policy-related implications. The individual associations provide insight into the overall relationship of loneliness or social isolation with cognitive aging outcomes and mortality risk, suggesting that either may be relevant for initial screening or risk assessment. The adjusted associations help us understand the unique contribution of each predictor. In a context of limited public health resources, understanding which aspect of social disconnection most strongly predicts adverse outcomes may guide more efficient resource allocation. Together, our findings highlight the value of focusing on loneliness in intervention efforts.

Loneliness is a potentially modifiable contributor to cognitive healthspan and longevity. This modifiability affords promising opportunities across social structures and contexts for enhancing cognitive resilience and maintaining independence in older adulthood, improving

well-being and quality of life, and potentially reducing the global financial burden associated with dementia care (Brookmeyer et al., 2007; Zissimopoulos et al., 2014). Individual-level interventions could focus on enhancing social connections or changing perceptions of social relationships, with interventions targeting emotional support, emotion regulation, cognitive appraisal, or expectations of social connection (e.g., CBT-based or social cognition–focused approaches). Clinically, the pattern of findings also supports the use of brief loneliness screening tools in primary care, geriatric settings, and memory clinics. Community-level interventions could focus on creating opportunities and spaces for social engagement and belongingness among older adults. At the policy-level, interventions could aim to address structural factors that contribute to loneliness in older populations, prioritizing programs that foster meaningful social engagement (e.g., The Friendship Line, peer support networks, community navigator models). Incorporating metrics that track loneliness in population health surveillance and healthy aging initiatives may also be helpful.

Other factors, such as physical activity or diet, may interact with social factors in influencing cognitive health. The relative importance of loneliness and social isolation is likely to vary across individuals. Future research should aim to integrate social, lifestyle, health, and genetic factors to provide a more comprehensive understanding of cognitive aging. Although research based on a single dataset can be valuable, replication is often needed to improve risk stratification and inform intervention strategies. Given the consistency of our results across several individual studies and statistical approaches, these findings hold promise for informing health care initiatives and strategies for extending cognitive healthspan.

Strengths, Limitations, and Future Directions

Despite the strengths of this Registered Report, several limitations warrant discussion. First, statistically adjusting for closely related constructs like loneliness and social isolation can be challenging to interpret due to their conceptual overlap. Adjusted associations may underestimate the true impact of each factor due to overcontrol. Although loneliness emerged as the more proximal predictor, limited social contact likely amplifies opportunities for loneliness. For instance, older adults higher in trait loneliness report less momentary loneliness following social interactions (Zhaoyang et al., 2022), emphasizing the importance of social contact in the experience of loneliness. Similarly, differential reliability and sensitivity of loneliness and social isolation measures may influence which causal pathways can be detected. When examining coupling between two variables, measurement properties of each variable affect the observed associations (Cole & Maxwell, 2003). Nevertheless, the effects of loneliness were robust to adjustment for social isolation and only slightly diminished with further adjustment for depressive symptoms. Future work could formally test mediation models to clarify the causal pathways linking social isolation, loneliness, and cognitive outcomes.

Second, future research should examine the interplay between loneliness and social isolation at the individual level. Recent work on social asymmetry – where individuals experience high loneliness despite low isolation, or feel connected despite minimal social contact – suggests that these patterns may reflect distinct psychosocial processes with different health implications (e.g., Ong et al., 2024, 2025). Extending this line of inquiry, Qin et al.

(2025) found that higher social asymmetry – defined as loneliness exceeding what would be predicted from objective isolation – was associated with increased risk of cardiovascular disease and all-cause mortality over 13 years of follow-up in a nationally representative cohort of English adults. Notably, individuals who were socially isolated but not lonely (the “discordant robust” group) showed no elevated risk for most health outcomes, further reinforcing the primacy of subjective experience in shaping health trajectories. Intensive longitudinal designs and measurement burst designs studies examining shorter timeframes in daily life could complement these findings and offer opportunities for early detection of negative outcomes prior to major events such as MCI and death.

Third, while POMP-scoring enhances comparability across datasets, differences in the original scales may still influence results. As shown in Supplementary Tables 6–8, there were notable differences in variable harmonization based on available data. For example, raw social isolation measures varied in their possible ranges (e.g., 0–2 vs. 0–4), meaning that studies with more items capture a broader range and contribute more statistical power. These discrepancies may introduce residual heterogeneity that POMP scoring cannot fully eliminate.

Fourth, despite spanning 18 countries, the datasets largely represent White, Western, Educated, Industrialized, Rich, and Democratic populations (Henrich et al., 2010). Future research should prioritize recruitment and inclusion of more racially, ethnically, and socioeconomically diverse samples, as differential sociocultural norms, structural constraints, and life-course experiences may shape both social connection and cognitive aging processes.

Fifth, we cannot determine directionality based on these observational data. Feelings of loneliness or reductions in social engagement often accompany cognitive impairment (Gibson & Springer, 2022; Yu et al., 2016). Both loneliness and social isolation have been associated with accelerated aging and increased cognitive impairment risk (Berkman, 1988; Crowe et al., 2021; Hawkley & Cacioppo, 2010; Kuiper et al., 2015), reflecting the broader importance of social interaction and relationships for maintaining cognitive health (Fratiglioni et al., 2004; Park et al., 2022; Penninkilampi et al., 2018). Previous longitudinal studies hint at reciprocal patterns whereby loneliness may precede faster cognitive decline while worsening cognitive functioning may increase loneliness (Boss et al., 2015; Lara et al., 2019). Future work should continue probing these potential cross-lagged effects.

Finally, conducting a Registered Report within a coordinated data analysis framework introduced practical challenges. Although all datasets were selected and preregistered in advance, three had to be excluded after data access due to unforeseen issues related to variable availability and research design structure (e.g., loneliness and isolation were administered at alternating occasions; see Supplementary Table 2 for more details). Additionally, mortality data that were publicly accessible at registration were no longer available for one dataset due to policy changes. These shifts reflect the realities of working with multiple independent longitudinal studies and underscore the substantial time, coordination, and adaptability required for registered coordinated data analysis projects. Future Registered Reports using multi-cohort designs may benefit from building in

explicit contingencies for dataset attrition, policy changes, and unanticipated harmonization constraints.

Conclusion

This Registered Report demonstrates that loneliness – the subjective experience of social disconnection – is a more robust predictor of cognitive impairment and mortality than social isolation across eleven independent longitudinal datasets. By applying a harmonized methodological approach through coordinated data analysis, we examined individual and adjusted effects of loneliness and social isolation with greater precision than any single study could provide. The consistency of results points to clear priorities for future research: unpacking the mechanisms that make loneliness detrimental, refining measures to capture social connection more accurately across sociocultural contexts, and testing scalable interventions that address subjective social disconnection. This work lays essential groundwork for advancing theory, informing policy, and ultimately improving outcomes for adults as they age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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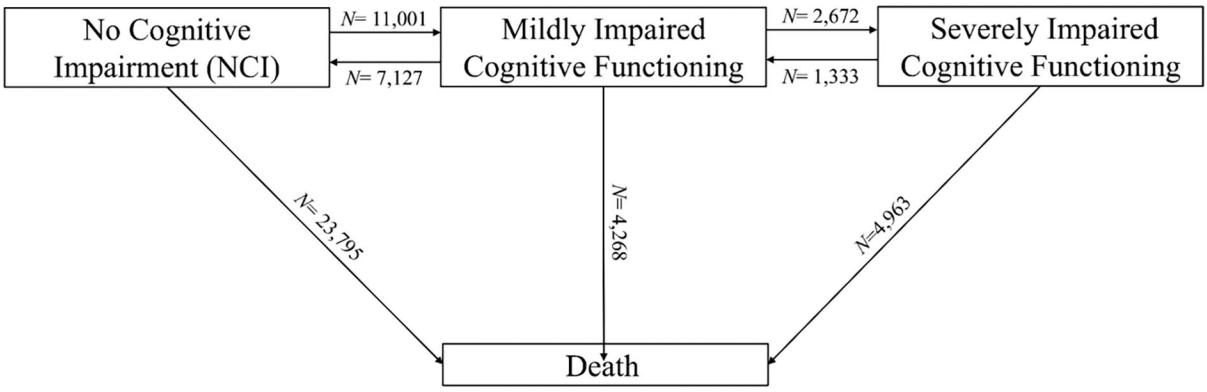

Figure 1. Possible Transitions between Cognitive Status Categories and Death in the Four-State Model

Note. N values represent the sum of the observed transitions of each type across all included datasets. Each participant may represent multiple transitions (i.e., participants may make multiple transitions during the study period).

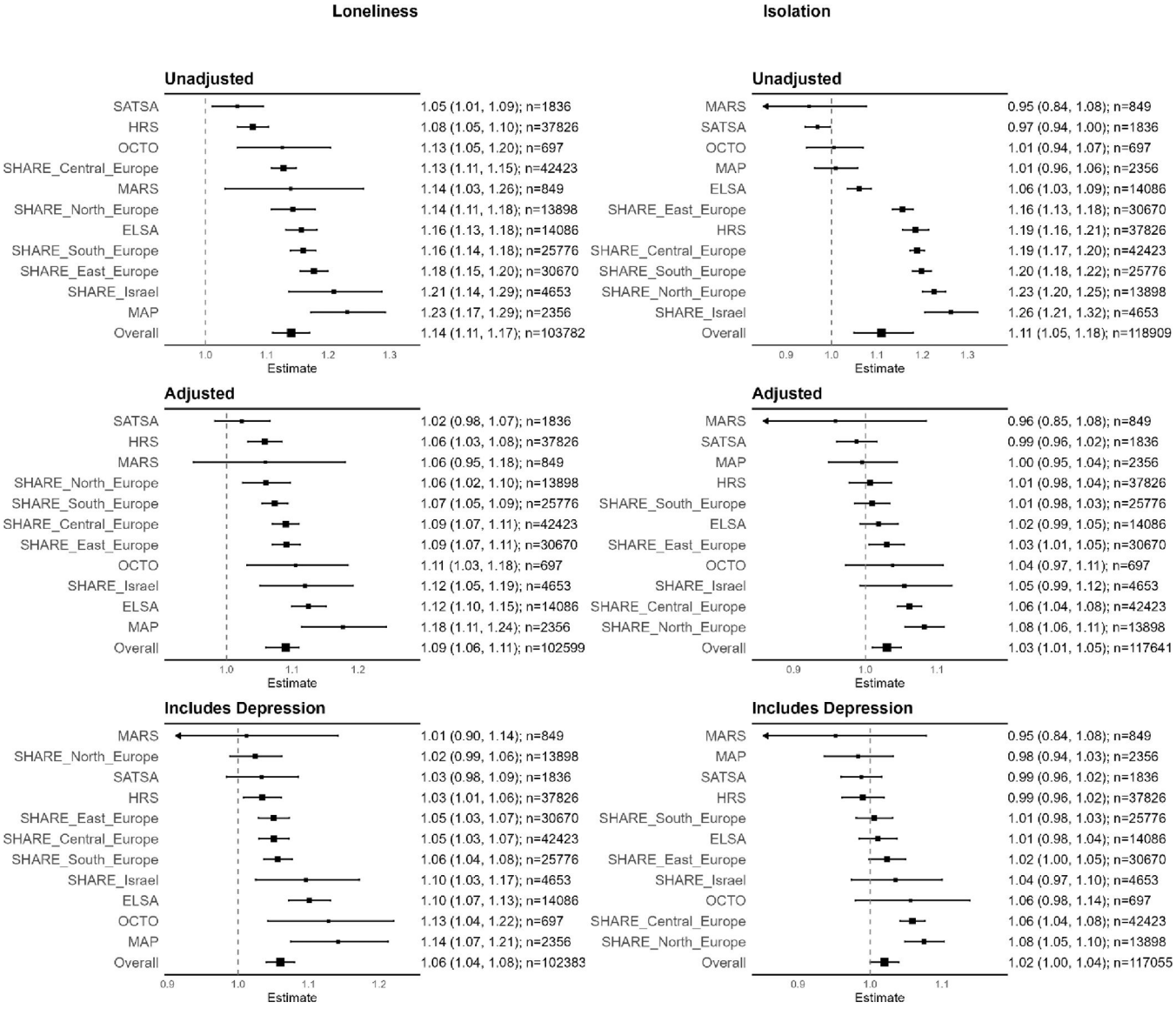

Figure 2. The Independent Effect of Loneliness and Social Isolation on Cognitive Impairment: Cox Proportional Hazard Models

Note. Unadjusted = no covariates; Adjusted = controlling for age, sex, and education; Includes Depression = controlling for age, sex, education, and depressive symptoms.

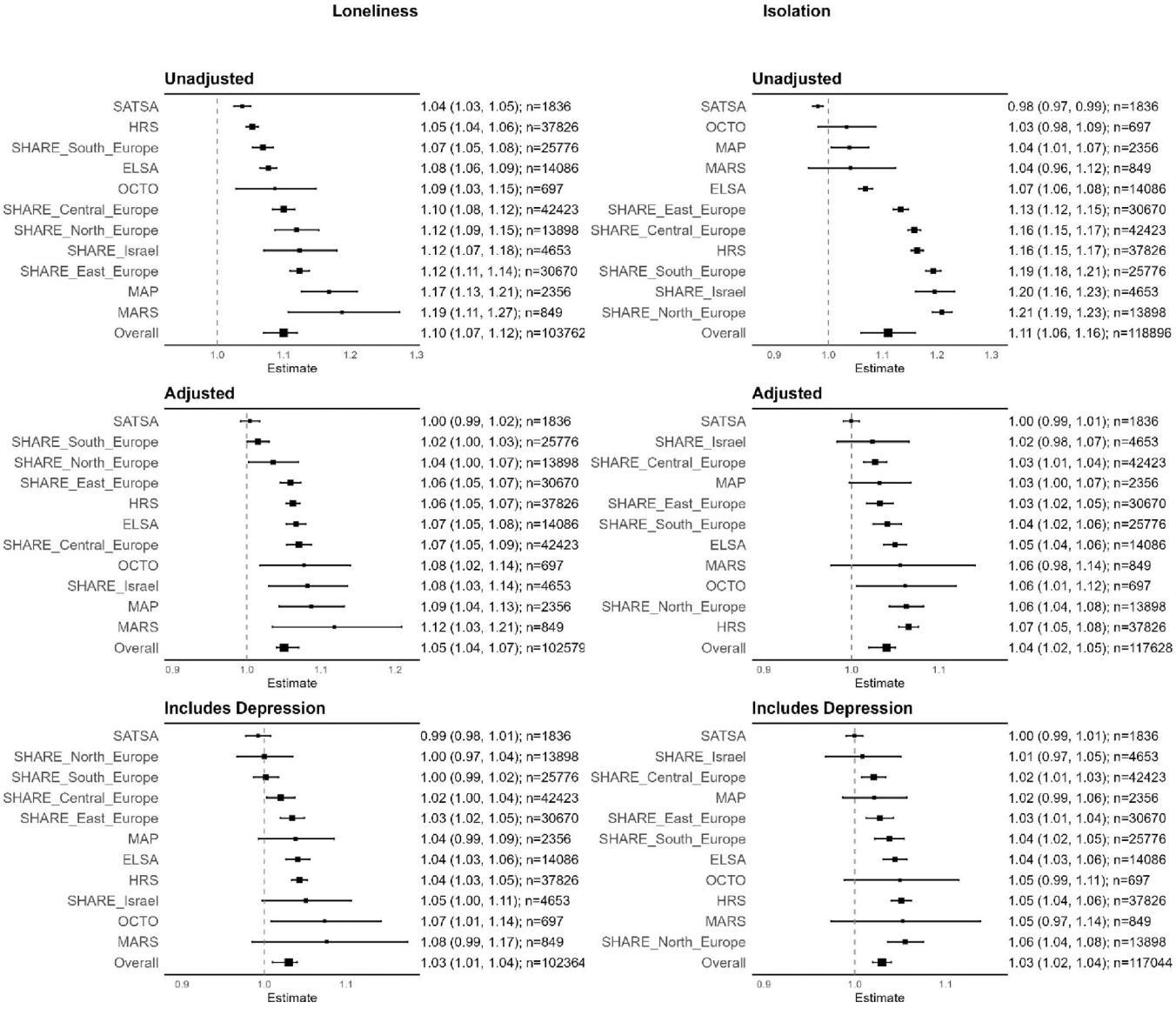

Figure 3. The Independent Effect of Loneliness and Social Isolation on Death: Cox Proportional Hazard Models

Note. Unadjusted = no covariates; Adjusted = controlling for age, sex, and education; Includes Depression = controlling for age, sex, education, and depressive symptoms.

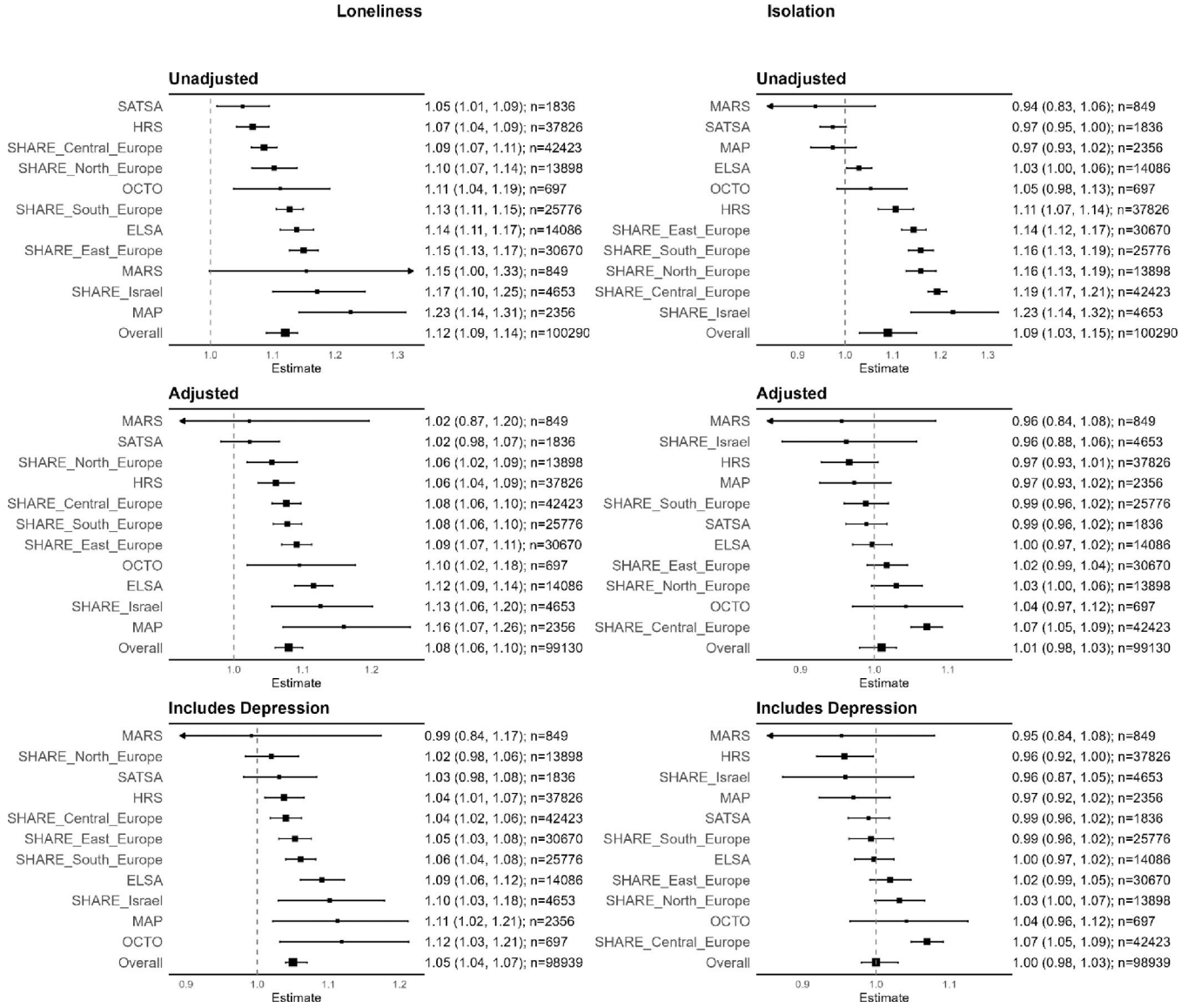

Figure 4. The Adjusted Effect of Loneliness and Social Isolation (Modeled Jointly) on Cognitive Impairment: Cox Proportional Hazard Models

Note. Unadjusted = no covariates; Adjusted = controlling for age, sex, and education; Includes Depression = controlling for age, sex, education, and depressive symptoms.

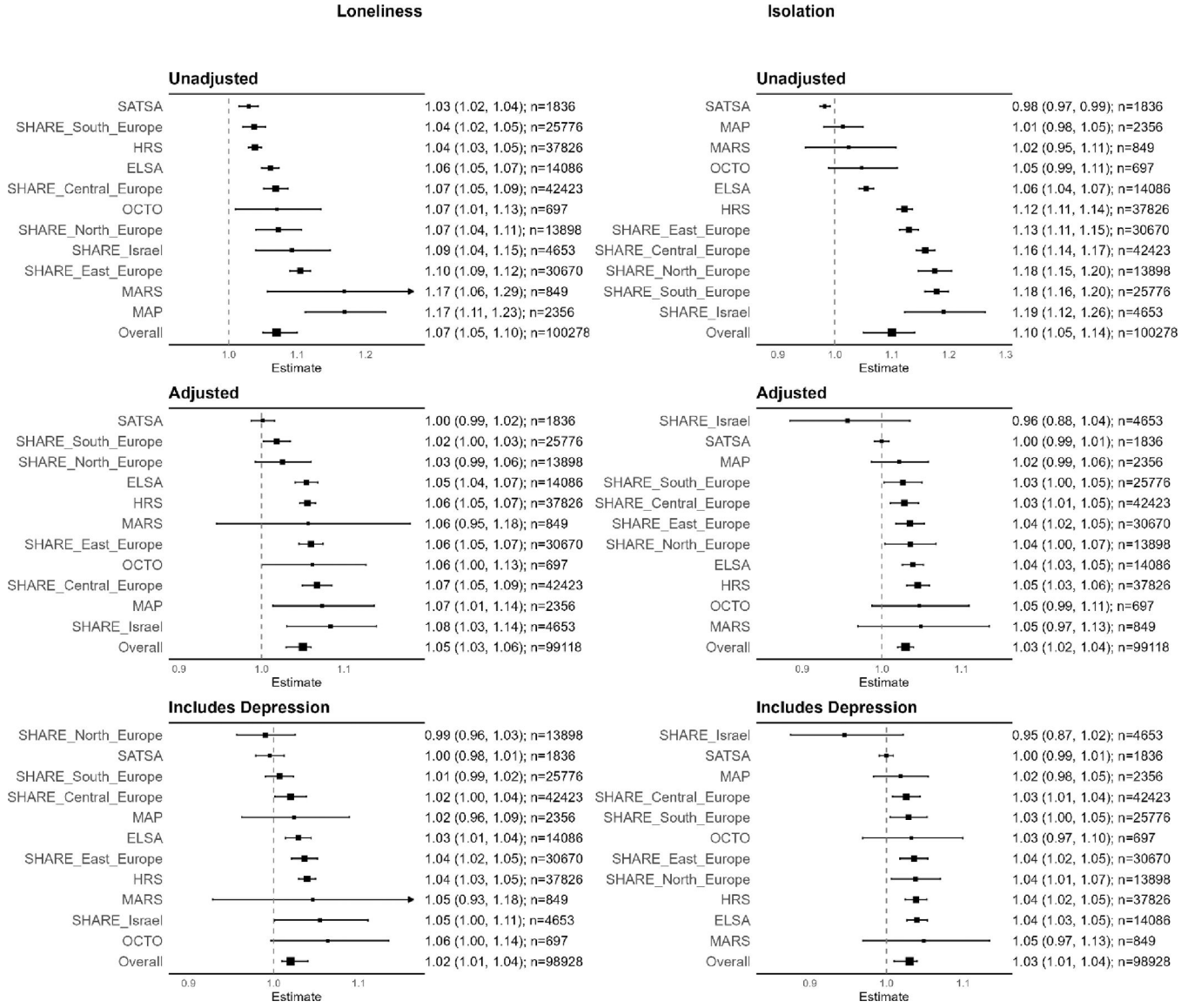

Figure 5. The Adjusted Effect of Loneliness and Social Isolation on Death (Modeled Jointly): Cox Proportional Hazard Models

Note. Unadjusted = no covariates; Adjusted = controlling for age, sex, and education; Includes Depression = controlling for age, sex, education, and depressive symptoms.

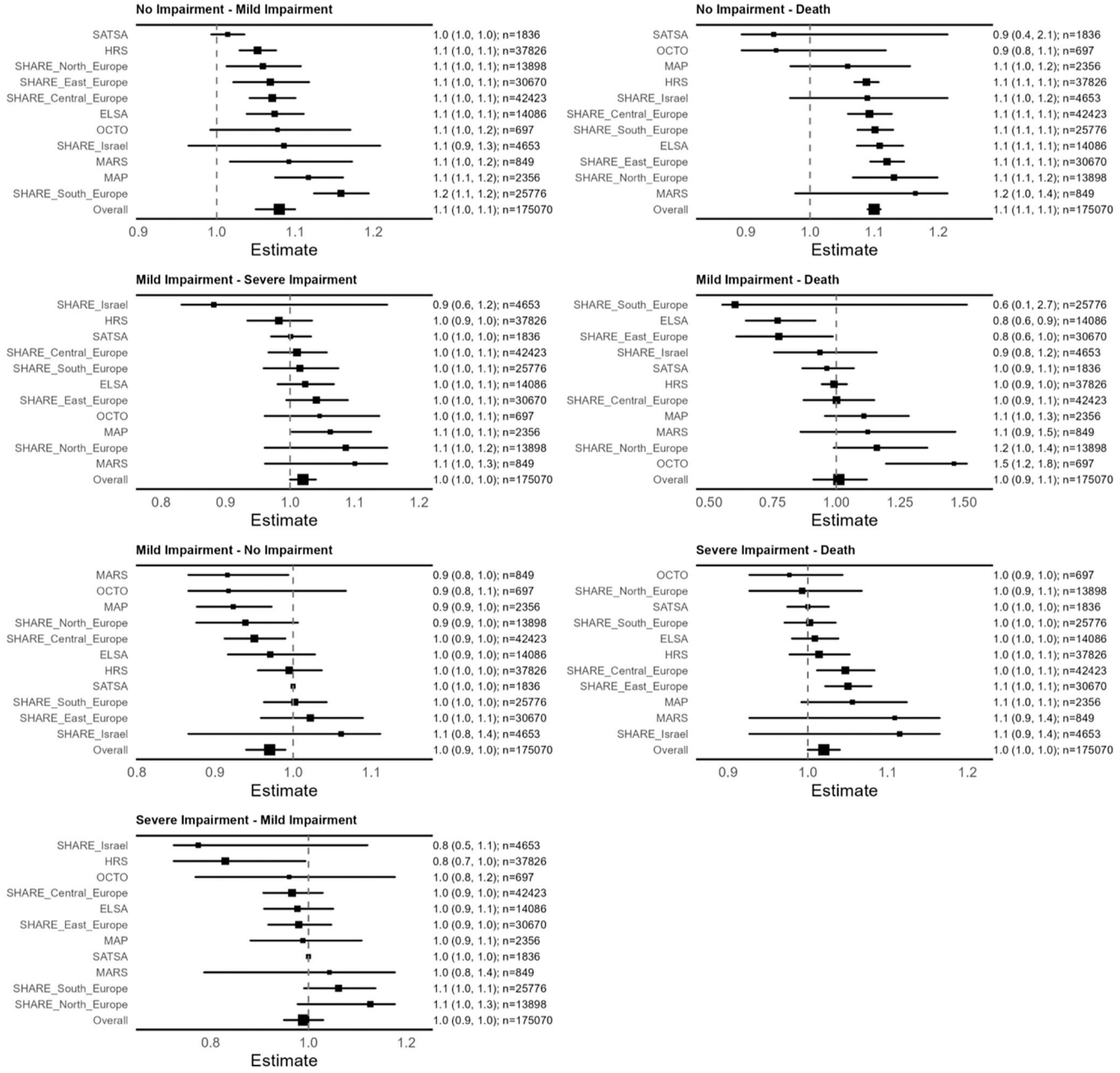

Figure 6. The Effect of Loneliness on Transitions between Cognitive Status Categories and Death: Multistate Survival Models

Note. These models control for age, sex, and education.

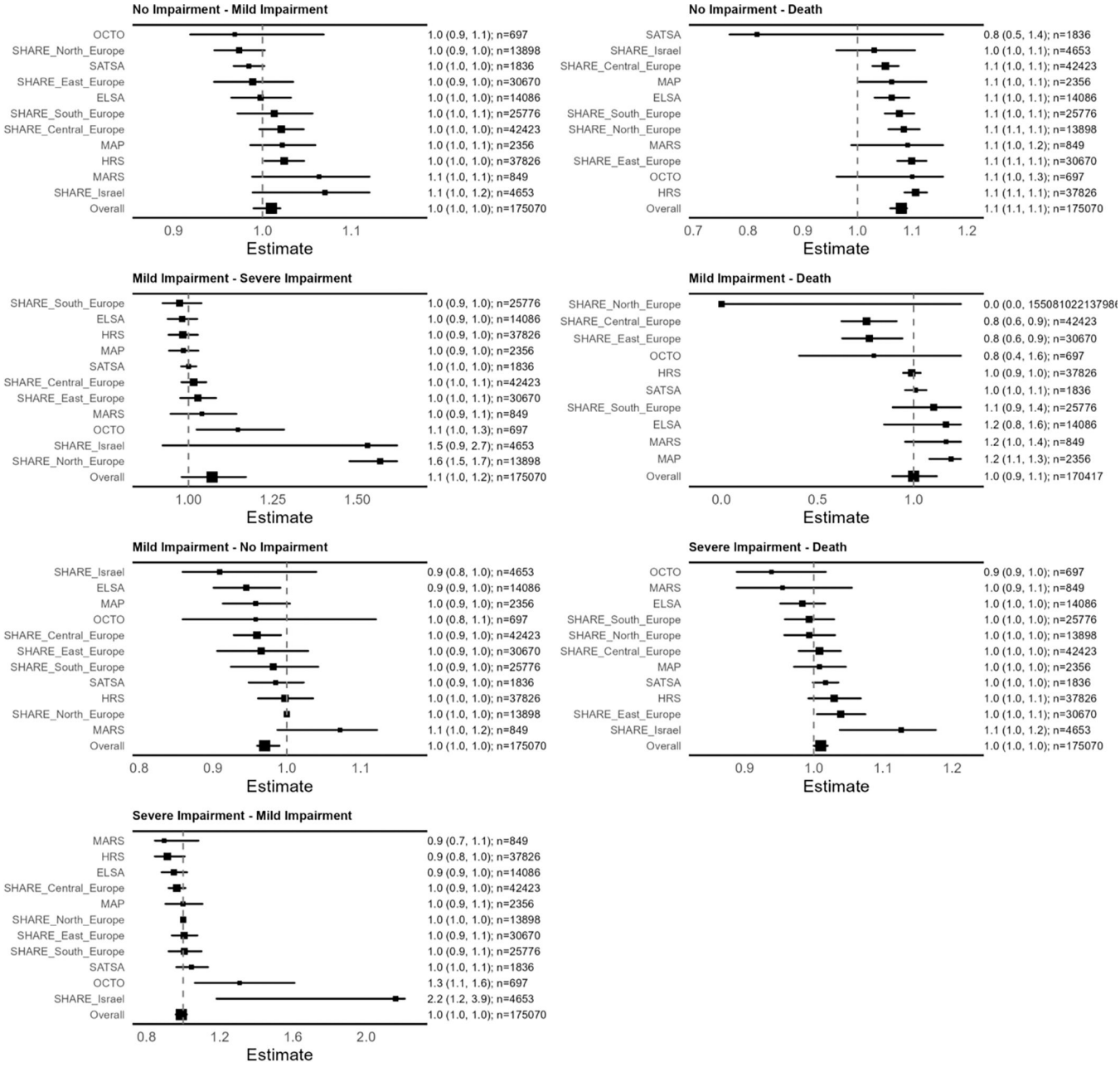

Figure 7. The Effect of Social Isolation on Transitions between Cognitive Status Categories and Death: Multistate Survival Models

Note. These models control for age, sex, and education.

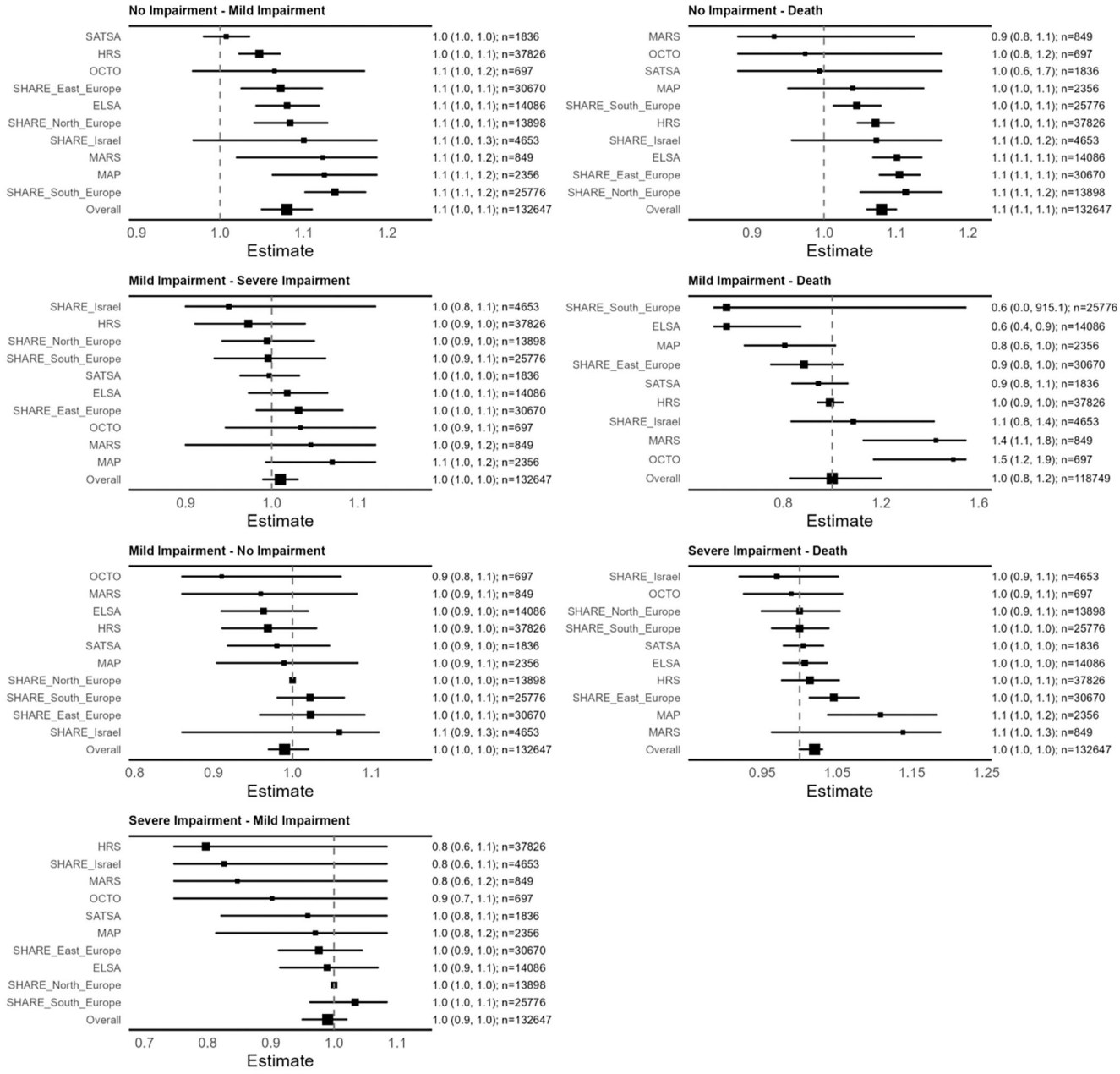

Figure 8. The Effect of Loneliness on Transitions between Cognitive Status Categories and Death, Adjusted for Social Isolation: Multistate Survival Models

Note. These models control for age, sex, and education.

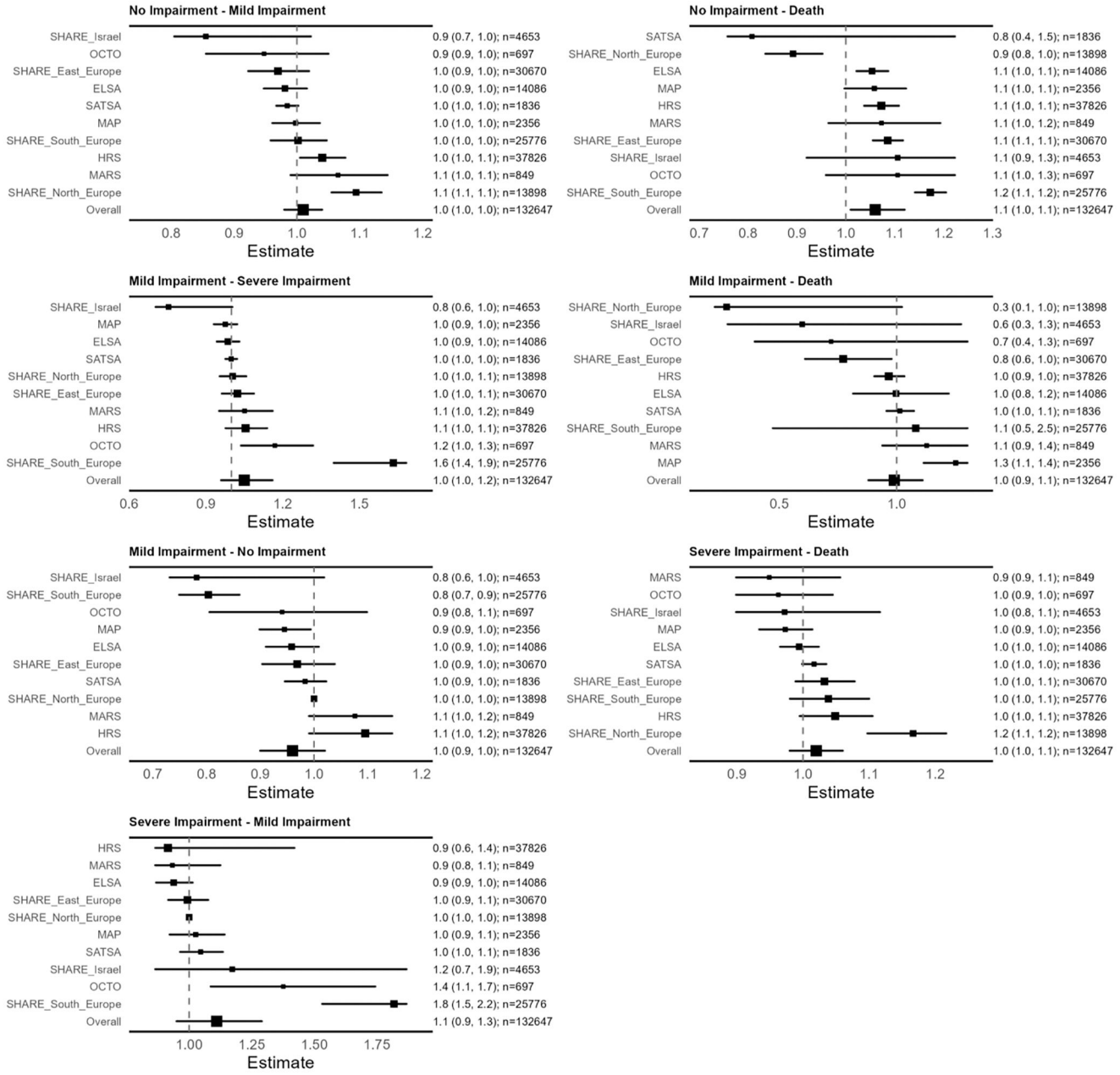

Figure 9. The Effect of Social Isolation on Transitions between Cognitive Status Categories and Death, Adjusted for Loneliness: Multistate Survival Models

Note. These models control for age, sex, and education.

Table 1

Research Questions 1–4 with Associated Analytic Approach, Hypotheses, and Number of Effect Sizes

	Individual predictors	Adjusted predictors
Individual outcomes	RQ1: Is loneliness or social isolation individually associated with the risk of severely impaired cognition or death? Analysis: Cox and Logistic regression, separate models for loneliness and social isolation, and for risk of severe cognitive impairment and for risk of death (4 models) Hypotheses: Loneliness and social isolation will be individually associated with the risk of severe cognitive impairment and the risk of death Number of effect sizes: *k*=4	RQ2: Is loneliness or social isolation independently associated with the risk of severely impaired cognition or death? Analysis: Cox and Logistic regression, including both loneliness and social isolation for risk of severe cognitive impairment, and for risk of death (2 models) Hypotheses: Social isolation will be a more robust predictor of severe cognitive impairment, when adjusting for loneliness Number of effect sizes: *k*=4
Adjusted outcomes	RQ3: Is loneliness or social isolation individually associated with risk of transitioning to mildly or severely impaired cognitive states and/or risk of death? Analysis: MSM (cognitive outcomes and mortality), separate models for loneliness and social isolation (2 models) Hypotheses: Loneliness and social isolation will be individually associated with the risk of transitioning forward through cognitive status categories, when accounting for death Number of effect sizes: *k*=14	RQ4: Are loneliness and social isolation independently associated with risk of transitioning to mildly or severely impaired cognitive states and/or risk of death? Analysis: MSM (cognitive outcomes and mortality), including both loneliness and social isolation (1 model) Hypotheses: Social isolation will be a more robust predictor of transitioning forward through cognitive status categories, when accounting for death and for loneliness Number of effect sizes: *k*=14

Note. RQ=Research Question; MSM= Multistate Survival Model; Number of effect sizes represent the number of individual meta-analyses we will fit per research question.

Table 2

Summary of Synthesized Results Across Cox Proportional Hazard Models and Multistate Survival Models

	Independent Predictors	Adjusted Predictors
Independent Outcomes (Cox Proportional Hazard Models)	***Loneliness:*** • ⬆ risk of severely impaired cognitive functioning (*HR*=1.09 [1.06,1.11], *p*<0.001) • ⬆ risk of death (*HR*=1.05 [1.04,1.07], *p*<0.001) ***Social Isolation:*** • ⬆ risk of severely impaired cognitive functioning (*HR*=1.03 [1.01,1.05], *p*=.009) • ⬆ risk of death (*HR*=1.04 [1.02,1.05], *p*<0.001)	***Loneliness:*** • ⬆ risk of severely impaired cognitive functioning (*HR*=1.08 [1.06,1.11], *p*<0.001) • ⬆ risk of death (*HR*=1.05 [1.03,1.06], *p*<0.001) ***Social Isolation:*** • No link with severely impaired cognitive functioning (*HR*=1.01 [0.98,1.03], *p*=0.643) • ⬆ risk of death (*HR*=1.03 [1.02,1.04], *p*<0.001)
Adjusted Outcomes (Multistate Survival Models)	***Loneliness:*** • ⬆ risk NCI to mildly impaired cognitive functioning (*HR*=1.08 [1.05,1.10], *p*<0.001) • ⬆ risk NCI to death (*HR*=1.10 [1.09,1.11], *p*<0.001) • ⬆ risk mildly to severely impaired cognitive functioning (*HR*=1.02, *95% CI* [1.00, 1.04], *p*=.027) • ⬆ risk severely impaired cognitive functioning to death (*HR*=1.02, *95% CI* [1.00, 1.04, *p*=.019) • ⬇likelihood mildly impaired cognitive functioning to NCI (*HR*=0.97, *95% CI* [0.94, 0.99], *p*=.010) • Not associated with any other transitions ***Social Isolation:*** • ⬆ risk NCI to death (*HR*=1.08 [1.06,1.09], *p*<0.001) • ⬇likelihood mildly impaired cognitive functioning to NCI (*HR*=0.97, *95% CI* [0.96, 0.99], *p*=.003) • Not associated with any other transitions	***Loneliness:*** • ⬆ risk NCI to mildly impaired cognitive functioning (*HR*=1.08 [1.05,1.11], *p*<0.001) • ⬆ risk NCI to death (*HR*=1.08 [1.06,1.10], *p*<0.001) • Not associated with any other transitions ***Social Isolation:*** • ⬆ risk NCI to death (*HR*=1.06 [1.01,1.12], *p*=0.024) • Not associated with any other transitions

Note. Independent predictors=loneliness or social isolation in separate models; Adjusted predictors=loneliness and social isolation included in the same model; Independent outcomes=severely impaired cognitive functioning or death as the outcome in separate models; Adjusted outcomes=transitions between cognitive functioning status categories and death modeled simultaneously; NCI=No cognitive impairment; HR=Hazard Ratio; all significant paths are consistent with hypotheses.