Loneliness and social isolation among older adults

Findings from the general population-based study "Good Aging in Skåne"

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Abstract:

Social isolation and loneliness among older adults have been linked with several health issues, including depression, cardiovascular disease, cognitive impairment, and mortality. However, associations of social isolation and loneliness with mental and somatic symptoms, sleep disturbances, and medication use are unclear. The aim of this thesis was to investigate these associations in a population-based cohort of older adults.

Paper I (cross-sectional, n=5804) examined prevalences of loneliness and social isolation and associations of these conditions with mental and somatic symptoms. 60% of participants reported loneliness feelings at least occasionally, and 6% were socially isolated. Multivariable linear and logistic regression models revealed associations of loneliness and social isolation with symptoms.

Paper II (longitudinal, n=2897) investigated associations of social isolation and loneliness with sleep disturbances at the 6-year re-examination. Social isolation and loneliness at baseline were in a multivariable logistic regression model associated with increased likelihood of reporting sleep disturbances at the 6-year re-examination.

Paper III (longitudinal, n=1526 in loneliness analysis, n=2556 in social isolation analysis) explored associations of incident polypharmacy with occurrence of loneliness and social isolation. Multivariable logistic regression models indicated that those with polypharmacy had increased risk of reporting occurrence of social isolation and loneliness during follow-up.

Paper IV (cross-sectional, n=6714) analysed associations of polypharmacy, psychotropic-, neurological-, and/or anticholinergic fall-risk-increasing drugs (pnaFRIDs), and cardiovascular drugs with social isolation and loneliness. pnaFRIDs were in multivariable logistic regression models associated with increased odds of reporting loneliness.

In conclusion, this thesis shows that social isolation and loneliness were associated with mental and somatic symptoms and sleep disturbances. Polypharmacy was associated with occurrence of social isolation and loneliness and pnaFRIDs were associated with loneliness.

Key words: loneliness, social isolation, older adults, symptoms, sleep disturbance, polypharmacy, fall-risk-increasing drugs, cardiovascular drugs

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Populärvetenskaplig sammanfattning på svenska

Bakgrund

Social isolering och ensamhetskänslor är två närbesläktade fenomen. Ensamhetskänslor brukar innefatta den subjektiva upplevelsen av att sakna meningsfulla relationer samt känslan av att sakna socialt stöd, medan begreppet social isolering ofta används för att beskriva en mer objektiv brist på sociala kontakter och interaktioner, exempelvis att man bor själv och sällan träffar andra människor. Det är alltså viktigt att särskilja objektiv ensamhet, såsom social isolering, från subjektiva ensamhetskänslor; man kan ju vara själv utan att nödvändigtvis känna sig ensam och vice versa. Hur vanligt social isolering och ensamhetskänslor är i den äldre befolkningen är inte helt klarlagt, men tidigare forskning indikerar att en betydande andel av äldre personer upplever någon form av ensamhet. Tidigare studier har också pekat på att ensamhetskänslor och social isolering kan ha en negativ inverkan på äldres välbefinnande och hälsa. Man har exempelvis sett samband mellan ensamhetskänslor och social isolering och en förhöjd risk att drabbas av hjärtkärlsjukdomar, depression, demens och att dö i förtid. Det är dock inte klarlagt om det även finns samband mellan ensamhetskänslor eller social isolering med subjektiv hälsa (såsom självupplevda symtom), sömnstörningar och läkemedelsanvändning hos äldre. Genom att klargöra förekomst av ensamhetskänslor och social isolering samt predisponerande faktorer och hälsoutfall kopplat till dessa tillstånd, så kan vi förhoppningsvis i framtiden bättre identifiera äldre som riskerar att drabbas och vidta åtgärder för att minska ensamhetskänslor och social isolering i denna grupp. Detta kan i sin tur på sikt förhoppningsvis minska de negativa hälsoeffekter som kopplats till ensamhet hos äldre.

Målsättningar med avhandlingen

Målsättningar för de fyra ingående delarbetena i avhandlingen var följande:

1. Undersöka förekomst av ensamhetskänslor och social isolering bland äldre samt studera samband mellan ensamhetskänslor och social isolering med psykiska och fysiska symtom.
2. Utreda samband mellan ensamhetskänslor, social isolering och sömnstörningar hos äldre.
3. Analysera om intag av många läkemedel samtidigt (polyfarmaci) är kopplat till ensamhetskänslor och social isolering hos äldre.
4. Identifiera eventuella samband mellan olika läkemedelsgrupper och ensamhetskänslor och social isolering bland äldre.

Metod och material

Till avhandlingen har data använts från populationsstudien "Gott Åldrande i Skåne" (GÅS), som är en del av den svenska nationella studien om åldrande och hälsa (Swedish National study on Aging and Care, SNAC). Vuxna individer 60 år och äldre inom vissa åldersgrupper som bor i någon av de fem skånska kommuner Eslöv, Hässleholm, Malmö, Osby och Ystad väljs slumpmässigt ut från folkbokföringsregistret för inbjudan. Kommunerna är valda för att representera både stad- och landsbygd. Deltagarna genomgår omfattande fysiska och psykologiska undersökningar och bjuds in till uppföljande undersökningar; vart sjätte år för de som är mellan 60 – 78 år och vart tredje år för de som är äldre än 78 år. GÅS-studien, som påbörjades 2001, pågår alltjämt och förutom återbesök rekryteras nya deltagare fortlöpande. Cirka 65% av de som bjudits in har tackat ja till att delta. Totalt omfattar studien hittills cirka 6800 deltagare.

I undersökningen ingår att deltagarna besvarar enkäter i avsikt att sammanställa information om bland annat ensamhetskänslor, social isolering, socio-demografiska data och livsstil. Medicinsk personal (sjuksköterskor, läkare och beteendevetare) genomför strukturerade intervjuer enligt fördefinierade protokoll och sammanställer uppgifter om bland annat sjukdomshistoria, medicinering, kognition (exempelvis bedömning av minnesförmåga) och depression. Studiebesöken genomförs vid ett av fyra forskningscentren i Eslöv, Hässleholm, Malmö eller Ystad. För de deltagare som har svårigheter att ta sig till studiecentren erbjuds hembesök alternativt telefonintervjuer.

GÅS-studien genomförs i enlighet med gällande juridiska och etiska riktlinjer och har godkänts av den regionala etikprövningsnämnden vid Lunds universitet.

Resultat

Artikel I

Målet med denna studie var att undersöka förekomst av ensamhetskänslor och social isolering i den äldre befolkningen samt eventuella samband till psykiska (exempelvis trötthet, nedstämdhet) och fysiska symtom (exempelvis smärta, hörselnedsättning). I denna tvärsnittsstudie ingick 5804 deltagare. Av dessa uppgav en majoritet (60%) att de känt sig ensamma vid åtminstone något tillfälle de senaste åren. Längre perioder med mer frekventa eller till och med konstanta ensamhetskänslor (14%) samt social isolering (6%) var mindre vanligt bland GÅS-deltagarna. Kvinnor över 80 år uppgav högst förekomst av ensamhetskänslor (74%) och social isolering (11%). Motsvarande siffror för män över 80 år var 52% för ensamhetskänslor respektive 8% för social isolering. En majoritet av deltagarna som var socialt isolerade uppgav ensamhetskänslor (80%), varav nära en av tre (32%)

uppgav längre perioder med mer frekventa eller konstanta ensamhetskänslor. Samband mellan ensamhetskänslor, social isolering och symtom undersöktes med statistiska metoder där hänsyn tagits till deltagarnas ålder, kön, utbildningsnivå, fysisk aktivitet, alkoholkonsumtion, rökning och hälsoattityder. Resultatet visade att äldre med ensamhetskänslor rapporterade betydligt fler symtom jämfört de som inte känt sig ensamma. Detta gällde för både psykiska och fysiska symtom.

Artikel II

Målet med denna studie var att undersöka samband mellan ensamhetskänslor, social isolering och sömnstörningar hos äldre. I denna uppföljningsstudie ingick 2897 deltagare. Förekomst av ensamhetskänslor och social isolering vid första studiebesöket var kopplat till ökad risk att ha sömnstörningar vid återbesöket 6 år senare. Detta gällde även efter hänsyn tagits till deltagarnas ålder, kön, civilstånd, utbildningsnivå, ekonomiska status, rökning, kroniska sjukdomar, depression, kognitiv funktion och eventuell sömnstörning vid första besöket.

Artikel III

Målet med denna studie var att undersöka samband mellan intag av flera läkemedel samtidigt (polyfarmaci) och nytillkomna ensamhetskänslor respektive social isolering. I uppföljningsanalysen för nytillkomna ensamhetskänslor ingick 1526 deltagare medan 2556 deltagare ingick i analysen för nytillkommen social isolering. Polyfarmaci definierades som intag av fem läkemedel eller fler. I de statistiska metoderna för att undersöka samband tog vi hänsyn till deltagarnas kön, ålder, utbildningsnivå, fysisk aktivitet, kroniska sjukdomar och depressiva symtom. Polyfarmaci var kopplat till ökad risk att rapportera nytillkomna ensamhetskänslor och social isolering under uppföljningstiden.

Artikel IV

Målet med denna studie var att undersöka samband mellan olika sorters läkemedel och ensamhetskänslor respektive social isolering. I denna tvärsnittsstudie ingick 6714 deltagare. Läkemedelsgrupper av intresse var bland annat läkemedel som kan påverka balansen och risken för att falla. Vi tog hänsyn till deltagarnas kön, ålder, utbildningsnivå, fysisk aktivitet och kroniska sjukdomar i sambandsanalyserna. En grupp fallriskläkemedel (innefattar bland annat sömnläkemedel, antidepressiva och ångestlindrande läkemedel) var kopplat till förhöjd risk att rapportera ensamhetskänslor.

Slutsats

Ensamhetskänslor är relativt vanliga bland äldre, men frekventa ensamhetskänslor och social isolering är mindre vanligt. Ensamhetskänslor och social isolering var bland annat kopplat till symtombörda, sömnstörningar samt användning av vissa

läkemedel. Sambanden som undersökts i denna avhandling är observationsbaserade och således inte några säkra orsakssamband. Fler studier behövs som undersöker mekanismer och riktningen på studerade samband samt om ensamhetskänslor och social isolering även är kopplat till sjukvårdskonsumtion och om åtgärder för att minska användning av vissa riskläkemedel även påverkar ensamhetskänslor och social isolering.

List of Papers

This dissertation is based on four papers, referred to in the text by their Roman numerals. All papers are published under the terms of open access agreements (CC-BY) that permits reproduction of the papers for this thesis.

Paper I

Svensson, M., Rosso, A., Elmståhl, S., & Ekström, H. (2022). Loneliness, social isolation, and health complaints among older people: A population-based study from the "Good Aging in Skåne (GÅS)" project. SSM - Population Health, 20, 101287.

Paper II

Ekström H, Svensson M, Elmståhl S, Wranker LS (2024). The association between loneliness, social isolation, and sleep disturbances in older adults: A follow-up study from the Swedish good aging in Skåne project. SAGE Open Med; 12:20503121231222823

Paper III

Svensson, M., Ekström, H., Elmståhl, S., & Rosso, A. (2024). Association of polypharmacy with occurrence of loneliness and social isolation among older adults. Archives of Gerontology and Geriatrics, 116, 105158.

Paper IV

Svensson, M., Ekström, H., Elmståhl, S., & Rosso, A. (2024). Association of polypharmacy, fall-risk-increasing drugs, and cardiovascular drugs with loneliness and social isolation among older adults. Archives of Gerontology and Geriatrics Plus, 1(4):100089.

The authors' contributions to the Papers

The authors are referred to as MS (Markus Svensson), SE (Sölve Elmståhl, main supervisor, PI for the GÅS study), AR (Aldana Rosso, co-supervisor), HE (Henrik Ekström, co-supervisor), and LSW (Lena Sandin Wranker, co-author Paper II).

Paper I

All authors (MS, AR, SE, HE) were involved in the conceptualization of the study. MS conducted the data curation and formal analysis. MS and HE wrote the original draft. All authors reviewed, revised, and approved the final version of the manuscript.

Paper II

All authors (HE, MS, SE, LSW) were involved in the conceptualization of the study. HE and MS conducted the data curation and formal analysis. HE and MS wrote the original draft. All authors reviewed, revised, and approved the final version of the manuscript.

Paper III

All authors (MS, HE, SE, AR) were involved in the conceptualization of the study. AR conducted the data curation and AR and MS wrote the statistical plan and conducted the formal statistical analyses. MS wrote the original draft. All authors reviewed, revised, and approved the final version of the manuscript.

Paper IV

All authors (MS, HE, SE, AR) were involved in the conceptualization of the study. AR conducted the data curation. AR and MS wrote the statistical plan and conducted the formal statistical analyses. MS wrote the original draft. All authors reviewed, revised, and approved the final version of the manuscript.

Abbreviations

ADE	Adverse Drug Events
ADL	Activities of Daily Living
ATC	Anatomical Therapeutic Chemical Classification System
CARE	Comprehensive Assessment and Referral Evaluation Scale
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPRS	Comprehensive Psychiatric Rating Scale
DAG	Directed acyclic graph
FRIDs	Fall-risk-increasing drugs
GDPR	General Data Protection Regulation
GÅS	Gott Åldrande i Skåne/Good Aging in Skåne
HLC	Health Locus of Control
ICD-10	International Classification of Diseases, 10th revision
LUSEC	Lund University's internal data storage platform
MADRS	Montgomery–Åsberg Depression Rating Scale
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
OR	Odds ratio
OTC	Over-the-counter medicine
PAL	Patientansvarig läkare
pnaFRIDs	Psychotropic-, neurological-, and/or anticholinergic fall-risk-increasing drugs
QoL	Quality of Life
RCT	Randomized controlled trial
RSVD	Region Skåne Healthcare databases
SCB	Swedish Central Bureau of Statistics
SDS	Sleep disturbance scale
SNAC	Swedish National study on Aging and Care
TUG	Timed-up-and-go test
WHO	World Health Organization
WMA	World Medical Association

Papers at a glance

Paper	I	II	III	IV
Aim	Investigate prevalence of loneliness and social isolation among older adults and examine associations of loneliness and social isolation with mental and somatic symptoms	Study associations of loneliness and social isolation with sleep disturbances among older adults.	Examine associations of polypharmacy (≥5 medications) with occurrence of loneliness and social isolation among older adults.	Identify associations of medication groups with loneliness and social isolation among older adults.
Population	Participants from GÅS. N=5804, mean age 70 years, 55% women	Participants from GÅS. N=2897, mean age at baseline 67 years, 56% women	Participants from GÅS. N=1526 in loneliness occurrence cohort (mean age at baseline 67 years, 41% women), N=2556 in social isolation occurrence cohort (mean age at baseline 66 years, 52% women)	Participants from GÅS. N=6714, mean age 70 years, 54% women
Design	Cross-sectional	Longitudinal	Longitudinal	Cross-sectional
Statistical method(s)	Linear regression, logistic regression	Logistic regression	Logistic regression	Logistic regression
Exposure variable(s)	Loneliness, social isolation	Loneliness, social isolation	Polypharmacy	Polypharmacy, psychotropic-, neurological-, and/or anticholinergic FRIDs (pnaFRIDs), cardiovascular drugs
Outcome variable(s)	Mental and somatic symptoms	Sleep disturbance at the 6-year re-examination	Loneliness, social isolation during follow-up	Loneliness, social isolation
Main results	60% of participants experienced loneliness at least occasionally, and 6% were classified as socially isolated. Loneliness was associated to an increased number of reported symptoms.	Social isolation and loneliness at baseline were associated with increased likelihood of reporting sleep disturbances at the 6-year re-examination	The odds for occurrence of loneliness and social isolation were higher for participants with polypharmacy compared to participants without polypharmacy	pnaFRIDs were associated with increased odds of loneliness

Introduction

Social isolation and loneliness among older adults are themes of clinical relevance (1, 2), since they have been linked with increased risk of depression, cognitive impairment, cardiovascular disease, and mortality (3).

The demographic transition in population age, with decreasing birth rates and increasing longevity, is a global phenomenon and entails that the proportion of older adults in the population is steadily increasing (4). The age distribution in a population has important implications for social services, healthcare, and economic productivity. A higher proportion of older adults may lead to increased demand for healthcare services and pensions, as well as a decreasing labor force (5). Since loneliness and social isolation are believed to be most prevalent among older adults (6, 7), these conditions are expected to increase with an ageing population (2). This may in turn increase the health burden associated with these conditions (3), and thus straining the social services and healthcare systems even further (2).

With these prospects in mind, the World Health Organization (WHO), in partnership with the European Commission and the Swedish Government, have initiated a Commission on Social Connection with specific goals to increase awareness of social isolation and loneliness and declared the problem as a global public health priority (8). The WHO stated in 2023 that "social isolation and loneliness have serious, and still under-recognized, impacts on our health and lifespan" (8). The Swedish Government issued in 2023 a declaration to government organs and the research community, requesting that these organs should strive to improve methods of measuring social isolation and loneliness and collect data on prevalence, risk- and protective factors, and health-related outcomes of social isolation and loneliness (9).

The Good Aging in Skåne study (GÅS) is a general population-based study of older adults living in southern Sweden (10). The comprehensive sampling in GÅS provides opportunity to investigate associations of social isolation and loneliness with several health-related factors, in a representative cohort of older adults. Since associations between social isolation and loneliness with subjective health, sleep disturbances, and medication use among older adults are not well understood, analyzing these associations was the main aim for this thesis.

Defining loneliness and social isolation

There are no widely accepted standard definitions for the concepts of social isolation nor loneliness (11-13). There may be several reasons for this. First, the research fields of social isolation and loneliness are inter-disciplinary (14, 15), involving for example anthropologists, sociologists, philosophers, theologians, psychologists, and medical professionals. The different disciplines may approach these concepts from varied angles, and establishing a common definition for all disciplines is thus challenging (14). Second, societies and cultures have varying norms about social interactions (15). In some societies, high levels of social engagement is expected (e.g., Portugal, Bulgaria), while in others, independency of other people is the norm (e.g., the United Kingdom, the Netherlands) (16). Deviations from societal norms may in turn affect loneliness, adding further complexity to defining and interpreting loneliness in different cultures (16). Third, quantifying and defining thresholds for concepts such as loneliness is difficult due to its inherently subjective, self-reported, nature and the potential stigma often associated with loneliness (17).

With these challenges in mind, definitions commonly applied in health-related research are presented below.

Loneliness

Loneliness may be defined as the *subjective* sense of lacking companionship, occurring when there is a discrepancy between perceived and desired quality and/or quantity of social relationships (18, 19). Central to most current research definitions of loneliness is that loneliness is considered a *subjective* and *negative/unpleasant* experience (20). To emphasize the subjectiveness, loneliness is sometimes referred to as "emotional loneliness" (21). Belongingness and embeddedness are often described as opposites to loneliness (20).

Social isolation

Social isolation is a concept used to describe people that are disconnected from the community, friends, and family (22). In contrast to loneliness, social isolation is often characterized as the *objective* absence of relations and social interactions (20). A person living alone with quantitively low frequency of social contacts may be considered as "objectively alone" and thus socially isolated (20, 23). Social connectedness is often labeled as an antonym to social isolation (22).

Although sometimes overlapping, many researchers consider loneliness and social isolation as separate concepts, since socially isolated people are not necessarily lonely and vice versa (20, 21, 24).

Other related concepts and antonyms

Solitude

Solitude is usually defined as being alone but not feeling lonely (24, 25). Solitude is often characterized by voluntary isolation from others. In contrast with loneliness, solitude is generally associated with a positive connotation, and associated with engagement in activities such as self-reflection, relaxation, and personal and spiritual growth (24, 25).

Existential loneliness

Existential loneliness refers to a feeling of disconnection that is by some researchers considered more profound than emotional loneliness and social isolation (24, 26). It is sometimes used to describe an awareness of a fundamental separateness from other people and the world (27), often associated with self-reflection of an individual's purpose of existence and feelings of meaninglessness (26). In medical research, existential loneliness has mostly been studied in end-of-life/palliative care settings (28).

Social capital

Social capital is a complex concept with somewhat varying definitions but may include consideration of both social- and cognitive factors, such as civic engagement, social participation, and trust (29, 30). While loneliness and social isolation are often being applied in the micro (individual) level, social capital can be used to describe social relations (and the value of such relations) on a broader scale, including contextual traits of societies at the macro (e.g., countries) and meso (e.g., neighborhoods) levels (30).

Social support

Social support can be defined "support accessible to an individual through social ties to other individuals, groups, and the larger community" (31). Thus, social support is often used to describe the perceived availability of social contacts that can fulfil certain functions, including practical support for daily activities but also emotional support in challenging situations (32).

Prevalence and incidence of loneliness and social isolation

Estimating the prevalence of social isolation and loneliness is challenging due to varying definitions, cultural differences, and varying measurements, which affect the internal and external validity of findings reported in the literature (3). Additionally, the prevalence of loneliness and social isolation alters with age (14). Previous cross-sectional studies in Western countries (e.g., the United States of America, the United Kingdom, Australia) have estimated that among older adults aged 60–79 years, 20–35% experience emotional loneliness, while 5–12% are considered socially isolated (14, 33-35). In comparison, among those aged 80 years and over, 30–50% report loneliness, and 9–34% are deemed socially isolated (6, 7, 14, 36-39).

Calculating incidences of social isolation and loneliness is even more challenging, since these conditions are potentially unstable, meaning that individuals may fluctuate back and forth between a lonely/not-lonely and isolated/non-isolated state over time (40). Longitudinal studies on older adults have found that during follow up (range 3-7 years), 13-26% went from not lonely to lonely, 3-16% went from lonely to not lonely, and 4-18% were steadily lonely (40-43). As for social isolation, a 4-year follow-up study found that among non-isolated participants at baseline, 38% reported increased isolation, 12% reported decreased isolation, and 50% were stable; and among those isolated at baseline, 15% reported increased isolation, 45% reported decreased isolation, and 39% remained stable (44).

Clinical relevance of loneliness and social isolation

Morbidity and geriatric syndromes

Chronic diseases and conditions (e.g., diabetes mellitus, cardiovascular diseases, neurological disorders) are common among older adults, with 45-80% of adults aged 65 and older having at least one chronic disease or condition (45, 46). Social isolation and loneliness have been associated with numerous diseases and health conditions (3, 47-49). Chronic disease may influence feelings of loneliness and social isolation in several ways, including functional impairments, which may limit mobility and meeting with friends and family, social stigma (e.g., symptoms such as incontinence, memory decline, coughing), and existential loneliness, especially among the terminally ill (28, 50). Associations between social isolation, loneliness and disease are in most cases believed to be bi-directional, meaning that diseases can increase the likelihood of feeling lonely and being isolated and vice versa; social

isolation and loneliness may increase the risk of developing disease (51). The evidence for associations of somatic diseases with social isolation and loneliness is relatively consistent concerning associations with cardiovascular diseases (e.g., coronary heart disease, stroke) (3, 47, 48). The mechanisms for these associations are largely unknown or ambiguous, although negative impact on health-behaviors (e.g., more smoking, less physical activity), depressive symptoms, sleep disturbance, less medication adherence, and inflammatory- and neuroendocrine dysregulation have been proposed as possible mechanisms for associations of social isolation, loneliness, and cardiovascular diseases (48).

In terms of mental and cognitive disorders, previous research is somewhat mixed regarding the role of loneliness and social isolation (3, 48). Associations of social isolation and loneliness with increased risk of depression are relatively consistent (3, 49). As for dementia and mild cognitive impairment (MCI), the evidence for associations with loneliness and social isolation is slightly mixed, although most studies indicate that loneliness and social isolation are associated with an increased risk of memory decline (52) and developing MCI and dementia (44, 48).

Frailty is usually defined and characterized by vulnerability to stressors and may include traits such as low physical capacity and activity, slow walking speed, muscle weakness, fatigue, and weight loss (53). Frail older adults are at increased risk of falling, disability, lack of independency in activities of daily living, and hospitalizations, which may hinder social contacts with others and thereby increase the likelihood of experiencing loneliness and social isolation (53, 54).

Mortality

Both social isolation and loneliness have been associated with an increased mortality rate (3, 44). In a systematic review of 90 cohort studies with over two million participants, loneliness and social isolation were associated with an increased risk of all-cause-, cardiovascular related-, and cancer-related mortality (11). Mechanisms for these associations are likely multifactorial and overlapping with disease-related mechanisms, such as inflammatory- and neuroendocrine dysregulation and negative impact on health-behaviors (11, 48).

Healthcare consumption

Previous research investigating associations of social isolation and loneliness with healthcare consumption has presented somewhat mixed findings (45). Older adults with social isolation and loneliness may be at increased risk of emergency department visits, early hospital readmissions and longer hospital stays (55-57), but they may also utilize preventive care services (e.g., dentist visits, cancer-screening programs, immunizations, general practitioner visits) less frequently (58-60). The

lesser utility of preventive care could potentially be a contributing mechanism for the associations reported for social isolation and loneliness with morbidity and mortality (11, 48).

Associations of social isolation and loneliness with subjective health, sleep disturbances, and medication use

Subjective health

Associations of social isolation, loneliness, and self-perceived health (e.g., self-reported symptoms, self-rated health) have in previous research mostly focused on associations with depressive symptoms (61-63). Associations with other symptoms, such as cardiopulmonary, musculoskeletal, gastrointestinal, metabolic, head-related, and urinary symptoms, have been less thoroughly investigated in the general population of older adults. In a study on frail older adults (frail defined in this study as being dependent in activities of daily living and having a high degree of healthcare consumption), loneliness was associated with an increased number of reported symptoms and increased healthcare consumption (e.g., emergency department visits) (57). However, a comprehensive assessment of associations of social isolation and loneliness with both somatic and mental health-related symptoms in the general population of older adults, along with analyses of specific symptom domains, was to my knowledge lacking prior to the planning of this thesis. Such analyses may provide additional evidence and detail to the potential associations of social isolation, loneliness, and subjective health in the general older population.

Sleep disturbance

The term ‘sleep disturbance’ is broad and may refer to a wide variety of sleep symptoms, including struggle falling asleep, staying asleep, early morning awakenings, excessive daytime sleepiness and experiencing non-restorative sleep (64). Sleep disturbances are common among older people, with prevalence ranging from 30% to 50% (64-66). Sleep disturbances among older adults can arise due to physiological changes associated with aging (e.g., decreased melatonin synthesis) and health conditions such as heart failure (e.g., orthopnea), obstructive sleep apnea (OSA), restless legs syndrome (RLS), chronic pain, and depressive disorders (64). Among younger adults, experimental research has found that sleep deprivation can result in a neural and behavioral phenotype characterized by social withdrawal and increased feelings of loneliness (67), and vice versa; social isolation and loneliness have been associated with increased risk of reporting sleep disturbances (68).

However, the literature on older adults is somewhat inconclusive and longitudinal associations between social isolation, loneliness and sleep were overall unclear when planning this thesis (69). Longitudinal studies examining associations between sleep disturbances, loneliness, and social isolation among older adults have been suggested as particularly important for future research, given the high prevalence of these conditions in this population and potential health implications associated with these conditions (67, 69).

Medications

Associations between medications, loneliness, and social isolation are overall poorly understood (70). A few cross-sectional studies have explored associations between medications and loneliness and social isolation, with mixed findings (71-77). Longitudinal studies on the general older population investigating these associations were to my knowledge lacking when planning this thesis (70).

There are several mechanisms by which medications may influence loneliness and social isolation. With increasing possibilities to treat and alleviate chronic diseases, polypharmacy, commonly defined as regular intake of five medications or more (78, 79), poses an increasing challenge in the healthcare of older adults (80, 81). The complexity of handling numerous medications may be overwhelming for an older individual, inducing feelings of stress and anxiety, which may be associated with social withdrawal (82). Polypharmacy also increases the risk of adverse drug events (ADEs), including drug–drug and drug–disease interactions, side-effects, less medication adherence, and increased healthcare consumption (70, 83-85). Older people often have reduced renal and hepatic drug elimination, as well as altered function of the target organs for the drug(s) (86). As a result, older individuals may be more vulnerable to the adverse effects of polypharmacy compared to younger individuals (86).

Older adults with polypharmacy may be exposed to many different kinds of medications with varying effects. The most common drug categories among older adults with polypharmacy in Sweden are cardiovascular drugs, psychotropics, and analgesics (87). Some of these medications may affect balance, steadiness, and alertness in a negative manner, thereby increasing the risk of falling (88). Such drugs, commonly known as fall-risk-increasing drugs (FRIDs), constitute a diverse group of medications which may include diuretics, antipsychotics, anxiolytics, hypnotics, sedatives, antidepressants, opioids, and antiepileptics (89-92). Hypothetically, by increasing the risk of falling and fear of falling, older adults taking FRIDs are possibly less mobile and thus hindered from engaging in social interactions with others. In the other direction, spousal bereavement may induce social isolation and loneliness (93), and increase the likelihood of being prescribed psychotropic medications (94), indicating that loneliness and social isolation may also increase the probability of FRID use.

Aims

General aim of the thesis

The overall aim of this thesis was to describe prevalence, certain predisposing factors, and self-reported health-related outcomes of loneliness and social isolation among older adults. All projects and objectives in this thesis were carefully designed and planned to offer new insights for the research field of social isolation and loneliness among older adults. Since there was insufficient understanding regarding associations between social isolation, loneliness, and subjective health (e.g., symptoms), sleep disturbances, and medication use, the specific aims of this thesis were to investigate these associations.

Specific aims of the separate papers

Paper I

To assess the prevalence of loneliness and social isolation among older adults and investigate their associations with mental and somatic symptoms.

Paper II

To examine associations between loneliness and social isolation and sleep disturbances in older adults.

Paper III

To explore associations of incident polypharmacy (≥5 medications) with occurrence of loneliness and social isolation among older adults.

Paper IV

To identify associations of different medication groups, including fall-risk-increasing drugs (FRIDs), with loneliness and social isolation in older adults.

Material and methods

The Good Aging in Skåne study

The study population for this thesis was drawn from the general population-based study Good Aging in Skåne (Gott Åldrande i Skåne, GÅS). GÅS is an ongoing longitudinal cohort study involving older adults (60+ years) living in five municipalities (Eslöv, Hässleholm, Malmö, Osby, and Ystad) in the county of Skåne in southern Sweden (10). Participants live in both urban and rural areas. GÅS is part of the Swedish National Study on Aging and Care (SNAC), as one of four participating regions (95). The four regions are Skåne (GÅS), Blekinge (SNAC-B), Stockholm (SNAC-Kungsholmen), and Gävleborg (SNAC-Nordanstig). The overall aims of GÅS and SNAC are to collect data from a large, representative panel of older adults from different age cohorts and follow the participants over time to document and describe the aging process from different aspects, including health- and psychosocial aspects.

The GÅS study began recruiting participants in 2001. Participants were invited via letter using information from the Swedish National Population Register. The selection of subjects for invitation was random within the pre-specified age groups living in the five municipalities. Four waves of recruitment have currently been carried out. Wave 1 recruited participants aged 60, 66, 72, 78, 81, 84, 87, 90, 93 years old from 2001 to 2004. For the subsequent recruitment waves, adults aged 60 and 81 years were invited. Wave 2 recruited participants from 2006 to 2012, Wave 3 from 2012 to 2016, and Wave 4 from 2017 to 2022. Non-respondents were contacted again via telephone or letter. Those unable to attend visits at the study centers were primarily offered visits at home and secondarily telephone interviews. Study subjects younger than 78 years of age were invited for re-examination every six years, while participants older than 78 years were invited back every three years. The participation rate (defined as $n_{[participants]}/n_{[eligible]}$) (96) was 60% in Wave 1, 73% in Wave 2, 70% in Wave 3, and 65% in Wave 4, giving an overall participation rate of 65% for the four waves (Table 1). Non-participants refers to those who were eligible but declined participation.

Table 1. The participation rates of the Good Aging in Skåne recruitment waves. Non-participants refers to those who were eligible but declined participation.

Recruitment wave	Selected for invitation	Eligible	Non-eligible	Participants	Non-participants	Participation rate (Participants /Eligible)
Wave 1 (2001-2004)	5370	4893	477	2931	1962	60%
Wave 2 (2006-2012)	2307	2098	209	1523	575	73%
Wave 3 (2012-2016)	2018	1919	99	1350	569	70%
Wave 4 (2017-2022)	1877	1580	297	1031	549	65%
Total	**11572**	**10490**	**1082**	**6835**	**3655**	**65%**

During their visits at one of the four study centers (Eslöv, Hässleholm, Malmö or Ystad), the participants typically underwent a full day, approximately 7 hours in total, of examinations and testing. The participants met four different professionals: a registered nurse, a behavioral scientist, a medical secretary, and a physician. The nurse carried out anthropometric measurements, blood laboratory sampling, spirometry, and functional tests (e.g., hand grip strength, timed-up-and-go test [TUG]). The behavioral scientist station included a thorough psychological examination with cognitive testing and interviews (e.g., Mini-Mental State Examination [MMSE], Comprehensive Psychiatric Rating Scale [CPRS]). The participants filled in questionnaires concerning socio-demographics, loneliness, lifestyle (e.g., diet, physical activity, tobacco- and alcohol use), work life, education, economy, self-perceived health, activities of daily life (ADL), and sleeping habits. The questionnaires were administrated by the medical secretary. The study physician reviewed the participants´ medical records and medical history, including assessment of current and former medications, and performed a comprehensive clinical examination (e.g., electrocardiogram, cardiopulmonary auscultation, blood pressure measurement, neurological status).

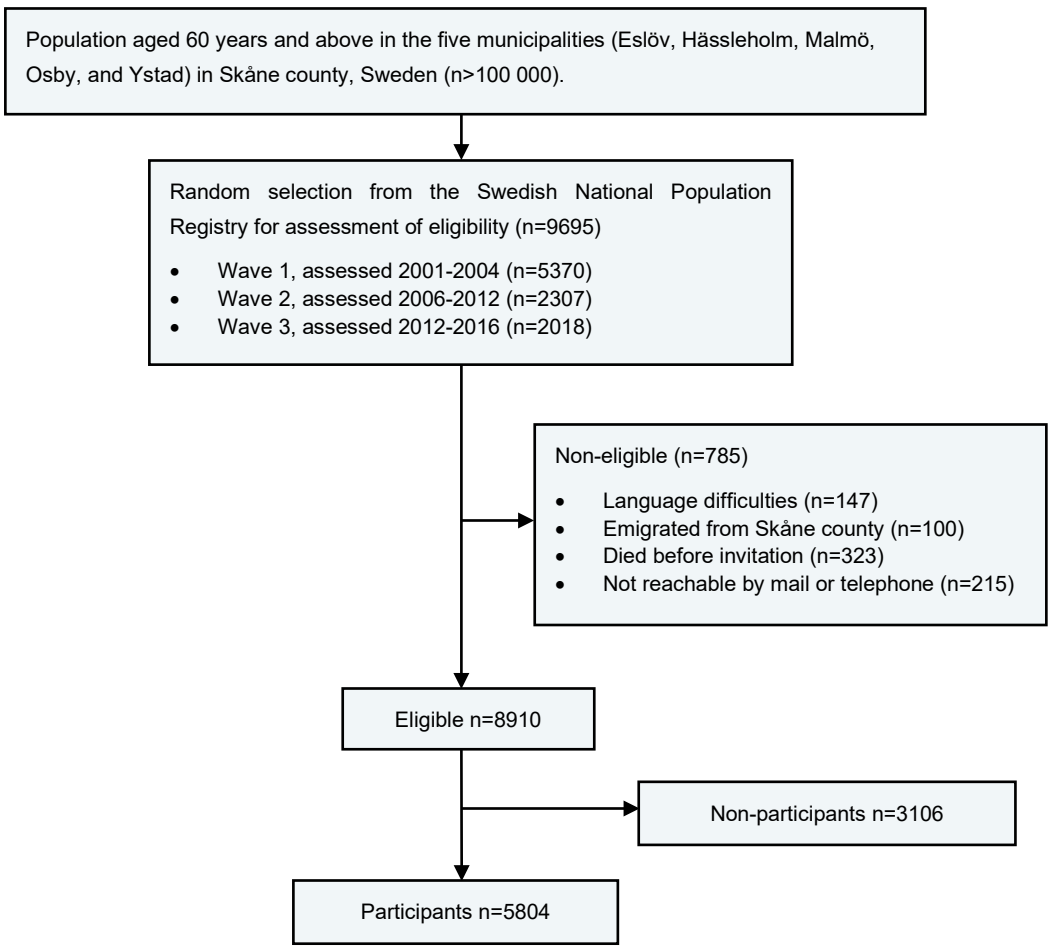
Study sample selections

Since the four papers in this thesis differs in terms of study design, research questions, and timepoint for the data analysis, study samples for the separate papers also varies. Details concerning sample selection for the four studies is described below.

Paper I

In this cross-sectional study, data from three baseline recruitment wave visits in the Good Aging in Skåne study were available at the timepoint for analysis.

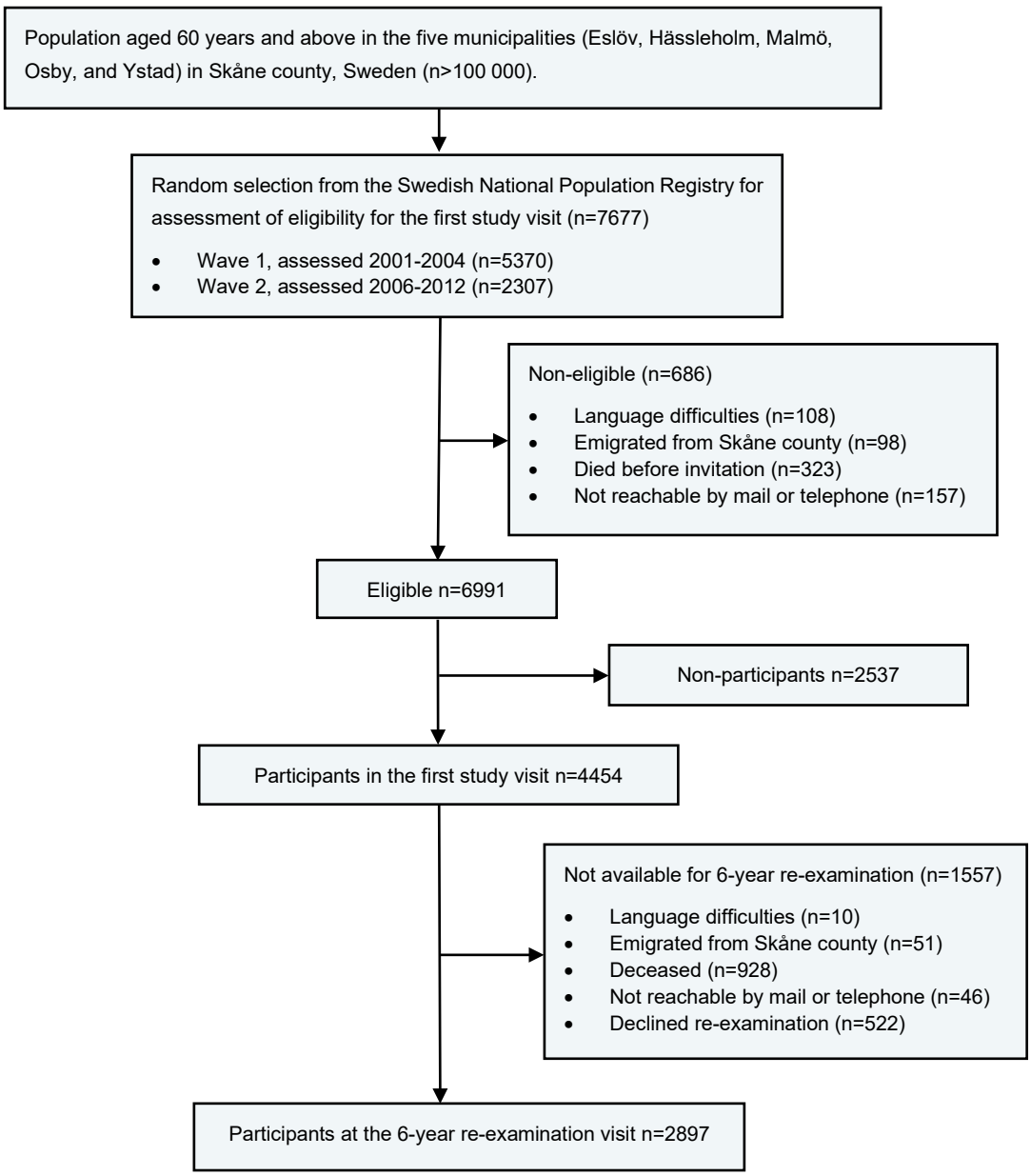
Figure 1. Flow diagram describing the selection of participants for the first study.



Paper II

In this longitudinal study, the aim was to investigate if social isolation and/or loneliness at baseline were associated with sleep disturbances at the 6-year re-examination in the Good Aging in Skåne study. At the time of analysis, 6-year follow-up data were available for the first and second recruitment wave.

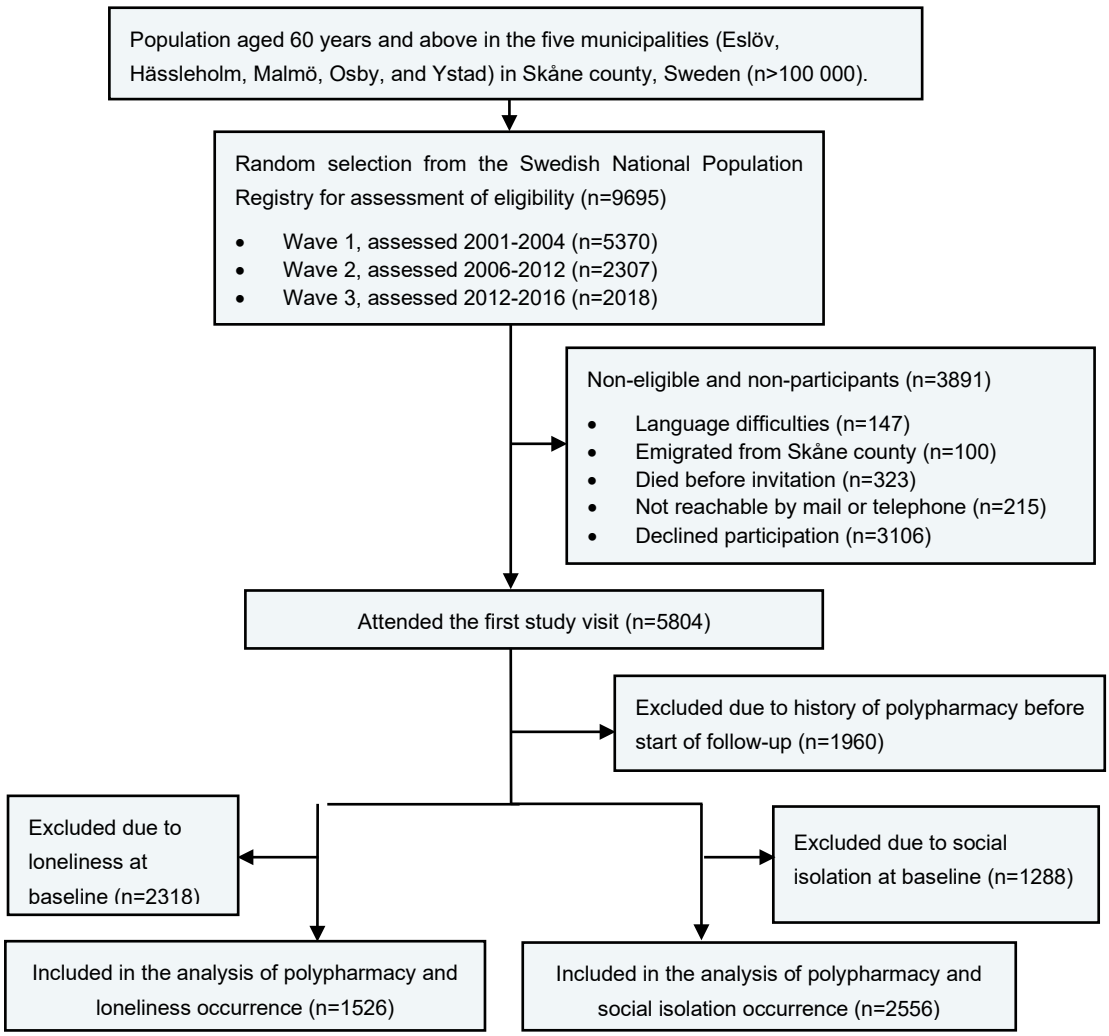
Figure 2. Flow diagram describing the selection of participants for the second study.



Paper III

In this longitudinal study, the aim was to examine associations between incident use of polypharmacy and incident occurrence of social isolation and loneliness among older adults. Data from three recruitment waves with re-examinations were available at the timepoint for analysis. Because we focused on incident occurrence of loneliness and social isolation, individuals who did not report feelings of loneliness at baseline were included in the 'incident loneliness' cohort, while those not classified as socially isolated at baseline were included in the 'incident social isolation' cohort. To mitigate prevalent medication user survivor bias (97), we focused on the influence of incident polypharmacy use, excluding individuals who had polypharmacy at baseline. All follow-up visits with available data at the timepoint for analysis (June 2021) were included in this study.

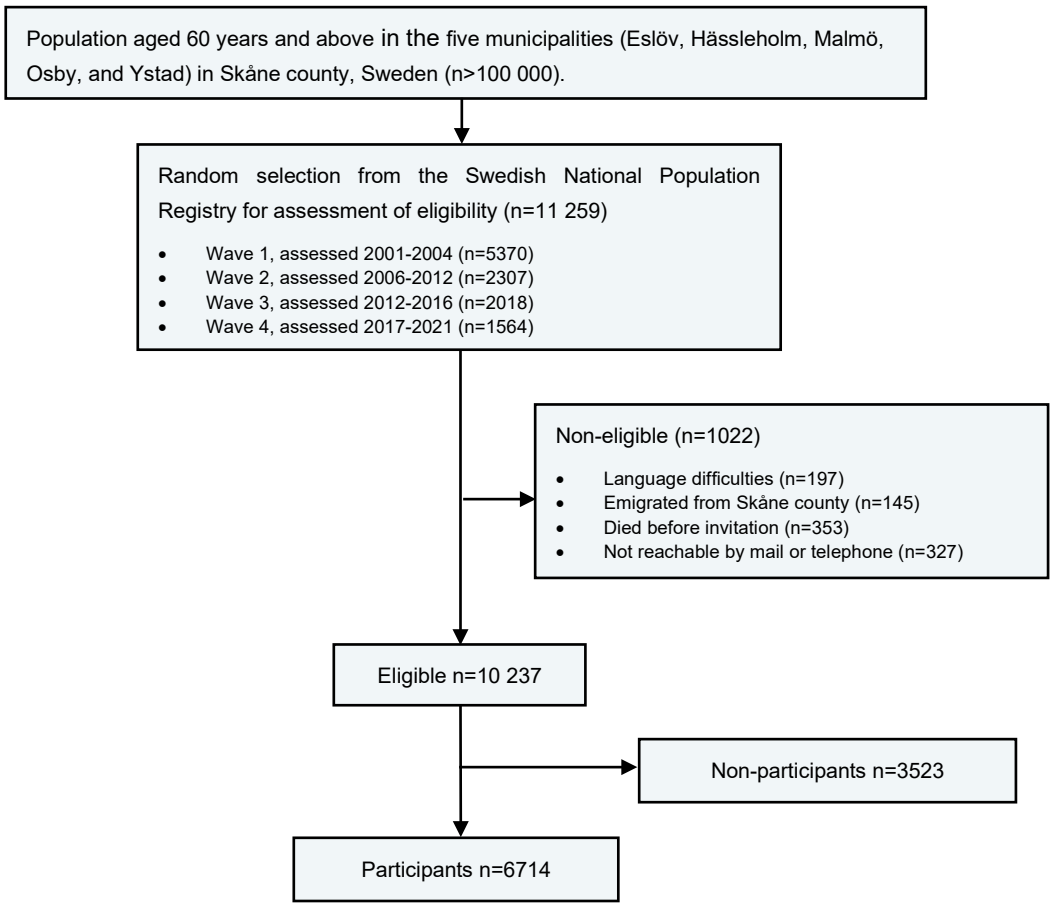
Figure 3. Flow diagram describing the selection of participants for the third study.



Paper IV

In this cross-sectional study, data from four baseline recruitment wave visits were available at the timepoint for analysis. Data for the fourth recruitment wave included participants assessed from 2017-2021. Participants in the fourth recruitment wave assessed in the year 2022 (n=121) were not included because their data were not yet available at the time point for the data analysis in this study.

Figure 4. Flow diagram describing the selection of participants for the fourth study.



Loneliness and social isolation measures

There are a multitude of loneliness and social isolation assessment tools and measures available (98). These tools are either multi-item scales (e.g., the UCLA Loneliness Scale (99), the de Jong Gierveld Loneliness Scale (100), the Lubben Social Network scale (101)), or single-item measures (e.g., questions such as “Do you ever feel lonely?”) (7).

Loneliness

In the GÅS questionnaires, loneliness was self-reported via single-item questions. To distinguish emotional loneliness from being objectively alone (i.e., social isolation), the questionnaires included the following explanation: "By loneliness, we refer to the actual feeling of being lonely, regardless of whether you are in the presence of other people or not". In Paper I-III, loneliness was for the primary analysis measured with the question: “When you look back at the past three to five years, which statement fits you? “I have never once felt lonely,” “I have felt lonely on single occasions,” “I have experienced recurring periods of loneliness,” “I have lived with a constant feeling of loneliness” (7). Participants who reported loneliness at least occasionally were categorized as lonely, while those with no loneliness feelings (never) were categorized as not lonely. In Paper IV, loneliness was assessed with the question: “Do you ever feel lonely?” with four alternatives “Yes, often”, “Yes, sometimes”, “No, seldom”, and “No, never” (7, 102). Participants who responded "Yes" (often or sometimes) were categorized as lonely, while those who answered "No" (seldom or never) were categorized as not lonely (102). The loneliness questions used from the questionnaires in GÅS are available in Appendix Figure 1.

Social isolation

Social isolation was assessed with two different categorization tools. The measures were self-reported via questionnaires. In Paper I and II, a definition used by the Swedish Central Bureau of Statistics (SCB) was applied to measure social isolation (103). According to this definition, individuals who lives alone and have infrequent contact with friends and relatives (defined as contact once a month or less) are categorized as socially isolated (103). Therefore, the social isolation variable for Paper I was operationalized as living alone and having physical (face-to-face) contact with friends or relatives no more than once a month (23). In Paper II, social isolation was further categorized into “less severe social isolation” if the participant was living alone and not being in direct contact with relatives or friends more than once a week and “severe social isolation” if the participant was living alone and not being in direct contact with relatives or friends more than once a month (23). The

social isolation classification used in Paper I and II has some drawbacks, since it is not widely utilized in international research, it does not account for non-physical contacts (e.g., telephone, digital media), other social activities (e.g., religious activities, social organizations/clubs), and did in our sample result in a considerably small group of "socially isolated" participants, making statistical comparisons between groups difficult. Therefore, in Paper III and IV, a different classification system was utilized for the primary analyses. This classification consists of a five-item index originally developed for the English Longitudinal Study of Ageing (ELSA) (104-106), where participants were given one point for each of the following: having less than monthly direct (face-to-face) or indirect (e.g., telephone, mail, email) contact with their children, friends, or other family members (including a spouse if living apart, parents, in-laws, grandchildren, siblings, and other relatives); not participating in social activities (such as social gatherings, organizations, clubs, or religious activities); or living alone (6, 44, 105, 106). Scores on this index ranged from 0 to 5. Consistent with previous studies, scores were categorized as <2 points (no isolation) and ≥2 points (social isolation) (6, 106). The social isolation questions used from the questionnaires in GÅS are available in Appendix Figure 2.

Symptoms, sleep disturbances, and medication measures

Mental and somatic symptoms

In Paper I, the outcomes of interest were mental and somatic symptoms. The symptoms were self-reported via questionnaires. The symptom assessment utilized was an adapted version of the Gothenburg Quality of Life instrument ad modum Tibblin and colleagues (107, 108). The symptom scale consists of the 30 most commonly reported symptoms in the general population and has previously demonstrated satisfactory reliability and construct validity (108, 109). Study subjects indicated whether they had experienced any of the 30 mental or somatic health-related symptoms in the past three months. Participants reported their symptoms using a Likert-type scale with four options: "not at all," "yes, a little," "yes, quite a lot," and "yes, a lot." To aid with the interpretation of the results, symptoms were dichotomized into "yes" if the participant had experienced the symptom to any degree in the past three months, and "no" if they had not experienced the symptom. The total number of symptoms reported by the participant was compiled into a composite variable, ranging from 0 to 30 symptoms.

In addition to the primary composite variable, the symptoms were also categorized into seven domains (108). A participant was categorized into one or more symptom domains if they had experienced at least one symptom from that domain in the past

three months (110). The symptoms are listed according to their corresponding domains in Table 2, and the symptom scale used in the questionnaires in GÅS is available in Appendix Figure 3.

Table 2. The 30 symptoms listed according their corresponding domain ad modum Tibblin et al (108).

Depressive symptoms	Tearfulness
	Depressed mood
	General fatigue
	Sleep disturbance
	Exhaustion
Tension symptoms	Irritability
	Nervousness
	Impaired concentration
	Difficulty in relaxing
	Restlessness
Gastrointestinal and urinary symptoms	Difficulty in passing urine
	Loss of appetite
	Nausea
	Diarrhea
	Constipation
	Abdominal pain
Musculoskeletal symptoms	Pain in the joints
	Backache
	Pain in the legs
Metabolic symptoms	Being overweight
	Weight loss
	Sweating
	Feeling cold
Cardiopulmonary symptoms	Cough
	Chest pain
	Breathlessness
Head symptoms	Dizziness
	Headache
	Impaired hearing
	Eye problems

Sleep disturbances

In Paper II, the outcomes of interest were sleep disturbances. The participants reported their sleeping habits and disturbances by questionnaires. Sleep disturbances were evaluated via questions about sleep difficulties from the Comprehensive Assessment and Referral Evaluation Scale (CARE) (111, 112). CARE is a research instrument used to assess several physical and mental conditions and disabilities among older people, including questions concerning sleep disturbances (111). The sleep questions from CARE have been adapted into a sleep disturbance scale (SDS) (113). The sleep disturbance scale (SDS) consists of eight

questions listed in Table 3, and the sleep disturbance scale used in the questionnaires in GÅS is available in Appendix Figure 4. The response options were yes or no, with each "yes" response counting as 1 point, resulting in a scale ranging from 0 to 8 points. Participants with scores of 4 or higher were categorized as having sleep disturbances, while those with scores below 4 were considered having minor or no sleep disturbance, a cut-off established in a similar population-based study sample (SNAC-B) (114). The sleep disturbance scale used has previously demonstrated satisfactory reliability and construct- and predictive validity (113, 115).

Table 3. The 8 questions included in the sleep disturbance scale (SDS) (112, 113).

Trouble falling asleep
Using sleep medication(s)
Interrupted sleep during the night
Struggle staying asleep due to mood or tension
Struggle staying asleep due to pain or itching
Trouble returning to sleep after waking
Early awakening
Daytime tiredness and sleeping more than two hours in the daytime

Medications

The participants reported their medication use at the time of the study visit, including prescribed, over-the-counter (OTC), herbal medications, and supplements. The medication lists were thereafter carefully reviewed by the study physician and prescribed medications were verified via regional medical records (e.g., PMO, Melior) and available national prescription records (e.g., Pascal, Förskrivningskollen) by the physician after consent from the participant. Eventual discrepancies were discussed and clarified with the participant.

Polypharmacy

In Paper III, the exposure variable of interest was polypharmacy. Polypharmacy was defined as the use of five or more medications, encompassing prescribed, OTC, herbal products, and supplements (78, 79). Medications were included in the polypharmacy definition regardless of dosing frequency, meaning that medications taken occasionally/irregularly were also considered. In the statistical analyses, polypharmacy was computed as a dichotomous variable, comparing those with polypharmacy (five or more medications) with those without polypharmacy (0 to 4 medications) (78).

Psychotropic-, neurological-, and/or anticholinergic fall-risk-increasing drugs (pnaFRIDs)

In Paper IV, the aim was to investigate associations of drug categories usually included in polypharmacy (87) with social isolation and loneliness. A drug category of interest was fall-risk-increasing drugs (FRIDs). FRIDs is a heterogeneous group of medications with the common denominator that they have been associated with increased risk of falling (89-91). Medications that have previously been associated with increased risk of falling includes opioids, loop diuretics, anticholinergic urinary incontinence drugs, antiepileptics, antipsychotics, antidepressants, anxiolytics, hypnotics, and sedatives (89-92, 116). A dichotomous variable was constructed, in which study subjects reporting use of at least one of the psychotropic, neurological and/or anticholinergic medications with the Anatomical Therapeutic Chemical (ATC) classification system codes (ATC codes) (117) listed in Table 4 were categorized as "psychotropic-, neurological- and/or anticholinergic FRIDs (pnaFRIDs) consumers" (89, 90, 116). Medications were included regardless of dosing scheme, meaning that medications taken occasionally/irregularly were also considered.

Table 4. Medications categorized as psychotropic-, neurological-, and/or anticholinergic fall-risk-increasing drugs (pnaFRIDs) (89, 90, 116). The ATC codes are in parentheses.

Anticholinergic urinary incontinence drugs (G04BD04-G04BD011)
Opioids (N02A)
Antiepileptics (N03)
Antipsychotics (N05A)
Anxiolytics (N05B)
Hypnotics and sedatives (N05C)
Antidepressants (N06A)

Cardiovascular drugs

Another common drug category often seen in patients with polypharmacy besides pnaFRIDs are cardiovascular drugs (87). In Paper IV, medications listed in Table 5 were classified as cardiovascular drugs (117). Similarly to the case of pnaFRIDs, study subjects reporting use of at least one cardiovascular drug were considered "cardiovascular drug consumers". Medications were considered regardless of dosing frequency, meaning that those taken occasionally/irregularly were also accounted for.

Table 5. Medications categorized as cardiovascular drugs (117). The ATC codes are in parentheses.

Anticoagulants (B01A)
Diuretics (C03)
Betablockers (C07)
Calcium antagonists (C08)
Renin-angiotensin system acting agents (C09)
Statins (C10AA)

Covariates in the regression models

Multivariable regression models were used in all four papers to mitigate confounding, for details of the models see Statistical methods. Categorization of covariates in these regression models are described below.

Socioeconomics

Education

Education level was self-reported by the participants in questionnaires and during the behavioral scientist interview. Education level was either utilized as a dichotomous variable (Paper I and II, assessed via questionnaires) or count variable (Paper III and IV, assessed via interview). For the dichotomous variable, education level was categorized into elementary school or below (9 years of education or lower), and secondary school or higher education (>9 years of education). For the count variable, education level was defined by the total number of education years.

Financial status

Financial status was self-reported in questionnaires and assessed dichotomously by asking the participants to respond "no" (good finances) or "yes" (poor finances) to the question, "Has it been difficult to make ends meet for living expenses in the past year?" (118).

Cohabiting status

Cohabiting status was reported by the participants via questionnaires and operationalized as married/cohabitant or divorced/unmarried/widowed/living separately (“särbo”).

Lifestyle habits

Physical activity

The participants reported their physical activity in questionnaires. Physical activity was categorized into three levels: mostly sedentary (little to no activity, mostly sitting, sometimes taking short walks, or doing light household tasks like heating prepared food), lighter activities (2 to 4 hours of light physical activity per week, such as ordinary gardening, longer walks, dancing, or routine household chores like cleaning, cooking, and making the bed), and moderate to strenuous activities (1 to 3 hours per week of intense exercise such as running, swimming, skiing, tennis, gymnastics, or other sports, as well as more than 4 hours per week of lighter activities) (119).

Alcohol use

Use of alcohol was self-reported in questionnaires and evaluated categorically by three levels: never users, alcohol consumption 1 to 4 times per month, or consumption ≥2 times per week (118).

Smoking habits

In questionnaires, the participants reported their smoking habits and were thereafter classified as never smokers, former smokers, or current smokers (119).

Health-related variables

Health Locus of Control (HLC)

The Health Locus of Control (HLC) scale consists of three subscales that measure how the participants believe their health is determined. The HLC subscales were assessed via self-report in questionnaires. One subscale assesses chance HLC (the perceived role of luck or fate in determining health), the second measures external HLC (the perception of how much others are responsible for one's health), and the third evaluates internal HLC (the belief in personal control over one's own health) (120). Each subscale encompasses 6 questions, with scores ranging from 6 to 30 points. Higher scores indicate stronger agreement with the statements in that subscale. For example, a high score on the internal HLC subscale suggests a stronger belief that the individual has control over their own health (120).

Morbidities

The study physician evaluated the diseases of the participants. The conditions were grouped based on the International Classification of Diseases, 10th revision (ICD 10) into the following: musculoskeletal disease (e.g., osteoporosis, osteoarthritis, rheumatoid arthritis, gout), heart disease (e.g., myocardial infarction, angina

pectoris, previous coronary procedures such as coronary artery bypass graft or angioplasty, heart failure, arrhythmia, or presence of a pacemaker), diabetes mellitus (type 1 or 2), cerebrovascular disease (e.g., transient ischemic attack, ischemic- or hemorrhagic stroke), epilepsy, hypertension, eye disease (e.g., age-related macular degeneration, glaucoma), cancer (all types of malignancies), and chronic pulmonary disease (chronic obstructive pulmonary disease or asthma) (121). In Paper III and IV, chronic conditions and diagnoses were translated into a chronic morbidity count, with participants receiving 1 point for each chronic condition (e.g., 1 point for musculoskeletal disease, 1 point for cerebrovascular disease, etc.). The study subjects were thereafter classified into four categories based on the number of chronic diseases and conditions: 0, 1, 2, or ≥3 conditions (122).

Cognitive status

The behavioral scientist measured and evaluated cognitive status and function with several instruments. As a screening tool for overall cognitive capacity, the Mini-Mental State Examination (MMSE) was utilized (123). The scale ranges from 0 to 30 points, and those with a score of 24 points or below were considered having impaired overall cognitive function (124).

Depressed mood

Two different measures were used to assess depressed mood. For Paper II, the diagnostic evaluation by the study physician was used, in which participants were dichotomized into two groups: 1) never been diagnosed with depression or 2) having a present or past diagnosis of depression. For Paper III and IV, the behavioral scientist interview containing the Comprehensive Psychiatric Rating Scale (CPRS) was utilized (125). Specifically, the ten items in CPRS concerning depressive symptoms, also known as the Montgomery–Åsberg Depression Rating Scale (MADRS) (126), were used to assess depressed mood. The ten items evaluates different characteristics of a depressed mood, including symptoms like anxiety, concentration difficulties, sleep disturbance, sadness, tension, and suicidal thoughts. The participants were given 0 to 6 points per item, which yields a total score ranging from 0 to 60 points, and higher scores reflect a more depressed mood (126).

Statistical methods

In all four papers, multivariable statistical models were created to minimize confounding. The choice of covariates for Paper I, II, III, and IV were made by constructing directed acyclic graphs (DAGs) (127, 128). The software tool DAGitty was used to create the DAGs for the papers (129). An example of a DAG designed with this software is presented in Figure 5. In all papers, the statistical significance threshold was set to 0.05. The statistical analyses were for Paper I and II conducted

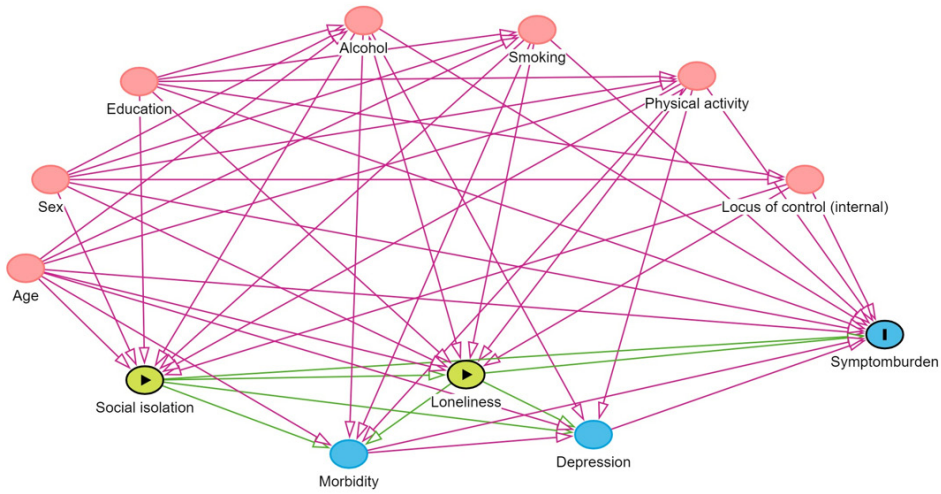
using SPSS® version 24 and 26 (IBM SPSS Statistics for Windows), and for Paper III and IV, the programs Stata SE 17 (StataCorp LLC, College Station, TX, USA) and Python 3.8.5 (Python Software Foundation, Fredericksburg, Virginia, USA) were utilized. A summary of the statistical methods is presented in Table 6.

Paper I

In this cross-sectional study, the hypothesis was that social isolation and loneliness would be associated with an increased number of symptoms reported by the participants. A linear regression model was developed to examine the relationship between social isolation, loneliness, and the total number of reported symptoms. Both loneliness and social isolation were included as independent variables in the primary model. Covariates included age, sex, alcohol consumption, education, smoking, physical activity, and internal health locus of control (HLC). The DAG designed for the choice of covariates for the primary model is presented in Figure 5. Multiple logistic regression models were also created to analyze associations between social isolation, loneliness, and prevalence of symptoms across the seven domains of symptoms (depressive, tension, musculoskeletal, gastrointestinal-urinary tract, cardiopulmonary, head-related, and metabolic symptoms). These models were also adjusted for age, sex, alcohol consumption, education, smoking, physical activity, and internal health locus of control (HLC) to mitigate confounding.

Sensitivity analyses were constructed to investigate the robustness of the results, including exchanging the internal HLC subscale with the external HLC subscale as covariate, having the internal HLC subscale as a continuous variable in the model, computing the education variable as a four-category variable (not finished elementary school, finished elementary school, finished secondary school, university degree), and having alcohol use as a variable with four categories (never use, consumption 1 to 4 times per month, 2 to 3 times per week, ≥4 times per week).

Figure 5. DAG designed for choosing the most relevant variables to be included in the primary model in Paper I. Loneliness and social isolation (green) are the exposure variables of interest and symptom burden (dark blue) is the outcome. Factors in red (e.g., age, sex, education) are in this model possible confounders for the association of loneliness and social isolation with symptoms. Morbidity and depression (light blue) are in this model possible mediators for the association of loneliness and social isolation with symptoms.



Paper II

The hypothesis in this paper was that social isolation and loneliness at baseline would be associated with increased risk of reporting sleep disturbances at the 6-year re-examination visit. To evaluate this, a logistic regression model was created. The model included reported social isolation and loneliness at baseline as exposure variables and sleep disturbances (defined as SDS score ≥4 (114)) at the 6-year re-examination as the primary outcome. Covariates assessed at baseline were included in the model to reduce confounding, and these included age, sex, education, financial status, cohabiting status, smoking habits, lung disease, heart disease, cancer, arthrosis, cognitive status (MMSE <24p or ≥24p), depression (presence of or previous diagnosis), and sleep disturbance (SDS score ≥4) at baseline.

In secondary analyses, associations of loneliness and social isolation with the separate items in the SDS were examined with logistic regression models. In addition, attrition analyses were performed to elucidate eventual differences in baseline characteristics between those who attended versus those who did not attend (e.g., deceased, emigrated, declined re-examination) the 6-year re-examination.

Paper III

In this longitudinal study, the hypothesis was that incident use of polypharmacy (≥5 medications) would be associated with an increased risk of incident occurrence of social isolation and loneliness. To examine this, logistic regression models were constructed to investigate if incident use of polypharmacy, defined as going from non-polypharmacy (0-4 medications) at baseline to polypharmacy (≥5 medications) at follow-up (97), was associated with incident occurrence of social isolation or loneliness, defined as going from no social isolation/loneliness at baseline to social isolation/loneliness at follow-up (42, 102). To reduce confounding, the following covariates were included in the models: sex, age, education (in years) (130), physical activity, depressed mood (MADRS score), and number of morbidities, as reported at the baseline visit.

In sensitivity analyses, influence of using different definitions and cut-offs for social isolation and loneliness were explored. Secondary sub-group analyses by wave cohorts and gender were also performed.

Paper IV

For this cross-sectional study, the hypothesis was that consumption of certain medication groups could be associated with increased risk of reporting social isolation and loneliness. To test this, logistic regression models were made to explore associations of psychotropic-, neurological- and/or anticholinergic FRIDs (pnaFRIDs), cardiovascular drugs, and polypharmacy, with loneliness and social isolation, respectively. The covariates included in the primary models to reduce confounding encompassed education level (in years) (130), sex, age, number of morbidities, and physical activity.

Sensitivity analyses involving a different cut-off threshold for loneliness and a model including assessment of depressed mood (MADRS score) as a covariate were also carried out.

Table 6. Summary of the statistical methods for Paper I-IV.

Papers	Design	Exposure	Outcome	Covariates	Main statistical methods	Sensitivity and secondary analyses
Paper I	Cross-sectional	Loneliness, Social isolation	Mental and somatic symptoms (0-30), 7 symptom domains	Age (60-79/≥80 years), sex (male/female), education (elementary/secondary school), alcohol (never/1-4 mo/≥2 w), smoking (never/former/current), physical activity (sedentary/light/moderate-strenuous), HLC (internal subscale)	Linear regression (number of symptoms analysis), logistic regression (symptom domain analysis)	External HLC subscale as covariate, internal HLC subscale as continuous variable, education as a four-category variable, alcohol as a four-category variable
Paper II	Longitudinal	Loneliness, Social isolation	Sleep disturbances (SDS score ≥4) at 6-year re-examination	Age (60-69 years/70-79 years/≥80 years), sex (male/female), education (elementary/secondary school), cohabiting status (married/unmarried), financial status (good/poor), smoking (never/former/current), lung disease, cancer, heart disease, arthrosis, depression, cognitive status (MMSE <24p/≥24p), sleep disturbances (SDS score ≥4) at baseline	Logistic regression	Associations with the separate items in the SDS. Attrition analysis comparing baseline characteristics for participants and non-participants at the 6-year re-examination
Paper III	Longitudinal	Polypharmacy (≥5 medications)	Loneliness, Social isolation	Age (60-70 years/71-79 years/≥80 years), sex (male/female), physical activity (sedentary/light/moderate-strenuous), education (in years), number of morbidities (0/1/2/≥3 conditions), depressed mood (MADRS score)	Logistic regression	Different cut-off and question for assessment of loneliness, different definition for social isolation (103). Subgroup analyses of wave cohorts, gender
Paper IV	Cross-sectional	Polypharmacy (≥5 medications), pnaFRIDs, cardiovascular drugs	Loneliness, Social isolation	Age (60-70 years/71-79 years/≥80 years), sex (male/female), physical activity (sedentary/light/moderate-strenuous), education (in years), number of morbidities (0/1/2/≥3 conditions)	Logistic regression	Different cut-off for assessment of loneliness, depressed mood (MADRS score) as covariate

Ethical considerations

The GÅS study efforts to in all regards follow the guidelines of The World Medical Association's (WMA) Declaration of Helsinki, which is often considered as the "gold standard" of ethical principles for medical research involving humans (131). The Papers involved in this thesis are part of the GÅS study project, which was approved by the Lund University regional ethics committee, registration number LU 744-00. All study participants provided written consent and granted access to data from the Region Skåne Healthcare databases (RSVD) and the Swedish National Patient Registry. The study subjects were also informed that they could withdraw from the study at any moment.

The data in the GÅS study was pseudoanonymized, meaning that the personally identifiable information (e.g., name, address, personal identity number) from the participants was replaced with an artificial identification code (study ID). For the researchers involved in the project, the study ID could not be traced back to the study subject's personally identifiable information. It is important to distinguish pseudoanonymized data from anonymized data. In anonymized data, it is not possible for anyone to trace the data back to an identifiable individual. However, when performing longitudinal research on human subjects, the data collected from repeated visits must be linked to the correct individual, and therefore the link (or key) between the personally identifiable information and artificial identification code is usually not deleted for as long as the study is ongoing. Since the link between personally identifiable information and the artificial identification code was not deleted in GÅS (ongoing project), the data cannot be referred to as anonymized data (132). Pseudoanonymized data is deemed as personal data according to the General Data Protection Regulation (GDPR) legislation (132). Several initiatives have been applied by the GÅS research group to ensure compliance with the GDPR legislation. For example, the research data from GÅS is stored, managed, and analyzed via the internal Lund University data environment tool - LUSEC (133). LUSEC is a local data storage platform with high level of encryption and two-factor authorization requirement for access, which meets the requirements of data security stated in the GDPR legislation (133). In addition, all projects using GÅS data must be approved by the PI before any data may be accessed. Furthermore, the individual researcher has only access to the necessary data for the approved specific project.

Older adults, particularly those with cognitive and functional impairments, may be considered a vulnerable group (134). Conducting research on potentially vulnerable subjects may be ethically challenging, for example if the ability of the participant to give informed consent is reduced or uncertain (134). However, excluding participants from research due to prejudiced understanding of their eventual vulnerability could also be considered unethical, especially if the research findings intends to be applied on said vulnerable population (134). In the GÅS study, participants were given written and oral information in a plain, easy-to-understand,

language. Furthermore, the research personnel offered aid with interpretation of the study information, consent form, and tasks involved in all the separate stations for examinations and testing. Withdrawal from the study was allowed at any time and the examinations and tests conducted were deemed overall non-harmful for the participants. If a suspected pathological finding was made during the examination (e.g., electrocardiogram abnormality), the GÅS study physician contacted the responsible physician of the participant (i.e., patientansvarig läkare, PAL) for further evaluation. The participants are annually provided with information from the PI about the status of the GÅS project and how the data is being used (e.g., publications, dissertations).

Results

Paper I

In this cross-sectional study, 60% of the participants reported that they had experienced at least occasional loneliness in the past three to five years. Nearly 6% were categorized as socially isolated. Women aged 80 years and older reported the highest prevalence of loneliness and social isolation, while men aged 60-79 years reported the lowest prevalence (Table 7). A comparison of perceived loneliness by social isolation status is also available in Paper I, Appendix Table 8.

Table 7. Demographic distribution (gender and age) of loneliness and social isolation.

	Never lonely n (%)	Lonely at single occasions n (%)	Recurring periods of loneliness n (%)	Constant loneliness n (%)	Not socially isolated n (%)	Socially isolated n (%)
Whole population	2100 (40.2)	2412 (46.1)	549 (10.5)	169 (3.2)	5297 (94.4)	317 (5.6)
Male, 60-79 years	921 (51.0)	734 (40.7)	121 (6.7)	29 (1.6)	1850 (96.3)	71 (3.7)
Female, 60-79 years	672 (34.1)	994 (50.5)	243 (12.3)	61 (3.1)	1988 (95.5)	93 (4.5)
Male, ≥80 years	282 (47.6)	235 (39.7)	56 (9.5)	19 (3.2)	595 (92.0)	52 (8.0)
Female, ≥80 years	225 (26.1)	449 (52.0)	129 (14.9)	60 (7.0)	864 (89.5)	101 (10.5)

Loneliness was associated with an increased number of reported mental and somatic symptoms in the multivariable linear regression model (Table 8).

Table 8. Multivariable linear regression model with loneliness and social isolation as exposure variables and number of symptoms as the outcome variable. Covariates are listed in Table 6.

Exposure variables	Estimate	CI 95 %	p-value
Loneliness (reference never lonely)			
Single occasions	2.47	2.14-2.79	<0.001
Recurring periods	6.03	5.51-6.56	<0.001
Constant loneliness	6.09	5.23-6.96	<0.001
Social isolation (reference not socially isolated)			
Yes	-0.12	-0.77-0.54	0.73

As for the separate domains of symptoms (depressive, tension, musculoskeletal, gastrointestinal-urinary tract, cardiopulmonary, head-related, or metabolic symptoms), the prevalences were highest among those with the most frequent feelings of loneliness (Table 9 and 10). Social isolation was not statistically significantly associated with symptoms in models where both loneliness and social isolation were included as exposure variables. However, in secondary analyses in which loneliness was excluded from the models, social isolation was associated with an increased number of reported symptoms and with an increased prevalence of depressive- and gastrointestinal-urinary symptoms (Paper I, Appendix Table 4 and 5).

Table 9. Prevalences of symptoms in seven symptom domains by loneliness and social isolation status.

	Depressive n (%)	Tension n (%)	GI-urinary n (%)	Musculo-skeletal n (%)	Metabolic n (%)	Cardio-pulmonary n (%)	Head n (%)
Loneliness							
Never	1440 (68.8)	1199 (57.2)	691 (33.0)	1406 (67.1)	1186 (56.6)	904 (43.2)	1179 (56.3)
Single occasions	2053 (85.3)	1821 (75.7)	1127 (46.8)	1804 (75.0)	1642 (68.2)	1232 (51.2)	1618 (67.3)
Recurring periods	527 (96.0)	485 (88.5)	345 (63.1)	460 (83.9)	433 (78.9)	341 (62.2)	456 (83.1)
Constant loneliness	162 (96.4)	153 (91.1)	112 (66.7)	146 (87.4)	137 (81.5)	118 (70.2)	132 (79.0)
Socially isolated							
No	4083 (79.2)	3582 (69.4)	2202 (42.7)	3756 (73.4)	3301 (65.1)	2500 (49.4)	3234 (64.3)
Yes	266 (88.7)	223 (74.8)	162 (54.0)	232 (77.3)	204 (68.0)	175 (58.5)	228 (76.0)

Table 10. Results from the multivariable logistic regression models with social isolation and loneliness as the exposure variables and reporting symptoms in the seven symptom domains as the outcome variables. Covariates are listed in Table 6.

	Depressive		**Tension**		**Gastrointestinal-urinary**		**Musculoskeletal**		**Metabolism**		**Cardiopulmonary**		**Head**	
	OR	CI 95 %	**OR**	CI 95%	**OR**	CI 95 %	**OR**	CI 95 %	**OR**		**OR**	CI 95 %	**OR**	CI 95 %
Loneliness (reference never)														
Single occasions	**2.47**	2.12-2.87	**2.28**	2.00-2.60	**1.74**	1.54-1.98	**1.39**	1.21-1.59	**1.55**	1.37-1.77	**1.38**	1.22-1.56	**1.52**	1.33-1.73
Recurring periods	**8.99**	5.78-13.98	**5.36**	4.03-7.12	**3.13**	2.54-3.84	**2.25**	1.74-2.90	**2.43**	1.93-3.07	**1.99**	1.62-2.44	**3.41**	2.65-4.39
Constant loneliness	**8.36**	3.65-19.14	**6.22**	3.61-10.73	**3.07**	2.17-4.34	**2.87**	1.75-4.72	**2.53**	1.68-3.83	**2.29**	1.60-3.27	**2.05**	1.37-3.09
Social isolation (reference not socially isolated)														
Yes	**1.15**	0.77-1.70	**0.86**	0.64-1.16	**1.06**	0.83-1.37	**0.86**	0.64-1.16	**0.88**	0.67-1.15	**1.07**	0.83-1.38	**1.05**	0.78-1.41

Paper II

In this re-examination study, severe social isolation and loneliness at baseline were statistically significantly associated with increased likelihood of reporting sleep disturbances (SDS score ≥4) at the 6-year re-examination (Table 11).

Table 11. Results from the multivariable logistic regression model with social isolation and loneliness at baseline as the exposure variables and reporting sleep disturbance at the 6-year re-examination as the outcome variable. Covariates are listed in Table 6.

	Sleep disturbances (SDS score ≥4)		
	OR	CI 95 %	p-value
Loneliness (reference never lonely)			
Single occasions	**1.37**	1.05-1.78	0.019
Recurring periods/Constant loneliness	**1.92**	1.32-2.78	<0.001
Social isolation (reference no social isolation)			
Less severe	**1.18**	0.78-1.79	0.44
Severe	**1.88**	1.01-3.49	0.046

In the secondary analyses, participants experiencing recurring periods or constant loneliness feelings at baseline had a statistically significantly increased risk of reporting sleep disturbance symptoms in all the eight separate items of the SDS at the 6-year re-examination compared to those without loneliness at baseline. Those categorized as 'severely socially isolated' at baseline had a statistically significantly increased risk of reporting sleep disturbance symptoms in five separate items ("Difficulty falling asleep", "Using sleep medication", "Difficulty staying asleep due to mood or tension", "Difficulty returning to sleep after waking", and "Sleeping 2 hours in the daytime") at the 6-year re-examination compared to those with no social isolation (Paper II, Table 2).

In the attrition analysis, those who did not attend the re-examination (i.e., participants at baseline but non-eligible or declined participation at the 6-year re-examination) were at baseline older and had a higher prevalence of cancer, heart disease, poor cognitive function (MMSE score of 24 points or lower), depression, severe social isolation, and recurrent periods or constant feelings of loneliness, as compared to the participants at the re-examination (Paper II, Table 4).

Paper III

In this longitudinal study, the median follow-up time was 6.5 years (range 0–20 years) and the median number of study visits was 2 (range 1–7). During follow-up, 414 participants reported incident occurrence of social isolation and 409 participants reported incident occurrence of loneliness feelings, corresponding to an incidence rate of 2.2 per 100 person-years (95% CI 2.0–2.5) in terms of incident social isolation and 4.1 per 100 person-years (95% CI 3.7–4.4) in terms of incident loneliness feelings. Participants with incident use of polypharmacy had increased likelihood of reporting incident occurrence of social isolation and incident occurrence of loneliness, compared to those without polypharmacy (Table 12).

Table 12. Results from the multivariable logistic regression models with incident use of polypharmacy as the exposure variable of interest and reporting incident occurrence of social isolation and incident occurrence of loneliness as the outcome variables. Covariates are listed in Table 6.

	Loneliness			**Social Isolation**		
	OR	CI 95 %	p-value	**OR**	CI 95 %	p-value
Incident use of polypharmacy (reference is no polypharmacy)	**1.37**	1.05-1.78	0.020	**1.29**	1.02-1.64	0.036

Results were overall consistent in the sensitivity analyses and across the different wave cohorts (Paper III, Appendix Table 2a-4b).

Paper IV

In this cross-sectional study, the mean number of medications taken by the participants was 3.6 (range 0-23) and 32% had polypharmacy (≥5 medications), 25% reported consumption of any psychotropic-, neurological-, and/or anticholinergic FRID (pnaFRID), and 47% reported consumption of any cardiovascular drug (Table 13).

Table 13. Medication consumption of the participants in the GÅS study.

Drug category		
Total number of medications	mean (SD) [min-max]	3.6 (3.5) [0-23]
Prescribed	mean (SD) [min-max]	3.1 (3.3) [0-22]
OTC	mean (SD) [min-max]	0.2 (0.6) [0-5]
Herbal products and supplements	mean (SD) [min-max]	0.3 (0.7) [0-8]
Polypharmacy, n (%)	No	4363 (65.0)
	Yes	2181 (32.5)
Consumption any psychotropic-, neurological-, and/or anticholinergic FRID, n (%)	No	4892 (72.9)
	Yes	1652 (24.6)
Anticholinergic urinary incontinence drugs (ATC code G04BD04-G04BD011), n (%)	No	6476 (96.5)
	Yes	68 (1.0)
Opioids (N02A), n (%)	No	6117 (91.1)
	Yes	424 (6.3)
Antiepileptics (N03), n (%)	No	6441 (96.0)
	Yes	100 (1.5)
Antipsychotics (N05A), n (%)	No	6449 (96.1)
	Yes	92 (1.4)
Anxiolytics (N05B), n (%)	No	6175 (92.0)
	Yes	366 (5.4)
Hypnotics and sedatives (N05C), n (%)	No	5750 (85.7)
	Yes	791 (11.8)
Antidepressants (N06A), n (%)	No	5951 (88.7)
	Yes	590 (8.8)
Consumption any cardiovascular drug, n (%)	No	3414 (50.8)
	Yes	3130 (46.6)
Anticoagulants (B01A), n (%)	No	4943 (73.7)
	Yes	1598 (23.8)
Antihypertensive Medications (C03, C07, C08, C09), n (%)	No	3772 (56.2)
	Yes	2772 (41.3)
Statins (C10AA), n (%)	No	6010 (89.5)
	Yes	534 (8.0)
Missing medication data, n (%)		170 (2.5)

Results from the multivariable logistic regression models show that participants consuming psychotropic-, neurological-, and/or anticholinergic FRIDs (pnaFRIDs) had increased likelihood of reporting loneliness feelings compared to those with no pnaFRID consumption. The odds for loneliness were comparable between those with and without cardiovascular drug consumption and between those with and without polypharmacy. As for social isolation, the odds were similar between those with and without reported pnaFRIDs, cardiovascular drugs, and polypharmacy consumption (Table 14).

Table 14. Results from the multivariable logistic regression models with polypharmacy, psychotropic-, neurological-, and/or anticholinergic FRIDs (pnaFRIDs), and cardiovascular drug consumption as the exposure variables of interest and reporting social isolation and loneliness as the outcome variables. Covariates are listed in Table 6.

	Loneliness			**Social Isolation**		
	OR	CI 95 %	p-value	**OR**	CI 95 %	p-value
Polypharmacy (reference is no polypharmacy)	**1.08**	0.93-1.25	0.34	**1.17**	0.99-1.38	0.073
pnaFRIDs consumption (reference is no pnaFRID consumption)	**2.00**	1.75-2.29	<0.001	**1.10**	0.95-1.28	0.20
Cardiovascular drugs (reference is no cardiovascular drug consumption)	**0.97**	0.84-1.13	0.71	**0.96**	0.81-1.14	0.63

The results were similar in sensitivity analyses with an alternative cut-off level for loneliness and in models where MADRS score was also incorporated as a covariate (Paper IV, Appendix Table 2a and 2b).

Discussion

Summary of main findings and interpretation of results

Prevalence and incidence of social isolation and loneliness

In Paper I, findings suggest that most of the participants in the GÅS study had experienced some feelings of loneliness in the past three to five years prior to their first study visit, although for most subjects this feeling was infrequent/occasional. A smaller proportion of participants reported recurrent longer periods (10%) or constant feelings of loneliness (3%) and 6% were classified as objectively socially isolated with the SCB definition (103). Of those who were socially isolated, a majority reported feelings of loneliness (80%), and nearly a third (32%) experienced recurrent longer periods or constant feelings of loneliness (Paper I, Appendix Table 8). In Paper III, incidence rates for occurrence of social isolation (ELSA definition, 104-106) were estimated to 2.2 per 100 person-years, and for occurrence of loneliness feelings to 4.1 per 100 person-years.

Depending on definitions, instruments, temporality, societal factors and cultural contexts, prevalence and incidence estimates for loneliness and social isolation show substantial heterogeneity across studies, even within similar geographical regions and subgroups analyzed (135). Due to the limitations of loneliness and social isolation measurements (see Internal validity), prevalence and incidence estimates from individual studies should be seen as indicative and interpreted with caution (135). As illustrated in this thesis, in Paper II, III, and IV, the study designs and research questions differed from Paper I, and slightly different social isolation and loneliness measures and cut-off levels were therefore applied in the primary- and sensitivity analyses to be suitable for the separate studies. As expected, estimates for social isolation and loneliness in Paper II, III, and IV varied somewhat from those reported in Paper I, but were still overall in line with estimates from previous research on comparable populations using similar measurements (7, 103, 135, 136).

In Paper II, those with social isolation and/or recurrent/constant loneliness were less likely to attend the 6-year re-examination and in Paper III, a majority (55%) of those who reported incident social isolation did not attend another study-visit. The relatively long time intervals between study visits and higher prevalence of

morbidity among those with social isolation and recurrent/constant loneliness may explain the relatively high attrition rate observed in this group. It should be noted that it was not an aim of this thesis to examine the potential reversibility of social isolation nor loneliness among older adults. Based on the attrition rates observed in GÅS among those socially isolated, future studies with shorter time intervals between assessments (e.g., annual surveys) may be considered to examine social isolation and loneliness stability and factors associated with reversibility of these conditions.

When comparing wave cohorts (e.g., participants recruited in 2001-2004 compared with participants recruited in 2012-2016), there were no substantial changes in the prevalence of social isolation nor loneliness (Paper I, Appendix table 2b). This indicates that prevalences of social isolation and loneliness have been relatively stable since 2001 among older adults in Skåne county, at least before the year 2020. There were concern raised during the COVID-19 pandemic that loneliness and social isolation among older adults would increase and even persist for a long time after the pandemic, but available data indicates that levels of social isolation and loneliness have largely reverted to pre-pandemic levels (137). The sampling in the GÅS study was largely halted during the pandemic, due to concern for the participants' safety and imposed restrictions by the Swedish government. The halted sampling hinders interpretation of eventual intra-pandemic effects regarding prevalence and incidence of social isolation and loneliness for the GÅS participants. Sampling in the GÅS study is ongoing concerning post-pandemic estimates of social isolation and loneliness, but these data were not yet available at the time of writing this thesis.

Associations of social isolation and loneliness with mental and somatic symptoms

In Paper I, loneliness feelings were associated with an increase in the number of reported mental and somatic symptoms. This association was seen for all seven investigated domains of symptoms (depressive, cardiopulmonary, tension, musculoskeletal, gastrointestinal-urinary tract, head-related, and metabolic symptoms). Associations of loneliness with depressive symptoms have been reported previously in several studies (7, 57, 61-63, 138). Findings from Paper I adds evidence that loneliness is also associated with symptoms often traditionally categorized as "somatic". There are several plausible mechanisms for the associations of loneliness and symptoms. Loneliness have been associated with increased risk of developing several mental and somatic conditions, including depression and cardiovascular diseases (3, 47-49), which in turn comes with disease-associated symptomatology. Underlying biological and psychological mechanisms for these associations remain mostly unclear, but dysregulation of inflammation- and neuroendocrine systems as well as adverse effects on health-

related behaviors have been suggested (48, 139). In the other direction, chronic diseases have been associated with increased risk of loneliness and social isolation (50, 140, 141). Mechanisms for these associations may be disease-associated disability and impaired mobility, possibly limiting social interactions (142). Thus, associations of loneliness with symptoms are likely bi-directional, with complex underlying mechanisms, yet the cross-sectional design of Paper I precludes any conclusions of direction of the associations and mechanisms.

Social isolation was only statistically significantly associated with symptoms in statistical models without loneliness. Hypothetically, loneliness may be a mediator for the association of social isolation with symptoms (Figure 6), which is supported by longitudinal data of depressive symptoms (143). Whether this hypothesis holds for all symptoms, including somatic-related symptoms, remains to be investigated in longitudinal settings.

Figure 6. DAG illustrating a possible pathway for the associations of social isolation, loneliness, disease, and symptoms.

The categorization of symptoms into seven domains was based on the original paper for the symptom scale used ad modum Tibblin et al. (108). Importantly, these domains of symptoms have not been established as diagnostic nor indicative for any specific syndrome nor disease and should thus, from a clinical perspective, be viewed with caution. Furthermore, the traditional description of symptoms as "mental" or "somatic" should also be problematized. Both biological and psychological factors are related to mental and somatic disorders (144). Symptoms often categorized as "somatic" (e.g., cardiopulmonary symptoms such as chest pain) are common among patients with psychiatric conditions (145), and vice versa, symptoms often deemed as "mental/psychiatric" (e.g., depressive symptoms) are common among patients with somatic conditions (146). Due to this, symptoms associated with loneliness and/or social isolation are by some researchers instead described as "psychosomatic" (147), thereby avoiding the oversimplified dichotomy of "somatic" and "mental" symptoms.

Lastly, it is important to note that Paper I only examines presence of symptoms experienced for at least the past three months. No analysis concerning symptom severity nor different duration times of symptoms was carried out. Further study investigating associations with symptom severity and duration (both short- and long term) may add granularity and nuances to the associations identified between loneliness, social isolation, and subjective health.

Associations of social isolation and loneliness with sleep disturbances

In Paper II, participants classified as socially isolated and/or reporting loneliness feelings at baseline had increased risk of reporting sleep disturbances six years later. These longitudinal findings are in line with the cross-sectional results from Paper I, where sleep disturbance was one of the symptoms investigated as well. Paper II adds granularity to the association of social isolation, loneliness, and sleep symptoms, since eight different sleep symptoms were examined, and not just the unspecific symptom "sleep disturbance", as was the case in Paper I.

Previous research have presented somewhat inconclusive findings regarding associations of social isolation and/or loneliness with sleep. Loneliness has in some studies been associated with certain aspects of sleep disturbances (poor sleep quality, poor sleep satisfaction) (148, 149), while others found no statistically significant associations of sleep quality and loneliness (150). Similar findings have been reported for social isolation, that is, in some studies a statistically significant association between sleep and social isolation was identified (150), while others did not (148). These discrepancies may have several explanations. For example, the limited sample size (n=400-640 participants) in some previous studies (148, 150) may limit the statistical power of their analyses and thereby their ability to detect statistically significant differences. Furthermore, meta-analyses, that combines data from several studies, have been difficult to conduct due to lack of longitudinal studies and substantial heterogeneity between studies in terms of follow-up length, confounding adjustments, populations studied, and different measures/instruments used (69). A systematic review published in 2023 concludes that social isolation and loneliness may be associated with poor sleep quality among older adults, but the data included in the meta-analyses was predominately cross-sectional and the authors were unable to analyze social isolation and loneliness separately due to lack of studies (151). Paper II, with its' longitudinal design, relatively large sample size, and individual estimates for social isolation and loneliness, may thus contribute to the growing literature of longitudinal associations between loneliness, social isolation, and sleep among older adults.

In Paper II, only associations of social isolation and/or loneliness at baseline with reporting sleep disturbance at the re-examination were analyzed, as prespecified in the analysis plan for that project. Another interesting analysis for future studies would be if changing social isolation/loneliness status (e.g., going from 'not lonely' to 'lonely' compared with 'stable/chronic loneliness') (43, 44) is associated with risk of sleep disturbances. Such analyses could provide insights into the relative importance of 'new/incident' loneliness/social isolation as compared with 'stable/chronic' loneliness/social isolation (44).

Gender differences concerning associations of social isolation and loneliness with sleep disturbances were not examined specifically in this project. However, a previous study on a similar cohort as GÅS (SNAC-B) found that insomnia (a type

of sleep disturbance) was associated with low Quality of Life (QoL) among men but not among women (152). Thus, since there may be differences in terms of how men and women experience sleep disturbances, future studies may consider stratifying analyses of associations between social isolation and loneliness with sleep disturbances by gender.

Associations of medications with social isolation and loneliness

In Paper III, longitudinal associations of incident polypharmacy with incident occurrence of social isolation and loneliness were identified. There are several plausible mechanisms through which medications may be associated with social isolation and loneliness. Chronic diseases, such as diabetes or cardiovascular diseases, often require multiple medications to effectively prevent secondary complications and alleviate disease-associated symptoms (153). Previous research has demonstrated links between diseases and loneliness and social isolation (140, 141). Thus, diseases may confound the association identified with polypharmacy (confounding by indication) (154). Chronic diseases at baseline were included in the models to reduce this type of confounding. However, we did not account for disease-specific severity in our models, and it is possible that those with more severe disease subsequently required more medications, and had increased risk of social isolation and loneliness (confounding by indication severity) (154). Reverse causation (155) (i.e., loneliness/social isolation increases the risk of having polypharmacy) is also possible, although longitudinal population-based studies analyzing the reverse association are to my knowledge currently lacking. Further longitudinal studies that include measures of disease severity and examines bi-directional associations are thus warranted.

There could also be mechanisms related to the medications themselves. For example, taking multiple medications increases the risk of side-effects from medications (85). The specific side-effects one individual experiences depends on many factors (156), one being the type of medications that the individual consumes. In Paper IV, we found that certain medications associated with increased risk of falling (psychotropic-, neurological-, and/or anticholinergic FRIDs, [pnaFRIDs]) were associated with increased risk of reporting feelings of loneliness. Side-effects of pnaFRIDs among older adults, besides increasing fall-risk and fear of falling (157), may include sedation and cognitive impairment (158). These side-effects may hypothetically affect older adults' social engagement, and thus increase the probability of reporting loneliness. However, we did not observe an increase in social isolation among participants reporting pnaFRIDs consumption, which somewhat contradicts the hypothesis that pnaFRIDs affects social engagement in a substantial manner. Yet, these findings are in line with previous research having qualitatively (159) and quantitively (160) assessed individuals experiencing side-effects, that found that seeking more social support (e.g., contacting friends and

relatives) is a common coping strategy when experiencing side-effects from medications (159, 160). Actively seeking more social support could thus possibly mitigate the association of social isolation and pnaFRIDs. Further qualitative in-depth interview studies may aid in discerning mechanisms for the association of pnaFRIDs and loneliness.

The findings in Paper III and IV regarding associations of polypharmacy with social isolation and loneliness may at first glance be interpreted as conflicting, since statistically significant associations between polypharmacy, loneliness, and social isolation were identified in Paper III, while no statistically significant associations with polypharmacy were detected in Paper IV. There are several probable explanations for these discrepancies. For example, the study design of Paper III and IV were different. In Paper III, longitudinal associations of incident use of polypharmacy with incident occurrence of loneliness and social isolation were examined, while in Paper IV, cross-sectional (baseline) associations were analyzed. Previous research indicate that incident use of polypharmacy differs from prevalent use, where those with incident use of polypharmacy are more often transiently exposed to polypharmacy, while those with prevalent use are more often chronically exposed (161). However, in our sample, very few participants (n=65) reverted to 'non-polypharmacy' in a subsequent visit after having reported incident use of polypharmacy in a previous visit. Since polypharmacy, and especially chronic polypharmacy, increases with age (161), the relatively long intervals (3 to 6 years) between the visits may explain the low reversion rate observed.

Another possibility is that the cross-sectional baseline data has prevalent use survivor bias (97). We did not consider the length of polypharmacy use at baseline, and it is possible that the prevalent polypharmacy users at baseline are "survivors" of polypharmacy while those who have experienced negative effects of polypharmacy (including potential negative psychosocial effects) are less represented, inducing selection bias in the baseline data (97). Why, then, were cross-sectional baseline comparisons conducted in Paper IV? The key reason lies in sample size. A major trade-off in longitudinal analyses using an 'incident use' design for exposures and outcomes is the exclusion of individuals who already have the exposure and/or outcome at baseline. When both are common at baseline, this exclusion significantly reduces the sample size. In Paper III, the precision of the association estimates (odds ratios) for incident use of polypharmacy with incident social isolation and loneliness is therefore limited, reflected by the relatively wide 95% confidence intervals. Furthermore, due to the relatively small sample size in Paper III, we could not conduct longitudinal 'incident use'-analyses concerning more specific medication groups. An attempt was therefore made in Paper IV, using cross-sectional baseline data, to disentangle if pnaFRIDs and/or cardiovascular drugs were associated with social isolation and loneliness.

Another explanation for the discrepancies concerning polypharmacy in Paper III and IV could be the inclusion of polypharmacy, pnaFRIDs, and cardiovascular

drugs simultaneously in the statistical models in Paper IV. As for loneliness, one possibility may be that pnaFRIDs is a mediator of the association of polypharmacy with loneliness. In addition, since participants may consume pnaFRIDs and cardiovascular drugs simultaneously, multicollinearity (i.e., high correlation between factors) may also be present (162). Multicollinearity can induce biased standard errors, which in turn can result in unreliable p-values for evaluating the statistical significance of associations (162). In Paper IV, robust standard errors were implemented to mitigate this issue (163).

Previous studies having investigated associations of polypharmacy with social isolation and loneliness are somewhat inconclusive, with some studies indicating an association (71-73, 75, 77), while others did not detect any statistically significant associations (74, 76). Differences in study designs, populations investigated, measures of loneliness, social isolation, and polypharmacy, confounding adjustments, as well as analytical approaches (e.g., incident use or prevalent use), may partly explain the discrepancies in results between the different studies. In comparison, studies having examined associations of pnaFRIDs and loneliness are more consistently indicating a positive association (71-73, 76), and longitudinal research suggests that the association between psychotropic FRIDs and loneliness may be bi-directional (164). Longitudinal studies examining associations of FRIDs and social isolation and the direction of such associations are to my knowledge currently lacking, and may thus be considered for future research.

We included participants recruited from 2001 to 2021 in our analyses. The medication prescription pattern for older adults in Sweden has changed during this time-period, where polypharmacy (≥5 medications), and especially excessive polypharmacy (≥10 medications), has increased, while the use of pnaFRIDs has slightly decreased (165). Given the changes in medication prescription patterns, wave cohort effects concerning associations of medications with social isolation and loneliness are possible. We examined this by stratifying the analyses by wave cohorts in Paper III and IV, and the results were overall consistent across the wave cohorts, contradicting substantial wave cohort effects of these associations in our sample.

Methodological considerations

Important methodological considerations in practically all disciplines of research are those of validity and reliability. Internal validity may be defined as the extent to which a study, experiment, instrument, or test measures/examines what it was meant to measure (166). Internal validity may in turn be sub-divided into different types, such as test-specific validity, including construct-, content-, face-, criterion-, and predictive validity (167, 168), but may also refer to concepts related to causal

inference, such as confounding (169). External validity usually refers to the generalizability of the research findings to other settings, populations, and times (170). In comparison, reliability commonly refers to the stability or consistency of a certain measurement/test over time and conditions (166).

Internal validity

Misclassification and concordance between different measurement tools/definitions

It is challenging to determine if study subjects have been correctly classified as 'lonely' or 'socially isolated' in a study. For example, since loneliness is by most definitions considered a subjective experience and may be associated with a negative stigma and adverse connotations, underreporting feelings of loneliness is a possibility (171). In GÅS, loneliness is measured with single-item questions. Single-item loneliness assessments have by some researchers been criticized for being unidimensional and possibly oversimplifying the concept of loneliness (172). Nevertheless, single-item loneliness assessments have similar reliability as multi-item assessments (173), are easy to use in research- and clinical settings (e.g., time efficient), and often quite straightforward for the participants to understand (172).

One way often utilized to examine the classification agreement of loneliness instruments is to test the concordance/agreement of two or more different measurement tools that aim at assessing loneliness. A common agreement assessment in loneliness research is to test the concordance of single-item questions with multi-item loneliness scales in a sample (174, 175). The concordance between single-item and multi-item loneliness measures is often very high (173, 175). This is not surprising, since many multi-item loneliness scales (e.g., the UCLA Loneliness Scale (99), the de Jong Gierveld Loneliness Scale (100)) were originally developed and validated with single-item measurement tools as the reference assessment (99, 100). Since we do not have multi-item loneliness scales available, concordance testing between such scales and single-item measures is not possible in our sample. However, we did compare the two single-item loneliness questions used in the different papers in this thesis. The concordance regarding loneliness classification between the two questions was 87-90% in the GÅS sample.

As for social isolation, the concordance between the two different measures/definitions used in Paper I-II versus Paper III-IV was 76%. The discordance (24%) for the different social isolation measures/definitions was expected and primarily due to more subjects being classified as 'socially isolated' with the measure used in Paper III and IV, as compared to the stricter measure used in Paper I and II. In Paper III and IV, we aimed at using a more lenient social isolation classification that is more established in the international research community (6, 44, 106). Thus, the definition and scale used in Paper III and IV

resulted in higher social isolation prevalences (22%) as compared to Paper I and II (4-6%), although the prevalences in Paper III and IV are comparable to previous studies applying the same instrument (6, 106) and other multi-item social isolation instruments (e.g., the Lubben Social Network scale) (39).

Medication exposures in a study can be assessed in different ways, for example by research staff (e.g., the study physician as in the GÅS study), or with data from prescription registries. There are benefits and drawbacks with both methods to measure medication exposures. The physician-based medication assessment in GÅS allows inclusion of non-prescribed medications, including OTCs, herbal medications, and supplements, while the prescription registries only include prescribed medications. The prescribed medication registry applicable to our studies would be the Swedish Prescribed Drug Register (SPDR) (176). However, the SPDR started in 2005 (176), meaning that we lack prescription register data for participants recruited before that date. In our studies, roughly 50% of the participants were recruited and had their baseline visit (Wave 1) before 2005. Because of this, we chose the physician-based documentation as the medication assessment for our studies.

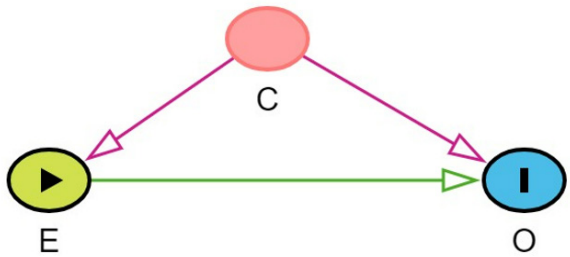
Causality and confounding

All studies involved in this thesis are observational, which means that exposure status is not randomly assigned to the participants, and confounding is therefore possible (169). In comparison, in randomized controlled trials (RCTs), the participants are randomly assigned to their exposure status (e.g., no treatment or treatment). Thus, in RCTs, there should be no variable (measured or un-measured) that non-randomly affects the exposure status, which mitigates the issue with confounding. However, RCTs are not suited for all research questions (e.g., due to ethical concerns). In addition, participants included in RCTs are often rigorously selected, and the strict study protocols do not necessarily reflect real-life clinical practice, which raises concern about the generalizability of findings from RCTs (177).

The strengths of observational studies are their potential generalizability ("real-world evidence") and possibility to investigate a wider range of exposures (e.g., smoking, health behaviours) and outcomes (e.g., long-term outcomes) not suited for RCTs (178). Yet, as said, exposure status is in observational research typically not assigned at random, and confounding is therefore possible (169). Some confounding factors may be well-known and measured in a study. In these cases, statistical methods can be applied in efforts to reduce confounding (e.g., matching, stratification, multivariable regression) and thereby better isolate the effect of the exposure on the outcome (169). For this thesis, directed acyclic graphs (DAGs) were utilized to illustrate the structure of possible confounding factors in the separate papers (127, 128, 169). In all four papers, we incorporated various socio-economic and health-related factors in our models in efforts to minimize confounding. The

DAGs were based on our clinical and scientific knowledge, but the selection of covariates for the statistical models is nonetheless a subjective choice. Also, since there may still be unknown and/or unmeasured factors that influences both exposures and outcomes in our studies (i.e., unmeasured confounding), causal relationships are difficult to determine. In addition, reverse causation may also be present (155). Thus, all correlations described in this thesis should be interpreted as associations.

Figure 7. DAG illustrating a variable (C), which potentially confounds the association of the exposure (E) on the outcome (O) (169).



Attrition

Attrition refers to the loss of study subjects over the course of a research project (179). In longitudinal studies, attrition can have several reasons, for example participant relocation, loss of interest for the study, and health conditions that hinder further participation (179). Attrition may affect longitudinal studies in different ways. For example, with fewer participants remaining in a study, the sample size decreases. Secondly, if the remaining participants do not adequately represent the initial target population, the generalizability of the results are limited (180). In GÅS, some measures were implemented aiming at reducing attrition, including offering home-visits and telephone interviews for participants unable to come to the study centers. Whether such measures decrease attrition in a substantial manner is debatable, and the evidence supporting retention measures is limited in general (181). The participation rate at the follow-up visits among eligible individuals in GÅS was 65 to 81%, which is comparable to other longitudinal studies on older adults (181). In Paper II, an attrition analysis showed that non-participants at re-examination were older and had a higher prevalence of heart disease, cancer, depression, poor cognitive function, sleep disturbances, recurrent periods or constant feelings of loneliness, and social isolation at baseline compared to participants. This implies that the GÅS participants at the follow-up visits were overall younger and healthier at baseline than the non-participants, indicating that the findings may not be fully transferable to the whole GÅS cohort at baseline nor to the general population of older adults (see External validity).

External validity

Generalizability

In our sample, older adults (≥60 years) from five municipalities in the county of Skåne in southern Sweden were invited. The municipalities (Eslöv, Hässleholm, Malmö, Osby, and Ystad) were selected to represent both rural and urban parts of Skåne county. The subjects were, within the prespecified age groups and municipality borders, selected at random for invitation via letter using information from the Swedish National Population Register, a register with adequate coverage of the total population (182). Yet, despite efforts to create a representative study sample of older adults living in Skåne at the invitation stage, those who accept participation in epidemiological studies are generally healthier, have lower prevalence of frailty, cognitive impairment and disability, and have higher education levels and financial status compared to non-participants (183, 184). In addition, participation rates in epidemiological studies are steadily declining (183-185), which poses a significant threat to the external validity of survey-based research. In GÅS, participation rates have been relatively steady from 2001-2022, ranging from 60 to 70%. The relatively high participation rate in GÅS may at least partly be explained by factors related to social capital: older adults in Skåne have a relatively high trust in the healthcare system and are more likely to participate in surveys compared to younger adults (185, 186).

Social isolation is a concept which by some definitions and researchers not only describes individuals who are living alone and having infrequent contact with friends and family (i.e., 'inner circle/micro level isolation'), but also includes those who are disconnected from the wider society and have low social- and civic participation and engagement (i.e., 'macro level isolation') (187). There is a correlation between micro- and macro level social isolation: those who live alone and have infrequent contact with friends and family are more likely to have low social- and civic participation (187). Thus, since individuals with social isolation tend to have lower social participation, it is likely that those with social isolation are under-represented in the GÅS sample (187). This is also supported by the findings in Paper II, where those with social isolation at baseline were less likely to participate at the re-examination.

Southern Sweden is a region with high socio-economic standard and well-functioning healthcare from a global perspective. Thus, the GÅS participants are likely comparable to relatively healthy, non-frail, socially engaged older adults living in countries with similar living- and societal conditions, such as other Nordic countries. However, the findings may not be transferable to older adults with severe social isolation, frailty, cognitive impairment and/or disability, nor to older adults living in middle- and lower income countries.

Wave cohort effects

Older adults were recruited in four different waves in our studies. Those aged 60 years in 2001 may differ from 60-year-olds recruited in 2021, for example in terms of health behaviors (e.g., smoking habits, physical activity) (119, 188, 189), cognition (190, 191), disease panorama (192), and medical treatment (165, 193). We investigated prevalence of social isolation and loneliness by stratifying by recruitment wave but found no profound differences between the waves. Similarly, we found no apparent differences in the results in Paper III and IV when stratifying by wave cohort.

Reliability

In longitudinal studies involving repeated examinations of subjects, reliability is an important aspect. Reliability may be defined as the consistency of a measurement or test, and relates to the agreement and correlation between measurements (166, 194). Since loneliness is often described as a potentially fluctuating experience (40), absolute consistency between measurements (e.g., test-retest evaluations) is not expected. However, single-item loneliness assessments have been shown to have acceptable reliability (173), with test-retest correlations comparable to multi-item loneliness assessments (173).

Other methodological considerations

Lack of community- and multilevel analyses

A limitation of our studies is that we primarily examined individual-level factors in our analyses of social isolation and loneliness. Community-, cognitive-, and other multilevel factors (e.g., factors related to social capital such as social- and civic participation and trust) may also play an important role, for example concerning the probability of psychotropic medication use (195, 196). Further longitudinal studies examining the role of different aspects of social capital concerning associations of symptoms and medications with loneliness and social isolation may be considered for future research.

Lack of medication adherence data

We did not have data on medication adherence in our sample. Low social participation (197) and low social support (198) have been associated with low adherence to medical treatment. Hypothetically, if medications would increase the likelihood of feeling lonely and/or being socially isolated, low adherence to these medications could possibly underestimate these associations.

Clinical implications and future directions

Findings from this thesis indicate that loneliness is relatively prevalent among older adults living in southern Sweden. Social isolation and loneliness have been linked with several health issues, including increased risk of depression, cardiovascular diseases, cognitive impairment, and mortality (3, 47-49). Evaluating prevalence of loneliness and social isolation among older adults and those at risk of these conditions is of importance to adequately understand how common these conditions are and to estimate the necessity of further research.

There are several challenges that needs to be addressed in the future. The research field still lacks an established standard definition for classifying social isolation and loneliness (11-13). This negatively affects the reproducibility and generalizability of research findings, and produces substantial heterogeneity between studies, limiting the possibility for systematic synthesis of data from different cohorts (11). Thus, determining standardized definitions of social isolation and loneliness may increase the research field's trustworthiness and legitimacy (199). Inspiration for standardization may be drawn from examples in clinical medicine, in which international expert panels establishes consensus definitions for clinical conditions (200). However, it would be challenging to standardize definitions across all disciplines involved in loneliness/social isolation research, but as a start I would suggest for future directions that consensus guidelines for definitions are developed for use in medical research.

The findings from our studies indicate that social isolation and loneliness are associated with increased reporting of a multitude of symptoms, including sleep disturbances, depressive symptoms, cardiopulmonary symptoms, and gastro-intestinal symptoms. A high symptom burden among older adults has been associated with deteriorating QoL (201) and the reported symptoms are common reasons for seeking healthcare among older patients (202). However, previous studies investigating links between social isolation and loneliness with healthcare consumption have shown mixed findings (45): lonely and/or socially isolated older adults tend to have increased risk of emergency department visits, hospital readmissions and longer hospital stays (55-57), but have also been found to utilize preventive healthcare (e.g., visits to general practitioners, dentists, vaccinations, cancer-screening programs) less frequently (58-60). Further longitudinal studies are warranted to clarify the direction of associations of social isolation and loneliness with symptoms, the role of these associations concerning healthcare consumption and the type/quality of care. Qualitative studies, such as individual interviews or discussion groups (focus groups), may also aid in clarifying if/how contexts and behaviors are related to symptoms among those who are lonely and/or socially isolated (203), and disentangling important themes (e.g., symptom interpretation, coping, interaction with healthcare, patient involvement) and aspects regarding seeking and receiving healthcare in this group (203-205).

Our studies indicate associations of medications with social isolation and loneliness. Further longitudinal studies, preferably with experimental/interventional designs, are warranted to elucidate mechanisms, direction of associations, and potential reversibility of these conditions. For example, clinical trials examining the effect of deprescribing certain medications (e.g., pnaFRIDs) regarding loneliness feelings and social isolation could be of value. Again, qualitative analyses, for example via individual interviews and/or discussion groups, may play an important role as well, for example by providing deeper insights into relevant themes (e.g., medication beliefs, body awareness, symptom interpretation) and coping strategies experienced by older adults who feel lonely and consume multiple medications (159).

Another important topic for further studies is existential loneliness and associations with health. In medical research, scientists have examined existential loneliness in primarily palliative/nursing home/end-of-life scenarios (28). Research examining predisposing factors and the role of existential loneliness in relation to health in long-term, non-palliative settings are lacking (26, 206). Given the conception by many researchers that existential loneliness is a more profound experience compared to emotional loneliness and social isolation (26, 28), further quantitative and qualitative research on representative samples drawn from the general population of older adults are warranted (26, 206).

In our studies, a small group of those classified as socially isolated reported no feelings of loneliness (n=59, corresponding to 20% of those classified as socially isolated, see Paper I, Appendix Table 8). This group may represent individuals who are objectively alone but not feeling lonely, commonly referred to as ‘solitude’ (24, 25). Previous research investigating associations of solitude with health among older adults have presented mixed findings (207), and further studies examining associations of solitude with subjective health (e.g., life satisfaction, symptom experience) in general population cohorts have been suggested (207).

Conclusions

Loneliness is relatively common among older adults, with a majority experiencing some degree of loneliness feelings. Loneliness and social isolation are associated with increased risk of reporting mental and somatic symptoms, including sleep disturbances, depressive symptoms, and cardiopulmonary symptoms. Incident use of polypharmacy is associated with increased risk of incident occurrence of social isolation and loneliness. Furthermore, certain medications with fall-risk-increasing properties (e.g., psychotropics, neurological drugs, anticholinergics) are associated with increased risk of feeling lonely. In the future, establishing standardized definitions for social isolation and loneliness are recommended. In addition, further studies with longitudinal, qualitative, and interventional designs examining mechanisms, direction of associations, and reversibility of social isolation and loneliness among older adults and their associated factors are suggested.

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References

1. Luhmann M, Buecker S, Rüsberg M. Loneliness across time and space. Nature Reviews Psychology. 2023;2(1):9-23.
2. Holt-Lunstad J. The Potential Public Health Relevance of Social Isolation and Loneliness: Prevalence, Epidemiology, and Risk Factors. Public Policy & Aging Report. 2017;27(4):127-30.
3. Leigh-Hunt N, Bagguley D, Bash K, Turner V, Turnbull S, Valtorta N, et al. An overview of systematic reviews on the public health consequences of social isolation and loneliness. Public Health. 2017;152:157-71.
4. Bengtsson T, Scott K. Population aging and the future of the welfare state: the example of Sweden. Popul Dev Rev. 2011;37(Suppl 1):158-70.
5. Bloom DE, Canning D, Fink G. Implications of population ageing for economic growth. Oxford Review of Economic Policy. 2010;26(4):583-612.
6. Kobayashi LC, Steptoe A. Social Isolation, Loneliness, and Health Behaviors at Older Ages: Longitudinal Cohort Study. Ann Behav Med. 2018;52(7):582-93.
7. Taube E, Kristensson J, Midlöv P, Holst G, Jakobsson U. Loneliness Among Older People: Results from the Swedish National Study on Aging and Care – Blekinge. The Open Geriatric Medicine Journal. 2013;6:1-10.
8. World Health Organization (WHO). WHO Commission on Social Connection: WHO; 2023 [Available from: https://www.who.int/groups/commission-on-social-connection#:~:text=Across%20all%20ages%20and%20regions,a%20global%20public%20health%20priority.
9. Stärk gemenskaperna – motverka den ofrivilliga ensamheten [press release]. Regeringskansliet; 2023.
10. Ekström H, Elmståhl S. Pain and fractures are independently related to lower walking speed and grip strength: results from the population study "Good Ageing in Skåne". Acta Orthop. 2006;77(6):902-11.
11. Wang F, Gao Y, Han Z, Yu Y, Long Z, Jiang X, et al. A systematic review and meta-analysis of 90 cohort studies of social isolation, loneliness and mortality. Nature Human Behaviour. 2023;7(8):1307-19.
12. Bandari R, Khankeh HR, Shahboulaghi FM, Ebadi A, Keshtkar AA, Montazeri A. Defining loneliness in older adults: protocol for a systematic review. Systematic Reviews. 2019;8(1):26.
13. Nicholson N. Social isolation in older adults: An evolutionary concept analysis. Journal of advanced nursing. 2009;65:1342-52.

14. Dykstra PA. Older adult loneliness: myths and realities. European journal of ageing. 2009;6(2):91-100.
15. Ozawa-de Silva C, Parsons M. Toward an anthropology of loneliness. Transcultural Psychiatry. 2020;57(5):613-22.
16. Heu LC. The Loneliness of the Odd One Out: How Deviations From Social Norms Can Help Explain Loneliness Across Cultures. Perspectives on Psychological Science. 2023:17456916231192485.
17. Barreto M, van Breen J, Victor C, Hammond C, Eccles A, Richins MT, et al. Exploring the nature and variation of the stigma associated with loneliness. J Soc Pers Relat. 2022;39(9):2658-79.
18. de Jong-Gierveld J. Developing and testing a model of loneliness. Journal of Personality and Social Psychology. 1987;53(1):119-28.
19. Peplau LA, Perlman D, Perlman D. Loneliness: A Sourcebook of Current Theory, Research and Therapy: Wiley, New York, US; 1982.
20. de Jong-Gierveld J, van Tilburg T, Dykstra P. Loneliness and Social Isolation 2006. Available from: https://doi.org/10.1017/CBO9780511606632.027.
21. Weiss RS. Loneliness: The experience of emotional and social isolation: The MIT Press; 1973.
22. Loneliness and social isolation in old age. correlates and implications. Hajek A, Riedel-Heller SG, König H-H, editors: Routledge; 2023.
23. Hawton A, Green C, Dickens AP, Richards SH, Taylor RS, Edwards R, et al. The impact of social isolation on the health status and health-related quality of life of older people. Quality of Life Research. 2011;20(1):57-67.
24. Tornstam L. Ensamhetens dimensioner — en begreppsdiskussion. Sociologisk Forskning. 1983;20(2):50-63.
25. Long CR, Averill JR. Solitude: An Exploration of Benefits of Being Alone. Journal for the Theory of Social Behaviour. 2003;33(1):21-44.
26. McKenna-Plumley PE, Turner RN, Yang K, Groarke JM. “It’s a feeling of complete disconnection”: experiences of existential loneliness from youth to older adulthood. BMC Psychology. 2023;11(1):408.
27. Bolmsjö I, Tengland PA, Rämgård M. Existential loneliness: An attempt at an analysis of the concept and the phenomenon. Nurs Ethics. 2019;26(5):1310-25.
28. Ettema EJ, Derksen LD, van Leeuwen E. Existential loneliness and end-of-life care: A systematic review. Theoretical Medicine and Bioethics. 2010;31(2):141-69.
29. Coleman JS. Social Capital in the Creation of Human Capital. American Journal of Sociology. 1988;94:S95-S120.
30. Lindström M. Social capital, anticipated ethnic discrimination and self-reported psychological health: A population-based study. Social Science & Medicine. 2008;66(1):1-13.
31. Lin N, Ensel WM, Simeone RS, Kuo W. Social Support, Stressful Life Events, and Illness: A Model and an Empirical Test. Journal of Health and Social Behavior. 1979;20(2):108-19.

32. Emerson E, Fortune N, Llewellyn G, Stancliffe R. Loneliness, social support, social isolation and wellbeing among working age adults with and without disability: Cross-sectional study. Disabil Health J. 2021;14(1):100965.
33. Hawthorne G. Perceived social isolation in a community sample: its prevalence and correlates with aspects of peoples' lives. Social Psychiatry and Psychiatric Epidemiology. 2008;43(2):140-50.
34. Iliffe S, Kharicha K, Harari D, Swift C, Gillmann G, Stuck AE. Health risk appraisal in older people 2: the implications for clinicians and commissioners of social isolation risk in older people. British Journal of General Practice. 2007;57(537):277.
35. Taylor HO, Taylor RJ, Nguyen AW, Chatters L. Social Isolation, Depression, and Psychological Distress Among Older Adults. J Aging Health. 2018;30(2):229-46.
36. Aoki T, Yamamoto Y, Ikenoue T, Urushibara-Miyachi Y, Kise M, Fujinuma Y, et al. Social Isolation and Patient Experience in Older Adults. Ann Fam Med. 2018;16(5):393-8.
37. Menec VH, Newall NE, Mackenzie CS, Shooshtari S, Nowicki S. Examining individual and geographic factors associated with social isolation and loneliness using Canadian Longitudinal Study on Aging (CLSA) data. PLoS One. 2019;14(2):e0211143.
38. Hajek A, Volkmar A, König H-H. Prevalence and correlates of loneliness and social isolation in the oldest old: a systematic review, meta-analysis and meta-regression. Social Psychiatry and Psychiatric Epidemiology. 2023.
39. Ran Z, Wei J, Yang G, Yang C. Prevalence of social isolation in the elderly: A systematic review and meta-analysis. Geriatr Nurs. 2024;58:87-97.
40. Hawkley LC, Kocherginsky M. Transitions in Loneliness Among Older Adults: A 5-Year Follow-Up in the National Social Life, Health, and Aging Project. Research on Aging. 2018;40(4):365-87.
41. Newall NE, Chipperfield JG, Bailis DS. Predicting stability and change in loneliness in later life. J Soc Pers Relat. 2014;31(3):335-51.
42. Yang F, Gu D. Predictors of loneliness incidence in Chinese older adults from a life course perspective: a national longitudinal study. Aging Ment Health. 2020;24(6):879-88.
43. Dahlberg L, Andersson L, McKee KJ, Lennartsson C. Predictors of loneliness among older women and men in Sweden: A national longitudinal study. Aging & Mental Health. 2015;19(5):409-17.
44. Lyu C, Siu K, Xu I, Osman I, Zhong J. Social Isolation Changes and Long-Term Outcomes Among Older Adults. JAMA Network Open. 2024;7(7):e2424519-e.
45. The National Academies Press. Social isolation and loneliness in older adults: Opportunities for the health care system. Washington, DC: The National Academies Press; 2020. Available from: https://ludwig.lub.lu.se/login?url=https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,uid&db=psyh&AN=2020-36005-000&site=eds-live&scope=site.
46. OECD/European Observatory on Health Systems and Policies. Sweden: Country Health Profile 2019, State of Health in the EU. OECD Publishing; 2019.

47. Golaszewski NM, LaCroix AZ, Godino JG, Allison MA, Manson JE, King JJ, et al. Evaluation of Social Isolation, Loneliness, and Cardiovascular Disease Among Older Women in the US. JAMA Network Open. 2022;5(2):e2146461-e.
48. Cené CW, Beckie TM, Sims M, Suglia SF, Aggarwal B, Moise N, et al. Effects of Objective and Perceived Social Isolation on Cardiovascular and Brain Health: A Scientific Statement From the American Heart Association. Journal of the American Heart Association. 2022;11(16):e026493.
49. Mann F, Wang J, Pearce E, Ma R, Schlief M, Lloyd-Evans B, et al. Loneliness and the onset of new mental health problems in the general population. Soc Psychiatry Psychiatr Epidemiol. 2022;57(11):2161-78.
50. Leeming A, Murray SA, Kendall M. The impact of advanced heart failure on social, psychological and existential aspects and personhood. Eur J Cardiovasc Nurs. 2014;13(2):162-7.
51. Barjaková M, Garnero A, d'Hombres B. Risk factors for loneliness: A literature review. Social Science & Medicine. 2023;334:116163.
52. Read S, Comas-Herrera A, Grundy E. Social Isolation and Memory Decline in Later-life. The Journals of Gerontology: Series B. 2020;75(2):367-76.
53. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
54. Andreasen J, Lund H, Aadahl M, Sørensen EE. The experience of daily life of acutely admitted frail elderly patients one week after discharge from the hospital. Int J Qual Stud Health Well-being. 2015;10:27370.
55. Valtorta NK, Moore DC, Barron L, Stow D, Hanratty B. Older Adults' Social Relationships and Health Care Utilization: A Systematic Review. Am J Public Health. 2018;108(4):e1-e10.
56. Hawker M, Romero-Ortuno R. Social Determinants of Discharge Outcomes in Older People Admitted to a Geriatric Medicine Ward. J Frailty Aging. 2016;5(2):118-20.
57. Taube E, Kristensson J, Sandberg M, Midlöv P, Jakobsson U. Loneliness and health care consumption among older people. Scand J Caring Sci. 2015;29(3):435-43.
58. Vozikaki M, Linardakis M, Philalithis A. Preventive health services utilization in relation to social isolation in older adults. Journal of Public Health (09431853). 2017;25(5):545-56.
59. Hajek A, Bock JO, König HH. The role of general psychosocial factors for the use of cancer screening—Findings of a population-based observational study among older adults in Germany. Cancer Medicine. 2017;6(12):3025-39.
60. Hajek A, König HH. Does Loneliness Predict Subsequent Use of Flu Vaccination? Findings from a Nationally Representative Study of Older Adults in Germany. Int J Environ Res Public Health. 2019;16(24).
61. Cacioppo JT, Hughes ME, Waite LJ, Hawkley LC, Thisted RA. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. Psychol Aging. 2006;21(1):140-51.

62. Ge L, Yap CW, Ong R, Heng BH. Social isolation, loneliness and their relationships with depressive symptoms: A population-based study. PLoS One. 2017;12(8):e0182145.
63. Lee SL, Pearce E, Ajnakina O, Johnson S, Lewis G, Mann F, et al. The association between loneliness and depressive symptoms among adults aged 50 years and older: a 12-year population-based cohort study. Lancet Psychiatry. 2021;8(1):48-57.
64. Miner B, Kryger MH. Sleep in the Aging Population. Sleep Med Clin. 2017;12(1):31-8.
65. Tatineny P, Shafi F, Gohar A, Bhat A. Sleep in the Elderly. Mo Med. 2020;117(5):490-5.
66. Gordon NP, Yao JH, Brickner LA, Lo JC. Prevalence of sleep-related problems and risks in a community-dwelling older adult population: a cross-sectional survey-based study. BMC Public Health. 2022;22(1):2045.
67. Ben Simon E, Walker MP. Sleep loss causes social withdrawal and loneliness. Nat Commun. 2018;9(1):3146.
68. Dworschak C, Mäder T, Rühlmann C, Maercker A, Kleim B. Examining bi-directional links between loneliness, social connectedness and sleep from a trait and state perspective. Scientific Reports. 2024;14(1):17300.
69. Griffin SC, Williams AB, Ravyts SG, Mladen SN, Rybarczyk BD. Loneliness and sleep: A systematic review and meta-analysis. Health Psychology Open. 2020;7(1):2055102920913235.
70. Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. J Am Med Dir Assoc. 2020;21(2):181-7.
71. Vyas MV, Watt JA, Yu AYX, Straus SE, Kapral MK. The association between loneliness and medication use in older adults. Age Ageing. 2021;50(2):587-91.
72. Kotwal AA, Steinman MA, Cenzer I, Smith AK. Use of High-risk Medications Among Lonely Older Adults: Results From a Nationally Representative Sample. JAMA Intern Med. 2021;181(11):1528-30.
73. Im JH, Bronskill S, Strauss R, Gruneir A, Guan J, Boblitz A, et al. Sex-based differences in the relationship between loneliness and prevalent polypharmacy in older adults in Ontario. Epidemiology (Cambridge, Mass). 2022;70(SUPPL 1):S261.
74. Junius-Walker U, Theile G, Hummers-Pradier E. Prevalence and predictors of polypharmacy among older primary care patients in Germany. Family Practice. 2007;24(1):14-9.
75. Oliveira-Dias C, Morais S, Costa AR. Sex differences in the association between social capital and healthcare use-Results from the survey of health, ageing and retirement in Europe (SHARE). Health & social care in the community. 2022.
76. Pietraszek A, Agrawal S, Dróżdż M, Makuch S, Domański I, Dudzik T, et al. Sociodemographic and Health-Related Factors Influencing Drug Intake among the Elderly Population. International Journal of Environmental Research and Public Health [Internet]. 2022; 19(14).

77. Rocha-Vieira C, Oliveira G, Couto L, Santos P. Impact of loneliness in the elderly in health care: A cross-sectional study in an urban region of Portugal. Family Medicine and Primary Care Review. 2019;21(2):138-43.
78. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC geriatrics. 2017;17(1):230-.
79. World Health Organization (WHO). Medication safety in polypharmacy: technical report. World Health Organization; 2019.
80. Elmstahl S, Linder H. Polypharmacy and inappropriate drug use among older people--a systematic review. Healthy Aging & Clinical Care in the Elderly. 2013:1+.
81. van den Akker M, Vaes B, Goderis G, Van Pottelbergh G, De Burghgraeve T, Henrard S. Trends in multimorbidity and polypharmacy in the Flemish-Belgian population between 2000 and 2015. PloS one. 2019;14(2):e0212046-e.
82. Jerjes W, Harding D. Confronting polypharmacy and social isolation in elderly care: a general practitioner's perspective on holistic primary care. Front Aging. 2024;5:1384835.
83. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med. 2015;13:74.
84. Haider SI, Johnell K, Thorslund M, Fastbom J. Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992 - 2002. Int J Clin Pharmacol Ther. 2007;45(12):643-53.
85. Kojima T, Akishita M, Kameyama Y, Yamaguchi K, Yamamoto H, Eto M, et al. High risk of adverse drug reactions in elderly patients taking six or more drugs: analysis of inpatient database. Geriatr Gerontol Int. 2012;12(4):761-2.
86. Kim J, Parish AL. Polypharmacy and Medication Management in Older Adults. The Nursing clinics of North America. 2017;52(3):457-68.
87. Wastesson JW, Cedazo Minguez A, Fastbom J, Maioli S, Johnell K. The composition of polypharmacy: A register-based study of Swedes aged 75 years and older. PLoS One. 2018;13(3):e0194892.
88. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc. 2014;62(12):2261-72.
89. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink AMAT, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. Journal of the American Medical Directors Association. 2018;19(4):372.e1-.e8.
90. Seppala LJ, Wermelink A, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. J Am Med Dir Assoc. 2018;19(4):371.e11-.e17.
91. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. J Am Med Dir Assoc. 2018;19(4):371.e1-.e9.

92. Johnell K, Jonasdottir Bergman G, Fastbom J, Danielsson B, Borg N, Salmi P. Psychotropic drugs and the risk of fall injuries, hospitalisations and mortality among older adults. Int J Geriatr Psychiatry. 2017;32(4):414-20.
93. Buecker S, Denissen JJA, Luhmann M. A Propensity-Score Matched Study of Changes in Loneliness Surrounding Major Life Events. Journal of Personality & Social Psychology. 2021;121(3):669-90.
94. Maura G, Blotière PO, Wastesson JW, Johnell K. Spousal bereavement and four-year trajectories of medication use: A nationwide register-based study in Swedish older adults. J Am Geriatr Soc. 2024;72(7):2048-59.
95. Lagergren M, Fratiglioni L, Hallberg IR, Berglund J, Elmståhl S, Hagberg B, et al. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). Aging Clinical and Experimental Research. 2004;16(2):158-68.
96. Ramadas A, Quek KF, Chan CKY, Oldenburg B. Web-based interventions for the management of type 2 diabetes mellitus: A systematic review of recent evidence. International Journal of Medical Informatics. 2011;80(6):389-405.
97. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158(9):915-20.
98. Valtorta NK, Kanaan M, Gilbody S, Hanratty B. Loneliness, social isolation and social relationships: what are we measuring? A novel framework for classifying and comparing tools. BMJ open. 2016;6(4):e010799.
99. Russell D, Peplau LA, Ferguson ML. Developing a Measure of Loneliness. Journal of Personality Assessment. 1978;42(3):290-4.
100. de Jong-Gierveld J. The Construct of Loneliness: Components and Measurement. Essence: Issues in the Study of Ageing, Dying, and Death. 1978;2(4):221-37.
101. Lubben JE. Assessing social networks among elderly populations. Lippincott Williams & Wilkins; 1988. p. 42-52.
102. Nicolaisen M, Thorsen K. Who are Lonely? Loneliness in Different Age Groups (18–81 Years Old), Using Two Measures of Loneliness. The International Journal of Aging and Human Development. 2014;78(3):229-57.
103. The Swedish Central Bureau of Statistics (SCB). Government report - Four percent are socially isolated in Sweden. The Swedish Central Bureau of Statistics (SCB); 2019.
104. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. Int J Epidemiol. 2013;42(6):1640-8.
105. Shankar A, McMunn A, Banks J, Steptoe A. Loneliness, social isolation, and behavioral and biological health indicators in older adults. Health Psychol. 2011;30(4):377-85.
106. Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. Proc Natl Acad Sci U S A. 2013;110(15):5797-801.

107. Tibblin G, Tibblin B, Peciva S, Kullman S, Svärdsudd K. "The Göteborg quality of life instrument"--an assessment of well-being and symptoms among men born 1913 and 1923. Methods and validity. Scand J Prim Health Care Suppl. 1990;1:33-8.
108. Tibblin G, Bengtsson C, Furunes B, Lapidus L. Symptoms by Age and Sex: The Population Studies of Men and Women in Gothenburg, Sweden. Scandinavian Journal of Primary Health Care. 1990;8(1):9-17.
109. Sullivan M, Karlsson J, Bengtsson C, Furunes B, Lapidus L, Lissner L. "The Göteborg Quality of Life Instrument"--a psychometric evaluation of assessments of symptoms and well-being among women in a general population. Scand J Prim Health Care. 1993;11(4):267-75.
110. Ekström H, Auoja NL, Elmståhl S, Sandin Wranker L. High Burden among Older Family Caregivers is Associated with High Prevalence of Symptoms: Data from the Swedish Study "Good Aging in Skåne (GÅS)". Journal of Aging Research. 2020;2020:5272130.
111. Gurland B, Golden RR, Teresi JA, Challop J. The Short-Care: An Efficient Instrument for the Assessment of Depression, Dementia and Disability1. Journal of Gerontology. 1984;39(2):166-9.
112. Livingston G, Blizard B, Mann A. Does sleep disturbance predict depression in elderly people? A study in inner London. Br J Gen Pract. 1993;43(376):445-8.
113. Teresi JA, Golden RR, Gurland BJ, Wilder DE, Bennett RG. Construct validity of indicator-scales developed from the Comprehensive Assessment and Referral Evaluation interview schedule. J Gerontol. 1984;39(2):147-57.
114. Hellström A, Hellström P, Willman A, Fagerström C. Association between Sleep Disturbances and Leisure Activities in the Elderly: A Comparison between Men and Women. Sleep Disord. 2014;2014:595208.
115. Teresi JA, Golden RR, Gurland BJ. Concurrent and predictive validity of indicator scales developed for the Comprehensive Assessment and Referral Evaluation interview schedule. J Gerontol. 1984;39(2):158-65.
116. Suehs BT, Caplan EO, Hayden J, Ng DB, Gaddy RR. The Relationship Between Anticholinergic Exposure and Falls, Fractures, and Mortality in Patients with Overactive Bladder. Drugs Aging. 2019;36(10):957-67.
117. The Anatomical Therapeutic Chemical (ATC) classification system [Internet]. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. Available from: https://www.whocc.no/.
118. Wranker LS, Elmståhl S, Ekström H. Pain and alcohol: a comparison of two cohorts of 60 year old women and men: findings from the Good Aging in Skåne study. Scandinavian Journal of Pain. 2018;18(4):611-20.
119. Wranker LS, Elmståhl S, Ekström H. Physical performance in relation to birth cohort: A comparison of 60 year old Swedish men and women born twelve years apart. Archives of Gerontology and Geriatrics. 2019;82:22-7.
120. Wallston BS, Wallston KA, Kaplan GD, Maides SA. Development and validation of the health locus of control (HLC) scale. J Consult Clin Psychol. 1976;44(4):580-5.

121. World Health Organization (WHO). International Classification of Diseases, 10th revision. Genève, Switzerland: WHO; 1993 [Available from: https://icd.who.int/browse10/2019/en.
122. Elmståhl S, Lundholm-Auoja N, Ekström H, Sandin Wranker L. Being an older family caregiver does not impact healthcare and mortality: Data from the study 'Good Aging in Skåne'. Scand J Public Health. 2020:1403494820960648.
123. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.
124. Grut M, Fratiglioni L, Viitanen M, Winblad B. Accuracy of the Mini-Mental Status Examination as a screening test for dementia in a Swedish elderly population. Acta Neurologica Scandinavica. 1993;87(4):312-7-7.
125. Asberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. A comprehensive psychopathological rating scale. Acta psychiatrica Scandinavica Supplementum. 1978(271):5-27.
126. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science. 1979;134:382-9.
127. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology (Cambridge, Mass). 1999;10(1):37-48.
128. Digitale JC, Martin JN, Glymour MM. Tutorial on directed acyclic graphs. J Clin Epidemiol. 2022;142:264-7.
129. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. International Journal of Epidemiology. 2016;45(6):1887-94.
130. Haider SI, Johnell K, Weitoft GR, Thorslund M, Fastbom J. The influence of educational level on polypharmacy and inappropriate drug use: a register-based study of more than 600,000 older people. J Am Geriatr Soc. 2009;57(1):62-9.
131. World Medical Association (WMA). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA; 2013. Available from: https://doi.org/10.1001/jama.2013.281053
132. Zerdick T. Pseudonymous data: processing personal data while mitigating risks: European Data Protection Supervisor; 2021 [Available from: https://www.edps.europa.eu/press-publications/press-news/blog/pseudonymous-data-processing-personal-data-while-mitigating_en.
133. Lund University. Managing data in a high-security environment – LUSEC 2024 [Available from: https://www.intramed.lu.se/en/research/managing-your-data-secure-manner/managing-data-high-security-environment-lusec.
134. Langmann E. Vulnerability, ageism, and health: is it helpful to label older adults as a vulnerable group in health care? Med Health Care Philos. 2023;26(1):133-42.
135. Surkalim DL, Luo M, Eres R, Gebel K, van Buskirk J, Bauman A, et al. The prevalence of loneliness across 113 countries: systematic review and meta-analysis. BMJ (Clinical research ed). 2022;376:e067068.

136. Siira E, Olaya-Contreras P, Yndigegn S, Wijk H, Rolandsson B, Wolf A. Older adults' provision of informal care and support to their peers – A cornerstone of Swedish society: Demographic characteristics and experiences of social isolation. Scandinavian Journal of Caring Sciences. 2022;36(2):468-81.
137. Malani, Singer, Kirch, Solway, Roberts, Smith, et al. Trends in Loneliness Among Older Adults from 2018-2023. University of Michigan National Poll on Healthy Aging; 2023.
138. Gan P, Xie Y, Duan W, Deng Q, Yu X. Rumination and Loneliness Independently Predict Six-Month Later Depression Symptoms among Chinese Elderly in Nursing Homes. PLoS One. 2015;10(9):e0137176.
139. Smith KJ, Gavey S, NE RI, Kontari P, Victor C. The association between loneliness, social isolation and inflammation: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2020;112:519-41.
140. Olano-Lizarraga M, Wallström S, Martín-Martín J, Wolf A. Causes, experiences and consequences of the impact of chronic heart failure on the person´s social dimension: A scoping review. Health Soc Care Community. 2022;30(4):e842-e58.
141. Sluiter A, Cazzolli R, Jaure A, Scholes-Robertson N, Craig JC, Johnson DW, et al. Experiences of social isolation and loneliness in chronic kidney disease: a secondary qualitative analysis. Clin J Am Soc Nephrol. 2024.
142. Bishop GM, Llewellyn G, Kavanagh AM, Badland H, Bailie J, Stancliffe R, et al. Disability-related inequalities in the prevalence of loneliness across the lifespan: trends from Australia, 2003 to 2020. BMC Public Health. 2024;24(1):621.
143. Santini ZI, Jose PE, York Cornwell E, Koyanagi A, Nielsen L, Hinrichsen C, et al. Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. The Lancet Public Health. 2020;5(1):e62-e70.
144. Li L, Zhang Y, Feng S, Cao Y, Li H, Li X, et al. Reliability and validity of the brief psychosomatic symptom scale (BPSS) in patients from general hospitals. General Hospital Psychiatry. 2023;83:1-7.
145. Kapfhammer HP. Somatic symptoms in depression. Dialogues Clin Neurosci. 2006;8(2):227-39.
146. Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and Anxiety in Heart Failure: A Review. Harv Rev Psychiatry. 2018;26(4):175-84.
147. Grigorian K, Östberg V, Raninen J, Brolin Låftman S. Loneliness, belonging and psychosomatic complaints across late adolescence and young adulthood: a Swedish cohort study. BMC Public Health. 2024;24(1):642.
148. McHugh JE, Lawlor BA. Perceived stress mediates the relationship between emotional loneliness and sleep quality over time in older adults. British Journal of Health Psychology. 2013;18(3):546-55.
149. Jacobs JM, Cohen A, Hammerman-Rozenberg R, Stessman J. Global sleep satisfaction of older people: the Jerusalem Cohort Study. J Am Geriatr Soc. 2006;54(2):325-9.

150. Yu B, Steptoe A, Niu K, Ku PW, Chen LJ. Prospective associations of social isolation and loneliness with poor sleep quality in older adults. Qual Life Res. 2018;27(3):683-91.
151. Deng M, Qian M, Lv J, Guo C, Yu M. The association between loneliness and sleep quality among older adults: A systematic review and meta-analysis. Geriatric Nursing. 2023;49:94-100.
152. Wranker LS, Rennemark M, Berglund J, Elmståhl S. Relationship between pain and Quality of Life-Findings from the Swedish National Study on Aging and Care-Blekinge study. Scand J Pain. 2014;5(4):270-5.
153. Nicholson K, Liu W, Fitzpatrick D, Hardacre KA, Roberts S, Salerno J, et al. Prevalence of multimorbidity and polypharmacy among adults and older adults: a systematic review. The Lancet Healthy Longevity. 2024;5(4):e287-e96.
154. Patten SB. Confounding by severity and indication in observational studies of antidepressant effectiveness. Can J Clin Pharmacol. 2008;15(2):e367-71.
155. Flegal KM, Graubard BI, Williamson DF, Cooper RS. Reverse causation and illness-related weight loss in observational studies of body weight and mortality. Am J Epidemiol. 2011;173(1):1-9.
156. Smith LE, Webster RK, Rubin GJ. A systematic review of factors associated with side-effect expectations from medical interventions. Health Expect. 2020;23(4):731-58.
157. Friedman SM, Munoz B, West SK, Rubin GS, Fried LP. Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. J Am Geriatr Soc. 2002;50(8):1329-35.
158. Milos V, Bondesson Å, Magnusson M, Jakobsson U, Westerlund T, Midlöv P. Fall risk-increasing drugs and falls: a cross-sectional study among elderly patients in primary care. BMC Geriatrics. 2014;14(1):40.
159. O'Donovan B, Rodgers RM, Cox AR, Krska J. 'You feel like you haven't got any control': A qualitative study of side effects from medicines. Journal of Patient Safety and Risk Management. 2019;24(1):13-24.
160. De Smedt RH, Jaarsma T, Ranchor AV, van der Meer K, Groenier KH, Haaijer-Ruskamp FM, et al. Coping with adverse drug events in patients with heart failure: Exploring the role of medication beliefs and perceptions. Psychol Health. 2012;27(5):570-87.
161. Wastesson JW, Morin L, Laroche ML, Johnell K. How Chronic Is Polypharmacy in Old Age? A Longitudinal Nationwide Cohort Study. J Am Geriatr Soc. 2019;67(3):455-62.
162. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiology (Sunnyvale). 2016;6(2).
163. Mansournia MA, Nazemipour M, Naimi AI, Collins GS, Campbell MJ. Reflection on modern methods: demystifying robust standard errors for epidemiologists. International Journal of Epidemiology. 2021;50(1):346-51.
164. Lam J, Vuolo M. Longitudinal Associations Between Loneliness and Prescription Medication Use. The Journals of Gerontology: Series B. 2023;78(4):730-5.

165. Wastesson JW, Fritzell J, Burström B, Johnell K, Fastbom J. Regional variations in excessive polypharmacy and potentially inappropriate drug use among older adults in Sweden: Trends from 2006 to 2020. Frontiers in pharmacology. 2023;14:1030849.
166. Lachin JM. The role of measurement reliability in clinical trials. Clin Trials. 2004;1(6):553-66.
167. Cronbach LJ, Meehl PE. Construct validity in psychological tests. Psychol Bull. 1955;52(4):281-302.
168. Messick S. Validity of psychological assessment: Validation of inferences from persons' responses and performances as scientific inquiry into score meaning. American Psychologist. 1995;50(9):741-9.
169. Hernán MA, Robins JM. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC. 2020.
170. Findley MG, Kikuta K, Denly M. External Validity. Annual Review of Political Science. 2021;24(Volume 24, 2021):365-93.
171. Pinquart M, Sorensen S. Influences on Loneliness in Older Adults: A Meta-Analysis. Basic and Applied Social Psychology. 2001;23(4):245-66.
172. Luanaigh CÓ, Lawlor BA. Loneliness and the health of older people. International Journal of Geriatric Psychiatry. 2008;23(12):1213-21.
173. Mund M, Maes M, Drewke PM, Gutzeit A, Jaki I, Qualter P. Would the Real Loneliness Please Stand Up? The Validity of Loneliness Scores and the Reliability of Single-Item Scores. Assessment. 2023;30(4):1226-48.
174. Kotwal AA, Cenzer IS, Waite LJ, Smith AK, Perissinotto CM, Hawkley LC. A single question assessment of loneliness in older adults during the COVID-19 pandemic: A nationally-representative study. J Am Geriatr Soc. 2022;70(5):1342-5.
175. Newmyer L, Verdery AM, Margolis R, Pessin L. Measuring Older Adult Loneliness Across Countries. The Journals of Gerontology: Series B. 2021;76(7):1408-14.
176. Wettermark B, Harnmar N, MichaelFored C, Leimanis A, Olausson PO, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiology and drug safety. 2007;16(7):726-35.
177. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet (London, England). 2005;365(9453):82-93.
178. Boyko EJ. Observational research--opportunities and limitations. J Diabetes Complications. 2013;27(6):642-8.
179. Okpara C, Adachi J, Papaioannou A, Ioannidis G, Thabane L. Exploring participant attrition in a longitudinal follow-up of older adults: the Global Longitudinal Study of Osteoporosis in Women (GLOW) Hamilton cohort. BMJ open. 2023;13(7):e066594.
180. Nunan D, Aronson J, Bankhead C. Catalogue of bias: attrition bias. BMJ Evid Based Med. 2018;23(1):21-2.
181. Teague S, Youssef GJ, Macdonald JA, Sciberras E, Shatte A, Fuller-Tyszkiewicz M, et al. Retention strategies in longitudinal cohort studies: a systematic review and meta-analysis. BMC Med Res Methodol. 2018;18(1):151.

182. Laugesen K, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdottir UA, Lunde A, et al. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. Clin Epidemiol. 2021;13:533-54.
183. Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol. 2007;17(9):643-53.
184. Keyes KM, Rutherford C, Popham F, Martins SS, Gray L. How Healthy Are Survey Respondents Compared with the General Population?: Using Survey-linked Death Records to Compare Mortality Outcomes. Epidemiology (Cambridge, Mass). 2018;29(2):299-307.
185. Folkhälsorapport Skåne 2023. Region Skåne, 2023. Available from: https://utveckling.skane.se/siteassets/verksamhetsomraden/halsa/dokument/folkhalsorapporter/folkhalsorapport-2023.pdf.
186. Lindström M, Pirouzifard M. Trust in the healthcare system and mortality: A population-based prospective cohort study in southern Sweden. SSM Popul Health. 2022;18:101109.
187. Watanabe M, Olson K, Falci C. Social isolation, survey nonresponse, and nonresponse bias: An empirical evaluation using social network data within an organization. Social Science Research. 2017;63:324-38.
188. Holford TR, Levy DT, McKay LA, Clarke L, Racine B, Meza R, et al. Patterns of Birth Cohort–Specific Smoking Histories, 1965–2009. American Journal of Preventive Medicine. 2014;46(2):e31-e7.
189. Ekström H, Elmståhl S, Sandin Wranker L. Physical Performance in Older Cohorts: A Comparison of 81-Year-Old Swedish Men and Women Born Twelve Years Apart-Results from the Swedish Study "Good Aging in Skåne". J Aging Res. 2021;2021:8813992.
190. Overton M, Pihlsgård M, Elmståhl S. Up to speed: Birth cohort effects observed for speed of processing in older adults: Data from the Good Ageing in Skåne population study. Intelligence. 2018;67:33-43.
191. Overton M, Pihlsgård M, Elmståhl S. Secular trends in prevalent mild cognitive impairment: Data from the Swedish population-based study Good Aging in Skåne. Alzheimers Dement (N Y). 2022;8(1):e12260.
192. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. The Lancet. 2015;385(9967):549-62.
193. van den Akker M, Vaes B, Goderis G, Van Pottelbergh G, De Burghgraeve T, Henrard S. Trends in multimorbidity and polypharmacy in the Flemish-Belgian population between 2000 and 2015. PLoS One. 2019;14(2):e0212046.
194. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.
195. Johnell K, Lindström M, Melander A, Sundquist J, Eriksson C, Merlo J. Anxiolytic-hypnotic drug use associated with trust, social participation, and the miniaturization of community: a multilevel analysis. Soc Sci Med. 2006;62(5):1205-14.

196. Johnell K, Merlo J, Lynch J, Blennow G. Neighbourhood social participation and women's use of anxiolytic-hypnotic drugs: a multilevel analysis. J Epidemiol Community Health. 2004;58(1):59-64.
197. Johnell K, Råstam L, Lithman T, Sundquist J, Merlo J. Low adherence with antihypertensives in actual practice: the association with social participation--a multilevel analysis. BMC Public Health. 2005;5:17.
198. DiMatteo MR. Social support and patient adherence to medical treatment: a meta-analysis. Health Psychol. 2004;23(2):207-18.
199. Ioannidis JP. How to make more published research true. PLoS medicine. 2014;11(10):e1001747.
200. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021.
201. Klompstra L, Ekdahl AW, Krevers B, Milberg A, Eckerblad J. Factors related to health-related quality of life in older people with multimorbidity and high health care consumption over a two-year period. BMC Geriatrics. 2019;19(1):187.
202. Finley CR, Chan DS, Garrison S, Korownyk C, Kolber MR, Campbell S, et al. What are the most common conditions in primary care? Systematic review. Can Fam Physician. 2018;64(11):832-40.
203. Eckerblad J, Theander K, Ekdahl A, Jaarsma T, Hellstrom I. To adjust and endure: a qualitative study of symptom burden in older people with multimorbidity. Applied Nursing Research. 2015;28(4):322-7.
204. Bennion AE, Molassiotis A. Qualitative research into the symptom experiences of adult cancer patients after treatments: a systematic review and meta-synthesis. Support Care Cancer. 2013;21(1):9-25.
205. Ekdahl AW, Linderholm M, Hellström I, Andersson L, Friedrichsen M. 'Are decisions about discharge of elderly hospital patients mainly about freeing blocked beds?' A qualitative observational study. BMJ open. 2012;2(6):e002027.
206. McKenna-Plumley PE, Turner RN, Yang K, Groarke JM. Experiences of Loneliness Across the Lifespan: A Systematic Review and Thematic Synthesis of Qualitative Studies. Int J Qual Stud Health Well-being. 2023;18(1):2223868.
207. Chen Y, Liu X. How solitude relates to well-being in old age: A review of inter-individual differences. Scandinavian Journal of Psychology. 2023;64(1):30-9.

Appendix

Appendix Figure 1. The questions used to assess loneliness in the GÅS questionnaires are listed here. The question 75 was slightly modified from the recruitment wave 2 and onwards concerning the number of past years (5 years was changed to 3 years).

75. När Du ser tillbaka på *de senaste fem åren*, vilket av nedanstående alternativ stämmer in på Dig?

- ☐1 Jag har inte känt mig ensam vid något tillfälle de senaste fem åren
- ☐2 Jag har upplevt enstaka tillfällen med ensamhetskänslor
- ☐3 Jag har upplevt återkommande perioder med ensamhetskänslor
- ☐4 Jag har levt med en mer eller mindre ständig känsla av ensamhet

75. När Du ser tillbaka på *de senaste tre åren*, vilket av nedanstående alternativ stämmer in på Dig?

- ☐1 Jag har inte känt mig ensam vid något tillfälle de senaste tre åren
- ☐2 Jag har upplevt enstaka tillfällen med ensamhetskänslor
- ☐3 Jag har upplevt återkommande perioder med ensamhetskänslor
- ☐4 Jag har levt med en mer eller mindre ständig känsla av ensamhet

71. Händer det att Du känner Dig ensam?

- ☐1 Ja, ofta
- ☐2 Ja, ibland
- ☐3 Nej, sällan
- ☐4 Nej, aldrig

Appendix Figure 2. The questions used to assess social isolation in the GÅS questionnaires are listed.

3. Vem eller vilka bor Du tillsammans med? *(Flera alternativ kan anges)*

- ☐1 Ensamboende
- ☐2 Maka/make/sambo
- ☐3 Dotter
- ☐4 Son
- ☐5 Barnbarn
- ☐6 Syskon
- ☐6 Svägerska/svåger
- ☐7 Annan, vem: ……..

60. Hur ofta brukar Du träffa Din/Ditt/Dina: *(Markera med ett X på varje rad)*

	Dagligen	Varje vecka	Varje månad	Varje kvartal	Mer sällan	Aldrig	Ej aktuellt
a. Make/maka (ej sammanboende)?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
b. Föräldrar?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
c. Barn?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
d. Svärson/svärdotter?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
e. Barnbarn?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
f. Syskon?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
g. Annan släkting?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
h. Granne?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
i. God vän?	☐1	☐2	☐3	☐4	☐5	☐6	☐7

61. Hur ofta har Du kontakt via telefon, brev eller E-mail med: *(Markera med ett X på varje rad)*

	Dagligen	Varje vecka	Varje månad	Varje kvartal	Mer sällan	Aldrig	Ej aktuellt
a. Make/maka (ej sammanboende)?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
b. Föräldrar?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
c. Barn	☐1	☐2	☐3	☐4	☐5	☐6	☐7
d. Svärson/svärdotter?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
e. Barnbarn?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
f. Syskon?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
g. Annan släkting?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
h. Granne?	☐1	☐2	☐3	☐4	☐5	☐6	☐7
i. God vän?	☐1	☐2	☐3	☐4	☐5	☐6	☐7

68. Om Du är medlem i en förening, skulle Du kunna säga att Du känner en stark samhörighet med denna förening och dess medlemmar?

- ☐1 Är ej föreningsmedlem
- ☐2 I hög grad
- ☐3 I viss mån
- ☐4 Inte speciellt
- ☐5 Inte alls

70. Deltar Du i religiösa aktiviteter? (T ex går i kyrkan, lyssnar på radiogudstjänster m m)

- ☐1 Nej, inte alls
- ☐2 Ibland
- ☐3 Ja, ofta

74. Är Du med i en grupp av vänner som har eller gör något gemensamt?
(T ex spelar kort, lyssnar på musik, gör utflykter etc)

- ☐1 Ja
- ☐2 Nej

Appendix Figure 3. The symptom assessment used in Paper I was an adapted version of the Gothenburg Quality of Life instrument ad modum Tibblin and colleagues (107, 108). The version used in the questionnaires in the Good Aging in Skåne study (GÅS) is available here. The 30 symptoms listed in the original scale by Tibblin et al (107, 108) were included in the symptom scale in Paper I.

Symtom

194. Besväras Du sedan minst tre månader tillbaka av något av följande symtom?

Markera med ett kryss på varje rad för det som stämmer in på Dig	**Nej, inte alls**	**Ja, lite**	**Ja, ganska mycket**	**Ja, mycket**
1. Lätt för att gråta	☐1	☐2	☐3	☐4
2. Lättirriterad	☐1	☐2	☐3	☐4
3. Svårt att kasta vatten	☐1	☐2	☐3	☐4
4. Dyster/nedstämd	☐1	☐2	☐3	☐4
5. Nervös	☐1	☐2	☐3	☐4
6. Dålig aptit	☐1	☐2	☐3	☐4
7. Trött	☐1	☐2	☐3	☐4
8. Koncentrationssvårigheter	☐1	☐2	☐3	☐4
9. Illamående	☐1	☐2	☐3	☐4
10. Sömnbesvär	☐1	☐2	☐3	☐4
11. Svårt att slappna av	☐1	☐2	☐3	☐4
12. Diarré	☐1	☐2	☐3	☐4
13. Overansträngd	☐1	☐2	☐3	☐4
14. Rastlös	☐1	☐2	☐3	☐4
15. Förstoppning	☐1	☐2	☐3	☐4
16. Ont i magen	☐1	☐2	☐3	☐4
17. Ledbesvär	☐1	☐2	☐3	☐4
18. Övervikt	☐1	☐2	☐3	☐4
19. Hosta	☐1	☐2	☐3	☐4
20. Ont i ryggen	☐1	☐2	☐3	☐4
21. Avmagring	☐1	☐2	☐3	☐4
22. Ont i bröstet	☐1	☐2	☐3	☐4
23. Ont i benen	☐1	☐2	☐3	☐4
24. Svettningar	☐1	☐2	☐3	☐4
25. Andfåddhet	☐1	☐2	☐3	☐4
26. Svårt att gå	☐1	☐2	☐3	☐4
27. Frusenhet	☐1	☐2	☐3	☐4
28. Yrsel	☐1	☐2	☐3	☐4
29. Huvudvärk	☐1	☐2	☐3	☐4
30. Hörselnedsättning	☐1	☐2	☐3	☐4
31. Ögonbesvär	☐1	☐2	☐3	☐4
32. Svårt att tala/uttrycka mig	☐1	☐2	☐3	☐4
33. Svårt att svälja	☐1	☐2	☐3	☐4
34. Nedsatt minnesförmåga	☐1	☐2	☐3	☐4
35. Svårt att hålla urin	☐1	☐2	☐3	☐4
36. Svårt att hålla avföring	☐1	☐2	☐3	☐4
37. Svårläkta sår	☐1	☐2	☐3	☐4

Frågeformulär B 47

Appendix Figure 4. Sleep disturbances in Paper II were evaluated via 8 questions about sleep difficulties originally from the Comprehensive Assessment and Referral Evaluation Scale (CARE) (111, 112). The version used in the questionnaires in the Good Aging in Skåne study (GÅS) is available here.

Frågor om Din sömn

162. Har Du svårigheter att somna in?

☐1 Ja
☐2 Nej

163. Tar Du eller är Du beroende av medicin för att kunna somna?

☐1 Ja
☐2 Nej

164. Vaknar Du under natten?

☐1 Ja
☐2 Nej

165. Har Du svårigheter att somna/förbli sovande på grund av sinnesstämning eller spänning?

☐1 Ja
☐2 Nej

166. Har Du svårigheter att sova på grund av smärtor eller klåda?

☐1 Ja
☐2 Nej

167. Är Du oförmögen att somna om efter att ha vaknat på natten?

☐1 Ja
☐2 Nej

168. Vaknar Du tidigt?

☐1 Ja
☐2 Nej

Frågeformulär A 38

169. Känner Du dig trött och sover mer än två timmar under dagen?

☐1 Ja
☐2 Nej