ESCOLA NACIONAL DE SAÚDE PÚBLICA

Is loneliness associated with chronic disease among older adults?

A longitudinal cohort study in 16 European countries.

Curso de Mestrado em Saúde Pública

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Dissertação apresentada para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Saúde Pública, realizada sob a orientação científica do Professor Julian Perelman e Professor Sergio Perelman.

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Table of Contents

List of Tables and Figures

Declaration of originality

The work presented in this thesis originated from a group coursework submitted to the module *Applied Health Economics*, together with Ivo Silva, Bernardo Coelho and Francisco Girão. Professor Julian Perelman, the module's responsible lecturer, encouraged us to pursue the scientific publication of this work, and me personally to further develop it for my masters' thesis in Public Health.

Initial ideas and project rationale was developed together with my colleagues; all analyses here presented were performed by me, as well as hypotheses and lines of investigation presented in this work, with attentive guidance of Professor Sergio Perelman and Professor Julian Perelman, my supervisors.

SHARE Database Acknowledgment

This paper uses data from SHARE Waves, 5, 6, 7, 8 and 9.[1–5] Please see Börsch-Supan *et al*. (2013) for methodological details.[6]

The SHARE data collection has been funded by the European Commission, DG RTD through FP5 (QLK6-CT-2001-00360), FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-2006-028812), FP7 (SHARE-PREP: GA N°211909, SHARE-LEAP: GA N°227822, SHARE M4: GA N°261982, DASISH: GA N°283646) and Horizon 2020 (SHARE-DEV3: GA N°676536, SHARE-COHESION: GA N°870628, SERISS: GA N°654221, SSHOC: GA N°823782, SHARE-COVID19: GA N°101015924) and by DG Employment, Social Affairs & Inclusion through VS 2015/0195, VS 2016/0135, VS 2018/0285, VS 2019/0332, VS 2020/0313, SHARE-EUCOV: GA N°101052589 and EUCOVII: GA N°101102412. Additional funding from the German Federal Ministry of Education and Research (01UW1301, 01UW1801, 01UW2202), the Max Planck Society for the Advancement of Science, the U.S. National Institute on Aging (U01_AG09740-13S2, P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11, OGHA_04-064, BSR12-04, R01_AG052527-02, R01_AG056329-02, R01_AG063944, HHSN271201300071C, RAG052527A) and from various national funding sources is gratefully acknowledged (see www.share-eric.eu).

Abstract

Introduction: Healthy ageing has emerged as a critical area of public health research, as increasing life expectancy has not been accompanied by a proportional rise in disease- or disability-free life years. Evidence indicates a strong link between loneliness and disease among older populations; this study aimed to investigate the longitudinal association between loneliness and the development of high-morbidity, high-mortality diseases.

Methods: We analysed the longitudinal relationship between loneliness, measured using the R-UCLA scale, and the development of five chronic disease groups. Logistic regression models were applied to a cohort of 38,893 adults aged 50 years and older from 16 European countries. Data were sourced from the Survey of Health, Ageing and Retirement in Europe (SHARE) database, spanning 2013 to 2022.

Results: Loneliness measured 2–4 years prior to disease diagnosis significantly increased ($p<0.001$) the odds of developing cardiovascular diseases (AOR=2.01, 95% CI: 1.79-2.23), neurological and psychiatric conditions (AOR=2.43, 95% CI: 2.16-2.69), rheumatism (AOR=2.26, 95% CI: 2.04-2.48), cancer (AOR=1.91, 95% CI: 1.72-2.13), and cataracts (AOR=1.74, 95% CI: 1.50-2.04), when adjusted for sex, age, prior illness or disease risk factors, socioeconomic status, social context and European welfare region

Conclusion: Our findings suggest loneliness significantly contributes to the development of chronic diseases in older adults, independently of socioeconomic and social factors, including commonly used variables of social isolation. Incorporating loneliness assessment into health and social care services could provide a powerful tool for predicting disease risk and improving health outcomes in ageing populations.

Resumo

Introdução: O envelhecimento saudável tem-se tornado uma área fundamental de investigação em saúde pública, dado que o aumento da esperança média de vida não se tem traduzido numa subida proporcional nos anos de vida sem doença ou incapacidade. A associação entre solidão e doença está amplamente descrita na literatura entre as populações mais velhas; este estudo teve como objectivo investigar a associação longitudinal entre a solidão e o desenvolvimento de doenças de alta morbilidade e mortalidade.

Métodos: Analisámos a relação longitudinal entre a solidão, medida através da escala *R-UCLA*, e o desenvolvimento de cinco grupos de doenças crónicas. Modelos de regressão logística foram aplicados a uma coorte de 38.893 adultos com 50 ou mais anos, provenientes de 16 países europeus. Os dados foram obtidos a partir da base de dados do *Survey of Health, Ageing and Retirement in Europe* (SHARE), abrangendo o período de 2013 a 2022.

Resultados: A solidão, medida 2 a 4 anos antes do reporte de diagnóstico, aumenta significativamente ($p<0.001$) a probabilidade de desenvolvimento de doenças cardiovasculares (AOR=2,01, IC 95%: 1,79-2,23), doenças neurológicas e psiquiátricas (AOR=2,43, IC 95%: 2,16-2,69), reumatismo (AOR=2,26, IC 95%: 2,04-2,48), cancro (AOR=1,91, IC 95%: 1,72-2,13) e cataratas (AOR=1,74, IC 95%: 1,50-2,04), quando ajustado para sexo, idade, doenças prévias, factores de risco para doenças, grupo socioeconómico, contexto social e a região Europeia.

Conclusões: Os resultados indicam que a solidão contribui significativamente para o desenvolvimento de doenças crónicas em adultos mais velhos, independentemente de factores socioeconómicos e sociais, incluindo factores de isolamento social tradicionalmente utilizados na literatura. A integração da avaliação da solidão nos serviços de saúde e de apoio social pode ser uma ferramenta valiosa na previsão do risco de doenças e na melhoria dos resultados de saúde nas populações envelhecidas.

Introduction

Loneliness, a universal human experience, which follows a U-shaped distribution across the life cycle, disproportionately affecting individuals under 25 and over 65 years old.[7] Nevertheless, in recent decades, research has focused on this public health problem, often referred to as an epidemic of the 21st century, in older adults, given their higher vulnerability to disease and positive correlation with loneliness itself.[8] Evidence shows a possible bidirectionality in this relationship; disease in older people can promote feelings of loneliness, and, on the other hand, psychological and physiological mechanisms may also impact overall health, potentially contributing to premature mortality.[9–11]

Sociodemographic shifts occurring in high-income countries, particularly in Europe, alongside increased life expectancy (*but not necessarily of quality of life*), make research into healthy ageing and reducing burden of disease in this population essential.

Using the SHARE longitudinal cohort database, spanning 2013-2022, we aimed to investigate whether loneliness preceded disease development in specific groups of diseases with different aetiologies, and if this relationship is further impacted by socioeconomic and individual changes, among European older adults.

1.1 Ageing and disease in Europe: morbidity and mortality.

The 11th World Health Organisation (WHO) International Classification of Diseases (ICD-11) included "*ageing-associated declining in intrinsic capacity*" as its own category, to encompass clinical symptoms not yet classified.[12] This decision was highly controversial amongst social scientists and health promotion advocates, who argued this 'medicalisation' of a natural process could cause increased discrimination towards the elderly.[13] Nonetheless, this approach of looking at ageing from a biological problem lenses has led to a significant amount of funding invested in biomedical research, in an attempt to find targets of the known hallmarks of ageing (telomere attrition, genomic instability, among others) and their physiological consequences, with some successes.[14] Moreover, ageing is a known risk-factor for many chronic conditions and increase susceptibility to infection, underscoring the relevance of biologically targeting these hallmarks on population health.

From a public health perspective, unhealthy ageing has become, and will continue to become, a dominant problem in high-income countries. In Europe, the difference in healthy life years at age 50, from 2013 to 2019 (pre-COVID), varied considerably: Portugal shows the largest decrease (-2.7 years), whereas Germany and Sweden lead with the largest increase (6.9 and 4.5, respectively). In absolute figures, in 2019, Sweden, Malta and Norway are at the top of the table with 27.8, 26.6 and 26.3 healthy life years; Eastern countries of Slovakia and Latvia are placed at the bottom, with 12.3 and 11.4 healthy life years expected at 50.[15] Still, this indicator highlights that in all countries, unhealthy life years are also expected, while health inequalities persist.

OECD's Health at a Glance: Europe 2022 provides a broad overview of the health and disease in the elderly (*used henceforth to refer to 65+*). It reports the main causes of death across the EU in 2019 continued to be cardiovascular diseases (the most common being heart attack and stroke), accounting for a third of all deaths, followed by cancer (26%). Alzheimer's and other neurodegenerative diseases accounted for 5% of deaths in the EU, disproportionally affecting women; the number of deaths for these specific ageing-related diseases has increased by a third between 2010-2019. Osteoarthritis has become one of the leading causes of disability, due to ageing in populations and rising in obesity prevalence. Furthermore, it is estimated that 36% of Europeans over 65 have multimorbidity (two or more chronic conditions), often requiring complex disease management and appropriate care integration.[16] Advances in medicine and public health, which have successfully increased life expectancy, are now required to focus efforts on reducing morbidity (especially prolonged morbidity) in this vulnerable group. Regardless of its inclusion in

the ICD, ageing undoubtedly plays a significant role in the pathogeneses here described; the focus on disease prevention and health promotion in this population is vital to protect health systems across the globe, given the rising pressure ageing-associated diseases exert on resources and expenditure.[17]

Public health research allows us to look at this issue from a different perspective, to consider and investigate the main determinants of health that contribute to a higher burden of disease throughout the life cycle, and more vulnerable populations such as the elderly (65+), starting from older adults (50+). Decades of research in this field have shown the social context (including networks, communities) where people are integrated, greatly affect mental health, as well as physical health. One crucial aspect that has been identified in one's social context and disease is loneliness.

1.2 Loneliness and social isolation: distinguishing being alone from feeling lonely.

Loneliness is described as the discrepancy between one's expectations regarding their social activities and engagements, and their reality. It is a highly complex issue which does not reflect necessarily one's aloneness or absence of others, but their internal perception.[9,18,19] Although it can affect people of any age, specific factors and life changes can make the elderly particularly vulnerable to experiencing loneliness.[19,20]

These factors, commonly associated with ageing, such as having a reduced number of activities which have a social component to them, (voluntary / charity work, attending community clubs, amongst others), reduced contact with friends and family, retirement, reductions in household size (i.e. children leaving home or loss of a partner) are often defined in the literature as loss of "social capital" or "social support" and its components commonly used to create social isolation indexes, which are related to loneliness, even considered its risk factors.[21–25]

Crucially, social isolation (albeit harder to define, even if it can be objectively measured) can be a closely related condition, although not sufficient, for one's feelings of loneliness.[9,26] The pathway from a reduced/ weaker social context to the development of feelings of loneliness can be profoundly influenced by individual characteristics (personality traits, even genetic predisposition)[27], socioeconomic context (financial stability, safety, education)[28,29], as well as

cultural and regional norms.[23,30] Specific factors that may influence how one experiences and self-assesses loneliness may differ across different cultures, due to the highly subjective nature of loneliness on one hand, and social and health policies within each country / economic region on the other.[23] Nevertheless, common trends can be observed: the elderly, women, poorer people, and people who live alone (without a co-habiting partner) tend to report feeling lonelier.[21,30,31]

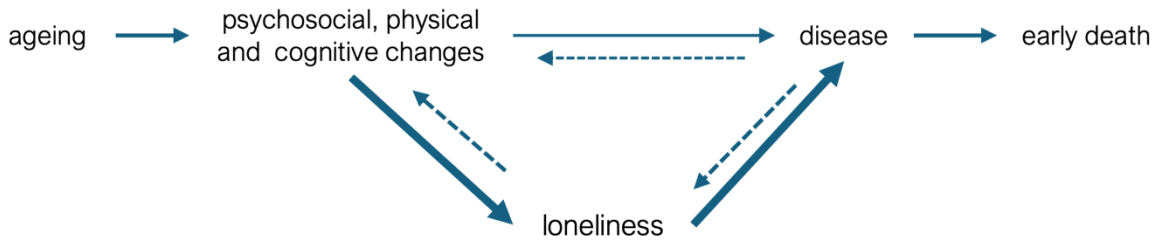


Figure 1. Summarised illustration of current evidence and hypotheses.

The complexities here described are synthesised in Figure 1, which tries to encompass the vast literature on these topics: changes associated with ageing, also linked to a decline in cognitive and physical abilities,[23] alongside psychosocial changes described above, can lead to loneliness. Persistent (or chronic, as also named in the literature) loneliness may act as a mediator between these changes and physical disease, making it a potential target to public health interventions to alleviate the burden of disease in this vulnerable population. However, physical and mental disease have also been shown to be associated with disease; people with depression, people who suffered from a stroke and those who have multimorbidity report higher loneliness scores (in specifically validated surveys) than healthy people.[32–34] This may lead to more social isolation, thus exacerbating the problem and the 'cycle' of loneliness and disease.

Cultural and regional differences have been described regarding prevalence of loneliness, which have been proposed to differ due to each region's reference systems and social/ family norms. Paradoxically, countries where social integration appears to be more developed are also the countries that report higher levels of loneliness: Mediterranean countries (Southern Europe) have reported higher levels of loneliness than Nordic countries (Scandinavia), despite fewer people living alone in the former countries, one of the strongest risk factors for experiencing loneliness.[30] Similar differences have been found between Western and Eastern European countries, with the latter having more people experiencing loneliness.[35]

Furthermore, loneliness and social isolation may also affect healthcare-seeking behaviour, which may be also affected by different welfare and health systems. A recent longitudinal study in Denmark, in the general population, has found loneliness has a modest, but significant effect in increasing contacts with the general practitioner's (GP), when adjusting for several diseases and demographics (income, sex, age), as well as a social isolation index. This effect was even larger when considering emergency room treatments and admissions.[36] Interestingly, planned treatments or consults, as well as hospital admission days, did not show a significant effect, suggesting an increased healthcare demand by people who feel lonely, but not necessarily reflecting on their clinical needs.

Fewer (and smaller) studies have focused on healthcare use and demand during the COVID-19 pandemic in lonelier, elderly people, leaving an important line of investigation to be explored, given that it may have played a role in future burden of disease in this vulnerable population.[37]

1.3 Physiological mechanisms between loneliness and disease.

Many studies have shown associations between loneliness and disease, both cross-sectional and longitudinal, in different populations.[38–40] For example, cardiovascular disease (CVD) has been previously shown to be associated with loneliness in the United States[41,42], although there is variability in effects seen in other populations, depending on individual and social characteristics[32]; having a higher body mass index (BMI) and multimorbidity is also related with higher reported loneliness.[21] Depression was shown to be worsened by higher loneliness scores at baseline in a recent longitudinal study in the UK.[38] Other mental illnesses, particularly related to neurodegeneration and loss of cognitive function, have been linked with loneliness.[43] Chronic conditions, such as diabetes, hypertension, and cancer have not shown a higher prevalence of this experience in most studies, but results are not entirely consistent.[31,39]

Moral and ethical consequences of loneliness are not the only ones to be considered in public policy and research; beyond these robust associations lies a potential direct effect of this psychological experience on physical and mental health. Not only loneliness naturally develops with certain types of disease, but it may precede it, biologically.

Hawkey and Cacioppo have described in detail all the potential underlying mechanisms between experiencing loneliness and developing physical disease.[9] The main hypothesis lies with the described "state of hypervigilance", where people who feel (persistently) lonely are in, thereby over-activating the hypothalamic-pituitary adrenocortical (HPA) axis, which, amongst many other key functions, regulates release of cortisol ("the stress hormone") from the adrenal glands. Cortisol is a crucial hormone for the "flight-or-fight" response; when released acutely, it provokes peripheral vasoconstriction, raises blood glucose concentration, and supresses non-essential functions: an exceptionally important set of responses when fleeing from a bear in the wild, less so when in a continued mode and in absence of real danger.[44] This dysregulation of the HPA axis and elevated cortisol levels in people reporting loneliness have been observed in a few studies, detailed in Hawkey and Cacioppo (2010), but not in longitudinal assessment with disease development, to the best of our knowledge.[9] Additional markers of low-grade inflammation (pro-inflammatory cytokines, which are the immune system' messengers, and other mediator signals) have also been shown to be elevated in people with fewer social connections.[9]

Beyond a physiological mechanism that leads to disease, an individual's vulnerability to experiencing loneliness may also be genetically influenced. Perry and colleagues have examined traits such as participation in social activities and perceived loneliness in genome-wide association studies (*which identify key regions of the human genome which are more prevalent in people with specific phenotypical traits*), using data from the UK Biobank. Fifteen *loci* were identified, with single-nucleotide polymorphisms in regions within the genome preferentially expressed in the central nervous system.[27]

1.4 Rationale for the study, added value and policy implications

Healthy ageing has become a priority for current health systems in high-income countries – to reduce disease burden and expand healthy life years is a crucial part of reducing health expenditure.[17] Understanding which socio-economic and welfare policy mechanisms have an impact on health in older adults and the elderly allows for better cross-sector policy design and care integration, thus promoting healthier ageing and subsequently, allows for more resources to be allocated into less preventable diseases. Loneliness in older adults can be a consequence of poor social integration policies and programmes, as well as a contributing factor to disease development.

Here, we hypothesised loneliness precedes disease development in the older population, thus contributing to it, and it may act independently of life changes associated with ageing that affect an individual's social and economic context. Additionally, we aimed to examine the impact of loneliness on disease development is influenced by cultural context, as well as social and health policies that characterise welfare regions in Europe, beyond socio-economic factors.

The longitudinal interaction between loneliness and specific chronic diseases in different European regions and welfare systems had not been previously explored to the best of our knowledge, nor had preceding levels of loneliness been considered in disease onset. With this study, we aimed to identify the magnitude of the effect of loneliness and changes in these factors on the development of specific chronic diseases prior to their diagnoses, and thus add to current literature on the subject. We hope this study can contribute to decision-making in health in all policies, by raising awareness of the relevance of this factor on health in older adults, across different European regions.

Research in context

Evidence before this study

Association of loneliness with morbidity and mortality has been well established for several population groups; nevertheless, evidence on specific chronic diseases is less clear and often contradictory. Few studies have included longitudinal data; most use small samples or use social isolation as a loneliness proxy.

Added value of this study

This work identifies loneliness as a strong disease-predictor tool. Here, we explore the longitudinal effect of loneliness on the onset of different chronic diseases, in a cohort of European older adults, while adjusting for social and economic context, prior illness, as well as different regions within Europe, during a mean period of 6 years. We focus our models on some of the highest causal factors of morbidity and mortality in the EU.[16]

Implications of all the available evidence

Loneliness may play a strong causal role in disease development, independently of social, economic, welfare region and individual context. The R-UCLA scale could be applied by healthcare or social sector professionals to 50+ adults as a disease predictor. Further research into social programmes and public policies' effect on loneliness and perceived social isolation are necessary.

Methods

2.1 Data and study population

Data used for these analyses were sourced from the Survey of Health, Ageing and Retirement in Europe (SHARE) database, from wave 5 (2013) to wave 9 (2022).[1–5] This Survey, primarily funded by the European Commission (COM), provides a large longitudinal dataset on health, socioeconomic status and social context in older adults (50+), currently in place in most countries in Europe and Israel. It was created as a longitudinal survey, in a multidisciplinary project promoted by COM, started in 2004/05 (wave 1). Given its multinational nature, differences in sampling resources exist between countries, which carry out the fieldwork. To achieve full probability sampling, sample frames are selected according to each country's available resources. Additionally, SHARE provides sampling design weights, to adjust for unequal selection probabilities, using public population registers.[45]

Analysed population included males and females, aged 50 years or older, from 16 European countries: Austria, Germany, France, The Netherlands, Switzerland, Belgium, Luxembourg, Sweden, Denmark, Spain, Portugal, Italy, Czechia, Poland, Slovenia, and Estonia (Supplementary Figure 2.), who participated in at least three waves of SHARE within this period.

Individuals with missing data (including refusals to answer, "Don't know" and "implausible value") in all analysed variables were excluded; 62930 participants were initially included (those who participated in at least 3 waves, from w5 to w9), using the *wave* variable and aggregate function (providing the number of valid responses, included if >2) to create this sub-sample. A rank variable was then computed, where the baseline for each participant (in our case, either wave 5 or 6) was defined as 1, and so forth. Participants were then excluded from the sample if they had no valid (*i.e. missing*) answers to the following variables at baseline: loneliness (19931), participation in activities (19790), current job situation (323), number of children (38), number of chronic diseases (127), is household able to make ends meet (868) and ISCED educational level (749). All other included variables did not have missing data after exclusion of these participants. Israel participants were also excluded, to allow for more precise analyses into European geographic regions (1685).[23] Age was restricted to those above 50 (some partners who are also interviewed in SHARE were below 50 years old) (1160). From this, a total of 38893 individuals were included in the analyses. Of those, 27.9% (10869) participated in 3 waves, 30.8% (11967) in 4 waves and

41.3% (16057) in 5 waves, from wave 5 to wave 9. Most of the sample (94.0%), 36552 people, had their baseline in wave 5, whereas the other 2341 participants entered this study at wave 6 (6.0%).

Characterisation of sample under analysis in Tables 1 and 2 include scale variables, presented as mean and standard error of the mean (SEM) and categorical variables, presented as percentage (%) within the variable and number of participants (n).

2.2 Variables

Exposure: Loneliness

To evaluate individuals' loneliness, we used the reduced version of the University of California Los Angeles (R-UCLA) Loneliness scale[46] included in SHARE, a 3-item questionnaire ranging from 3 points ("not lonely") to 9 points ("very lonely") points, previously validated and widely used in the literature (R-UCLA).[21,47] The items focus on three dimensions of loneliness, without mentioning the concept itself: relational connectedness "How often do you feel you lack companionship?"; social connectedness "How often do you feel left out?"; and self-perceived isolation "How often do you feel isolated from others?", with the scale response for each ranging from "Hardly ever" (1), "Some of the time" (2) and "Often" (3).

We then applied a threshold of 6 points to dichotomise this variable, as published in Steptoe et al. (2013)[48]; participants with a score below 6 points were categorised as not lonely, while those scoring above or equal to 6 points were classified as experiencing loneliness. Our study period starts in wave 5 due to the inclusion of the questionnaire for the first time in SHARE.

To evaluate our hypothesis, we used the loneliness score value of the interview preceding the one when disease was reported. For example, for an individual who developed a heart condition at the third interview (in their case, the third interview is computed as t_0), the loneliness score for heart condition was computed and dichotomised at interview 2 (t_{-1}) for that participant. If the person did not suffer from any disease, the mean score of all waves they participated in was computed, then dichotomised. People who reported the specific disease on the first wave they entered were excluded from that specific disease/ group of diseases' models. A visual representation of the study design for the final inferential models can be found in Figure 2. Illustration of study design.

Outcomes: Selection of chronic diseases

In its *ph module*, SHARE includes questions where the participant is asked if they have ever been diagnosed or currently have specific chronic diseases / disease groups (17 in total), allowing for an estimation of disease development through time.

We selected as outcomes for our models the development of new chronic diseases throughout the study period which had prior evidence of association with loneliness and/ or social isolation in the literature, also drawing from the initial analysis from our sample (highest AOR, Table 3.). Three main groups were selected initially. In each specific disease model, participants who had reported currently having or having ever been diagnosed with the disease at baseline were excluded, and new only diagnoses were included from the second interview onwards. In addition, we used putative "control" diseases, which have either low biological plausibility and/or little evidence of association.

Chronic diseases/ groups of diseases were included in separate inferential tests, as listed below; besides the criteria of prior known association with loneliness, these disease groups represent some of the highest causes of morbidity and mortality in Europe.[16] The first interview where the participant reported a positive value (the disease or one of the diseases within the group) was considered as t_0 for that model (Figure 2).

1. Cardiovascular diseases (*at least one of two*): heart attack or stroke;
2. Neurological / psychiatric disorders (*at least one of three*): Alzheimer's/ dementia/ senility, Parkinson or other affective or emotional disorders;
3. Rheumatic diseases (*at least one of two*): Rheumatoid arthritis or osteoarthritis and other rheumatism;
4. Cancer;
5. Cataracts.

Covariates

All covariates included in the descriptive and inferential analyses are detailed in Supplementary Table 1. Multimorbidity (defined as two or more chronic diseases) was included, given its well-established association with loneliness and disease development, as well as to control for reverse causality-like effects.[21,49]

Variables commonly associated with social isolation and loneliness[50,51], such as living alone, engaging in social activities (at least two out of the seven considered in SHARE, ac module)[23], and having an occupation (answers of "employed or self-employed" and "homemaker" were considered as having an occupation, whereas "retired" and "unemployed" were considered as not having one) were included. These three variables were computed and measured at baseline, as well as their variation (as a time-varying variable), described below. Having children, a variable also associated with reduced loneliness in our sample, was also added to characterise the social and individual context (fixed at baseline) – the variable more commonly used in the literature, "frequency of contact with children", was not contemplated due to too many missing values. These social context variables provide an objective measure of social isolation risk, independently of perceived social isolation (loneliness).

As socioeconomic variables, which are known to be associated both with disease and loneliness[23], answers to the question "does the household have ability to make ends meet?" and Education level (ISCED 1997) were included. Ability to make ends meet is a broadly used indicator to assess financial conditions across different countries/ welfare regions, rather than disposable income, which is more difficult to standardise, especially across time. We dichotomised this variable between "easily" or "fairly easily" and "somewhat difficult" or "difficult", thus providing an assessment of the experience of financial stability, or the lack of it. Education level was also used, through recategorising the International Standard Classification of Education (ISCED, 1997) into low (0-2), medium (3-4) and high (5-6) education, according to Eurostat's aggregation.[52] Education level was considered at baseline, and the ability to make ends meet was considered both at baseline and as a time-varying variable.

Time-varying variables

We examined if changes in people's social and individual context (occupation, living alone, engaging in activities) as well as financial security (ability to make ends meet) impacted disease development independently of the exposure. Hence, we computed changes between the interview when disease was first reported (t_0) and the previous interview (t_{-1}).

Exposure (loneliness) was also measured at (t_{-1}), but not at (t_0), to avoid capturing potential effects of the diagnosis. Since we included only participants which participated in 3, 4 or 5 waves of the SHARE waves 5 – 9, the mean period between each interview is 1.9 years (95% CI: 1.92, 1.93). For each participant who developed one of the chronic diseases included in the analyses, changes

between t_0 and t_{-1} were considered in three categories, as following: "Negative change" (i.e. Stopped being able to make ends meet, started living alone, stopped engaging in activities, stopped having an occupation), "Always negative" (i.e. Was never able to make ends meet, always lived alone, never engaged in activities, never had an occupation), and "Always positive or positive change" (i.e. Is now or was always able to make ends meet, never lived alone or started living with company, always was or started engaging in activities, now has or always had an occupation). Positive change and always positive were aggregated due to the very reduced number of people who had positive changes in these variables.

Additionally, age was also treated as a time-varying variable; for those who reported disease, the mean age between (t_0) and (t_{-1}) was computed, and further grouped into three categories. 50 – 64; 65 – 79; 80 + years old. For those who did not report that disease, age at last interview was used and categorised.

Regarding different health and care sector systems in our sample, as well as to capture differences in social and cultural norms, we grouped countries into 4 welfare regions; Bismarckian, Scandinavian, Southern and Eastern European, as previously described in Leão et al. 2018 and Fawaz and Mira 2023.[23,53] Sample distribution per country and welfare region can be found in Supplementary Table 2.

2.3 Study Design

We carried out retrospective longitudinal analyses on individual level data from the SHARE database on the aforementioned population. *Baseline* corresponds to the first SHARE wave when participants enter this study, from wave 5; 94.0% entered at wave 5 (2013), 6.0% entered at wave 6 (2015). SHARE wave interviews were ranked from interview 1 (*baseline*) to 3 (10869, 27.9%), 4 (11967, 30.8%) or 5 (16057, 41.3%).

Figure 2 shows two representative examples of participants and how data were included in the inferential models; id 1 participated in 4 SHARE waves, and did not report disease (one of the specific outcomes tested) during the follow-up period; id 2 (who has participated in 3-5 waves) reported disease (between interview 2 and 5); their lag loneliness score (t_{-1}) was dichotomised, and changes in socioeconomic variables were computed. Age was calculated between t_{-1} and t_0,

and categorised as explained above. For participant id1, mean values of time-varying variables and age at last interview were included in the models.

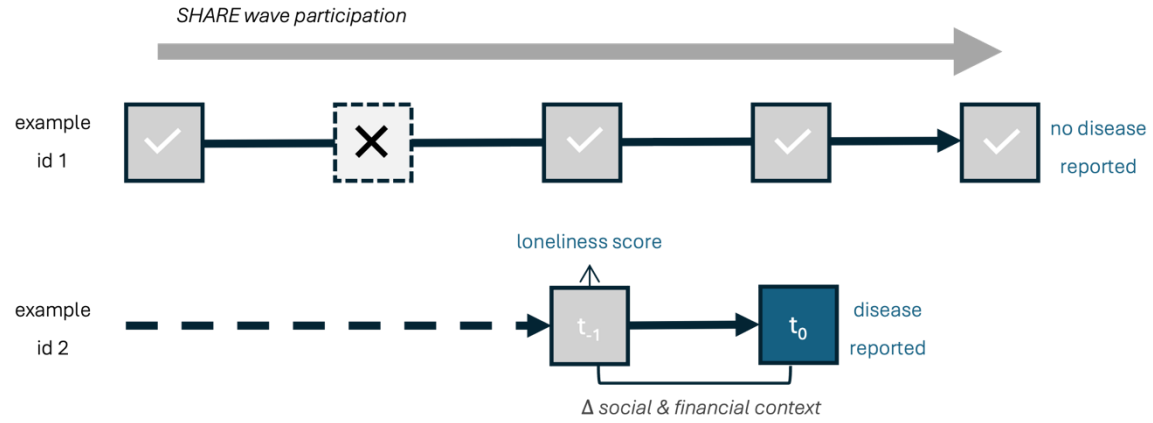


Figure 2. Illustration of study design

2.4 Statistical analyses

Univariate chi-squared analysis between our exposure of interest and all covariates and outcomes at baseline. Given the strong association between sex, age and disease, we used multivariate logistic regression to assess association of specific chronic diseases and loneliness while adjusting for these two covariates, also at *baseline* (defined here as the first wave when individuals entered the study, from 2013 – wave 5 of SHARE).

For disease development assessment, multivariable logistic regression models for each of the diseases were computed, in sequential groups of variables, as depicted in Figure 3. The tested outcomes were specific disease outcomes developed and reported during the study period. For each disease model, people who reported having been diagnosed or currently having the disease under analysis at baseline were excluded.

To control for effects of other diseases on the outcome and exposure, multimorbidity was included, with two exceptions. Hypertension and/or high blood cholesterol were used in the cardiovascular disease models instead of multimorbidity, for being stronger predictors of this group of diseases. Likewise, having depression at baseline (measured by EURO-D caseness scale, above 4 points[54]), also substituted multimorbidity in the Neurological/ Psychiatric models.

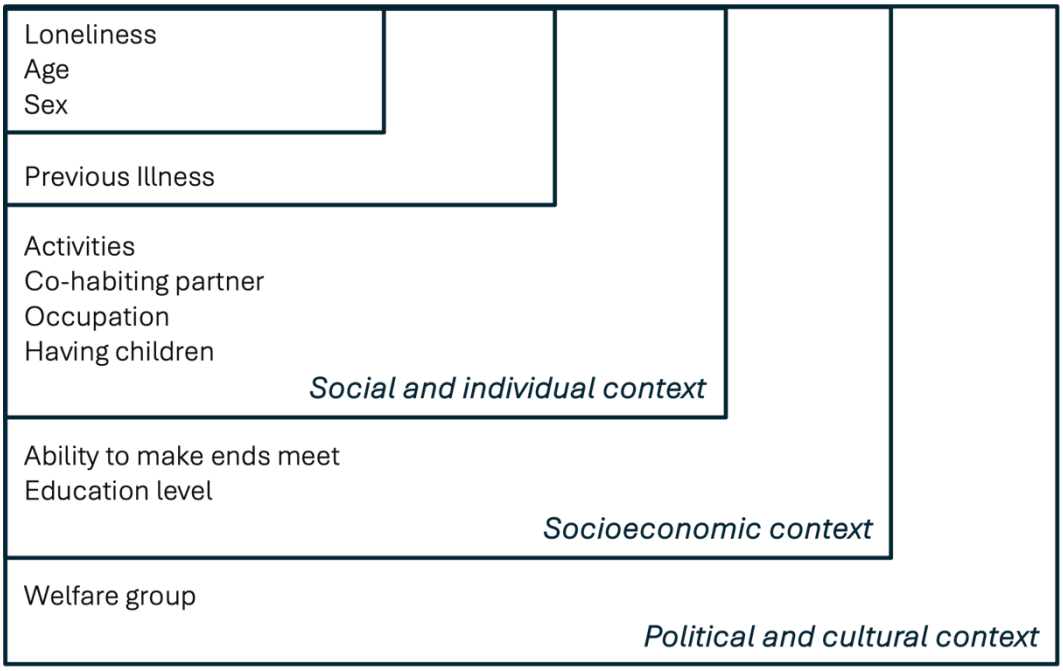


Figure 3. Multivariate logistic regression (additive) models to assess association with development of new chronic diseases.

For all models, adjusted odds ratios (AOR) were computed and are presented with 95% confidence intervals (95% C.I.).

Sensitivity analyses were performed by changing the cut-off points on the loneliness scale considered for an individual to be lonely: from 5 points to 7 points. Other analyses included diseases which did had low biological plausibility of preceding loneliness and / or had evidence of no association in the literature (*i.e.* cancer and cataracts).

Data was analysed using the IBM SPSS statistical software, version 29.01.00. All variables included in the analysis can be found in Supplementary Table 1.

Results

3.1 Characterisation of sample

We analysed 38 893 people (194465 observations) from 16 European countries that participated in at least three waves of the Survey of Health, Ageing and Retirement in Europe (SHARE) database from 2013 (wave 5) to 2022 (wave 9)[1–5], above 50 years of age. The mean follow-up period (time between first and last interview) was 6.01 years (Table 1); median value was 8 years.

Table 1. Characterisation of sample at baseline.

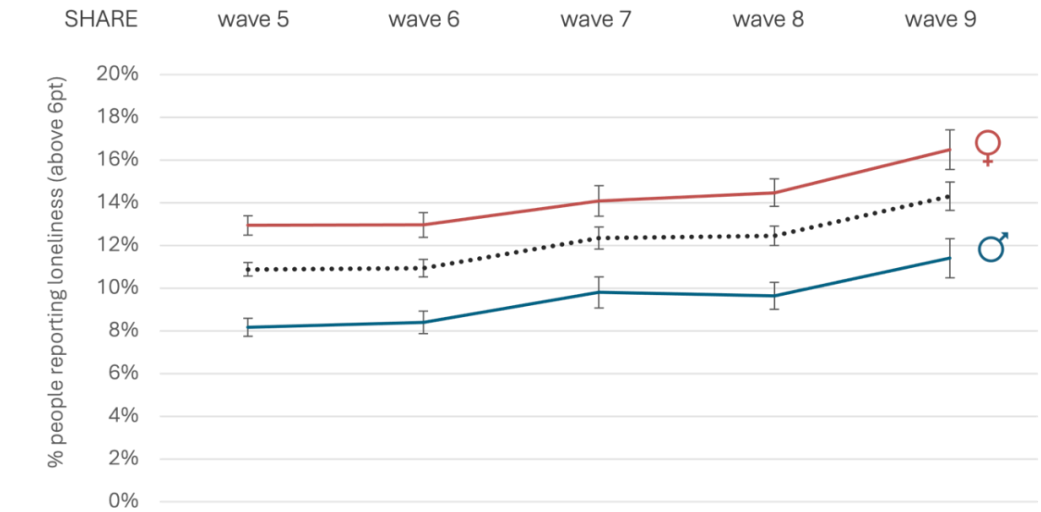
age during study (mean, SEM)		66.08	0.05
female (n, %)		22131	56.9%
loneliness score (R-UCLA) (mean, SEM)		3.80	0.01
mean follow-up period (mean, SEM)		6.01	0.01
Health: chronic diseases			
number of chronic diseases (mean, SEM)		1.14	0.01
multimorbidity (2+ chronic diseases) (n, %)		19290	49.6%
Social and individual context (n, %)			
lives alone		7884	20.3%
fewer than two activities		12929	33.2%
does not have children		4122	10.6%
no occupation		24864	63.9%
Socioeconomic factors (n, %)			
difficult or somewhat difficult to make ends meet		12998	33.4%
education (ISCED-1997)	low education	14487	37.2%
	medium education	15146	38.9%
	high education	9260	23.8%
welfare groups	Bismarckian	15552	40.0%
	Scandinavian	5675	14.6%
	Southern	7412	19.1%
	Eastern	10254	26.4%

SEM – Standard error of the mean

Average age of participants at baseline was 66.08 years (± 0.05, SEM), and the majority was female (56.9%). Nearly half suffered from 2 or more chronic illnesses (49.6%), nevertheless, the mean number of chronic diseases was 1.14 (± 0.01).

Regarding their social and individual context, a significant majority did not have any occupation (either retired or unemployed); this is in line with the average age being close to or above the retirement age in most European countries. Only 10.6% reported not having any children; 20.3% reported living alone and one third (33.2%) had not engaged in at least two activities (voluntary or charity work, being part of a sports or social club – for the full list, please see Supplementary Table 1.) in the past year. Equally, regarding socioeconomic status, a third of the sample reported having difficulty (or some difficulty) in making ends meet (33.4%), whereas in education, nearly 40% had completed a medium level of education and only 23.8% had attained high level of education (ISCED classification).[52] Bismarckian countries represent 40% of our sample, followed by Eastern (26.4%), Southern (19.2%) and Scandinavian (14.6%) (Table 1). Supplementary Table 2. provides the full list and number of participants from each country.

To assess the loneliness levels of participants across the period under study, we calculated the percentage of people who scored 6 points or above on the R-UCLA scale (Figure 4) per SHARE wave/ year.



Year	2013	2015	2017	2019-20	2021-22
Obs per year	36552	22374	15070	19283	10357
age (mean)	66.02	68.00	70.12	72.27	73.50
SEM	0.05	0.05	0.05	0.06	0.05

Figure 4. People reporting loneliness per interview year (%) and average age (mean, SEM).

Loneliness levels increased throughout the study, both in males and females, with females (dark red) reporting 3-5% higher levels than males (dark green, Figure 4). Total percentage of people reporting loneliness above 6 points (dashed grey line, Figure 4.) rose from 10.9% in 2013 to 14.3% at the last available SHARE wave (2021-22). Number of observations (Obs) per year/wave are indicated below the graph, as are average age ± SEM.

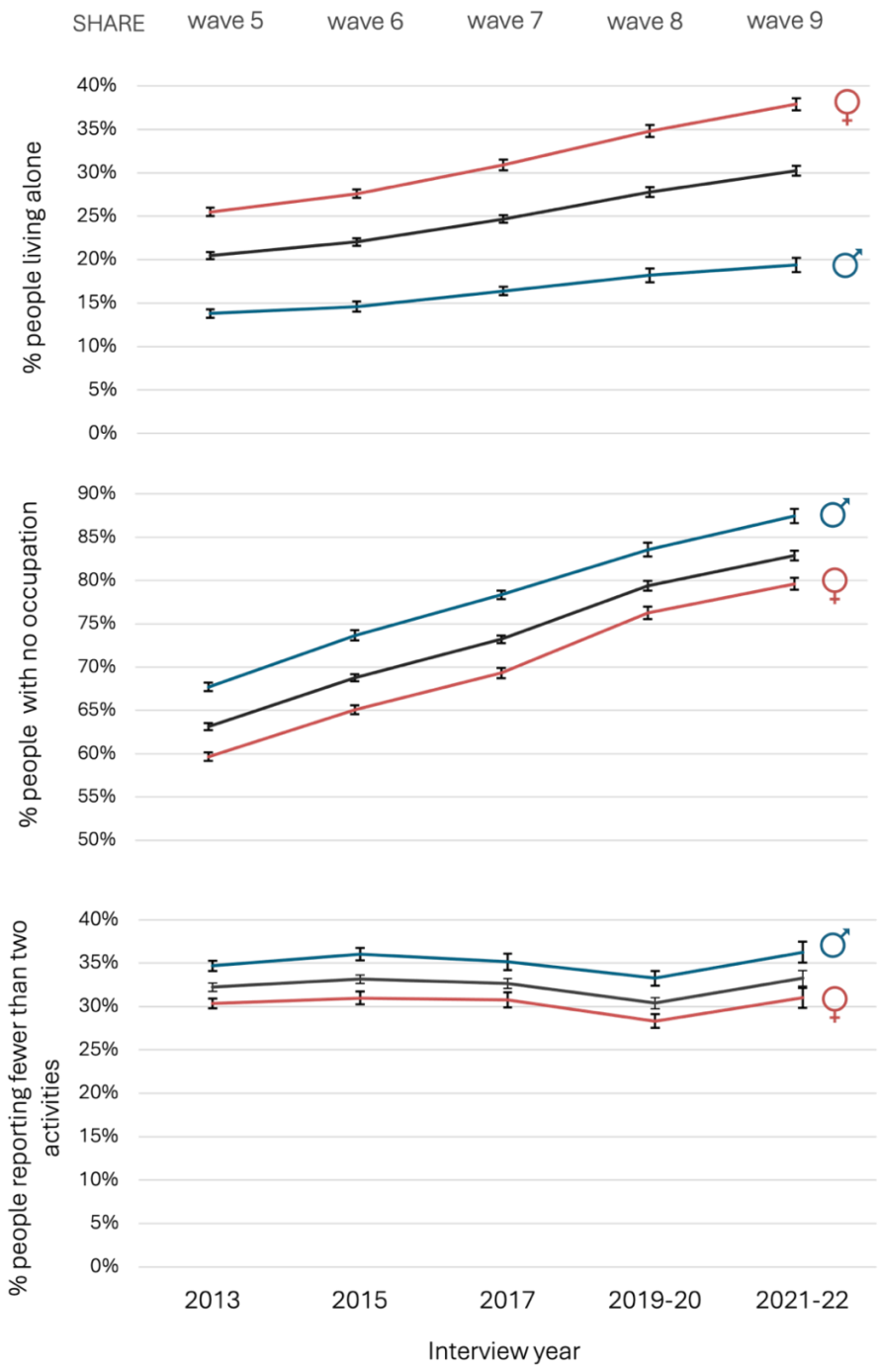


Figure 5. Social and individual context components over the period under study.

Additionally, we looked at how the main social context components varied in our sample across the study period (Figure 5). The percentage of women living alone increased from 25.5% to nearly 40% at the last interview, whereas men reported living alone at a much lower rate (13.8%), rising to 19.4% at the last interview. This disparity observed between sexes across time is potentially due to women surviving their male partners, by having a higher life-expectancy than men.[16]

Conversely, on the other observed dimensions, women reported having fewer than two activities at a lower percentage than men (which remained relatively stable throughout the study period for both sexes), as well as having no occupation was also reportedly higher for men. This difference observed in occupation levels may be due to the inclusion of "homemaker" in having an occupation, a role typically assumed by women, particularly in the older generations.

Table 2. Sample at baseline by initial exposure (loneliness ≥ 6 points on the R-UCLA scale).

		not lonely		lonely	
age (mean, SEM)		65.84	0.05	68.04	0.15
number of chronic diseases (mean, SEM)		1.10	0.01	1.50	0.02
gender	male	15361	44.4%	1401	32.5%
	female	19224	55.6%	2907	67.5%
no multimorbidity		18166	52.5%	1437	33.4%
has multimorbidity (2+ chronic diseases)		16419	47.5%	2871	66.6%
mean follow-up period (mean years, SEM)		6.05	0.01	5.83	0.03
Social and individual context					
lives alone		6349	18.4%	1535	35.6%
lives with someone		28236	81.6%	2773	64.4%
fewer than two activities		10831	31.3%	2098	48.7%
two or more activities		23754	68.7%	2210	51.3%
no children		3511	10.2%	611	14.2%
at least one child		31074	89.8%	3697	85.8%
does not have occupation		21682	62.7%	3182	73.9%
has occupation		12903	37.3%	1126	26.1%
Socioeconomic status					
difficult or somewhat difficult to makes ends meet		10675	30.9%	2323	53.9%
easily or fairly easily to make ends meet		23910	69.1%	1985	46.1%
low education level		12280	35.5%	2207	51.2%
medium education level		13724	39.7%	1422	33.0%
high education level		8581	24.8%	679	15.8%
welfare groups	Bismarckian	14122	40.8%	1430	33.2%
	Scandinavian	5382	15.6%	293	6.8%
	Southern	6298	18.2%	1114	25.9%
	Eastern	8783	25.4%	1471	34.1%
Total sample		34585	88.9%	4308	11.1%

SEM – Standard error of the mean

In our sample, 11.1% (4308) of participants reported being lonely (≥ 6) at baseline (Table 4). These participants were older on average (by approximatively 2 years), reported more chronic diseases, and were more likely female, less educated, with greater difficulty in making ends meet, and without an occupation.

Educational levels also show a socioeconomic gradient inequality; 51.2% of people scoring equal to or above 6 points on the loneliness scale have attained a low level of education, compared to 35.5% of people who did not report loneliness. Conversely, 15.8% of lonely people had attained a high educational level, compared to 24.8% of those not feeling loneliness.

Regarding welfare groups, a higher proportion of lonely people is observed both in Southern and Eastern countries, with the lowest in Scandinavian countries. When considering within group percentages, Southern countries have the highest proportion of people reporting loneliness (15.0%), followed by Eastern (14.3%) and Bismarckian (9.2%), whereas Scandinavian countries report the lowest (5.2%).

When observing their social and individual context components, lonelier people tended to live alone at a higher proportion, to have fewer than two activities, not to have an occupation nor children. Interestingly, mean follow-up period was significantly lower for lonelier people in our study (5.83 ±0.03 versus 6.05 ± 0.01, Table 2. 95% confidence intervals not overlapping – data not shown). This is possibly due to a greater loss to follow-up, given the more advanced age in the lonely group, as well as a previously reported higher premature death rate.[23,48]

Univariate analyses were performed for all categorical variables here presented, which showed a significant association with loneliness (Chi-squared tests, $p<0.001$). These results are in line with previous research on loneliness and social isolation.[21,30,31]

3.2 Association of loneliness with chronic diseases

Next, we aimed to examine the association of specific chronic diseases with loneliness, and to identify which diseases or disease groups were good candidates for further investigation into their longitudinal association. Logistic regressions of cross-sectional (baseline) data were carried out, to compute odds ratios of having specific conditions with loneliness, adjusted for sex and age.

Table 3. Prevalence of chronic diseases and AOR of association with loneliness at baseline.

Chronic diseases	(n, %)		AOR (95% CI)	Sig.
psychiatric and neurological				
at least one	**2971**	**7.6%**	**3.26 (3.02, 3.53)**	***
other affective disorders	2467	6.3%	3.58 (3.29, 3.89)	***
Alzheimer's	360	0.9%	2.22 (1.79, 2.75)	***
Parkinson	274	1.3%	2.05 (1.59, 2.63)	***
cardiovascular and metabolic				
stroke or heart attack	**5147**	**13.2%**	**1.53 (1.43, 1.64)**	***
ht or hbc	19725	50.7%	1.25 (1.19, 1.31)	***
stroke	1274	3.3%	1.97 (1.74, 2.22)	***
heart attack	4234	10.9%	1.41 (1.31, 1.53)	***
high blood cholesterol (*hbc*)	9583	24.6%	1.23 (1.17, 1.30)	***
hypertension (*ht*)	16142	41.5%	1.22(1.16, 1.28)	***
diabetes	4992	12.8%	1.33 (1.25, 1.44)	***
rheumatic diseases				
at least one	**10146**	**26.1%**	**1.50 (1.42, 1.58)**	***
rheumatoid arthritis	3403	8.7%	1.72 (1.59, 1.86)	***
osteo & other rheumatism	7950	20.4%	1.48 (1.40, 1.57)	***
fractures				
at least one	2687	6.9%	1.40 (1.28, 1.53)	***
hip or femoral fracture	621	1.6%	1.63 (1.37, 1.94)	***
other fracture	2200	5.7%	1.37 (1.24, 1.51)	***
others				
gastrointestinal ulcers	1526	3.9%	1.77 (1.59, 1.99)	***
chronic lung disease	2333	6.0%	1.69 (1.54, 1.86)	***
cataracts	3375	8.7%	1.21 (1.12, 1.32)	***
cancer	1990	5.1%	1.06 (0.95, 1.18)	p=0.297
other types of chronic disease	6975	17.9%	1.26 (1.19, 1.35)	***
no disease (never diagnosed)	8298	21.3%	0.54 (0.50, 0.58)	***

*** p<0.001

At baseline, cancer was the only disease type that was not associated with loneliness, when adjusted for sex and age (Table 3., 95% C.I. AOR = 0.95, 1.18), in line with some previous reports.[39] Conversely, diabetes and hypertension had been previously reported not be associated with loneliness, but did so in our sample.[31] In contrast with all other chronic disease types, people feeling lonely had a 46% lower chance of never having been diagnosed with a chronic condition at baseline (95% CI= 0.50, 0.58), which represented nearly a fifth of the whole sample (8298 people, 21.3%).

Three groups of diseases were selected to further the investigation into the longitudinal association of loneliness and disease development, based on our cross-sectional analysis (highest AOR) and previous studies: cardiovascular diseases (specifically stroke and heart attack), neurological and psychiatric (affective disorders, Alzheimer's, Parkinson), and Rheumatism (rheumatoid arthritis, and osteoarthritis and other rheumatism). Cataracts and cancer were used as potential control diseases; for cataracts, even though there was an association at baseline, it was relatively low (AOR 95%: 1.12 – 1.32, Table 3.), and no plausible, direct biological mechanism has been described to the best of our knowledge, whereas for cancer, there is a plausible potential biological mechanism (*depending on the type of cancer*)[9], but there is little evidence in the literature, and no association observed in this sample.

3.3 Exploring loneliness levels in disease development

After seeing an association of loneliness at baseline with all chronic diseases included in the survey, with the exception of cancer, we further investigated if higher loneliness levels were present in each of the selected disease groups before disease developed.

For these analyses, people who had reported having each specific disease at baseline were excluded from the subsequent tests, as detailed in the Methods section. Table 4 shows the distribution of participants in each disease specific sub-sample; those who had reported the disease at baseline ("currently has or ever diagnosed") – excluded; those who reported developing the disease during the follow-up period and those who never reported that specific disease or group of diseases. From the available SHARE data, it is not possible to compute true incidence rates per year for each diagnosis; nevertheless, we calculated the percentage of people who reported developing each disease throughout the study period, which may influence our analysis.

Table 4. Distribution of participants per disease development throughout study period (n, %)

	Cardiovascular		Neuro / Psych		Rheumatic		Cataracts		Cancer	
Had developed disease at or before baseline	5147	13.2%	2971	7.6%	10146	26.1%	3375	8.7%	1990	5.1%
Developed during study	5422	13.9%	4259	11.0%	8089	20.8%	5330	13.7%	2429	6.2%
Did not develop during study	28321	72.8%	31657	81.4%	20654	53.1%	30186	77.6%	34473	88.6%
Participants included in specific disease models	**33743**	***86.7%***	**35916**	***92.4%***	**28743**	***73.9%***	**35516**	***91.3%***	**36902**	***94.8%***

Firstly, we computed the average loneliness score of participants who developed disease in the interview before the diagnosis (t_{-1}), for each disease group. Figure 6 shows the average lagged loneliness score (at t_{-1}) for each disease (mean, 95% CI) for those who reported having been diagnosed, compared to those who never developed the disease throughout the study.

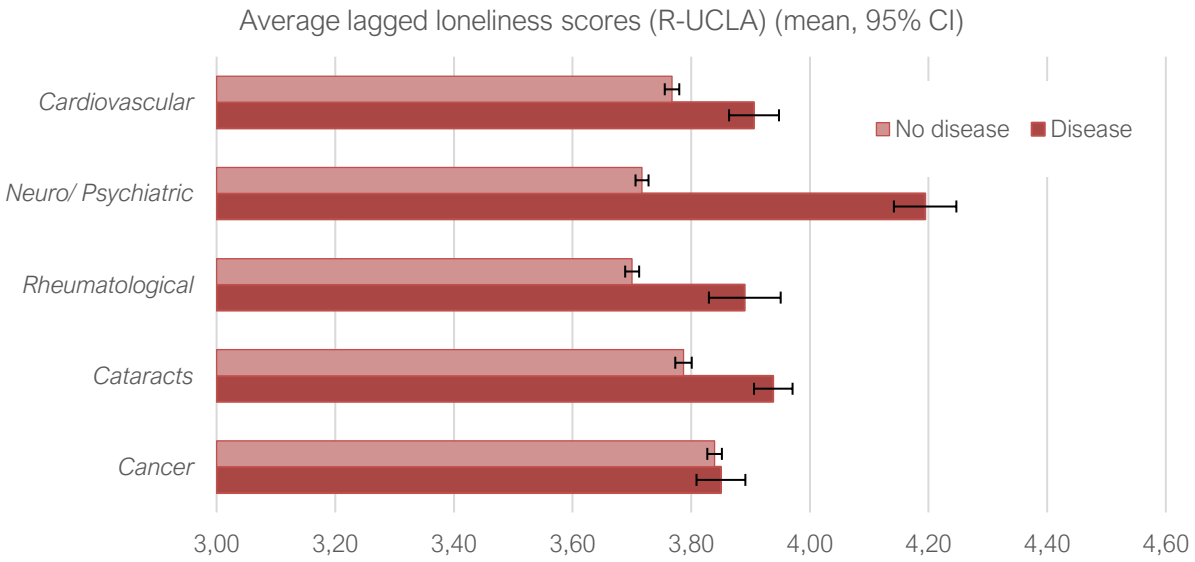


Figure 6. Average of lagged loneliness scores for each disease group.

In line with the cross-sectional association analyses, people reporting a cancer diagnosis during the follow-up period had similar loneliness lagged scores (at t_{-1}) when compared with mean loneliness scores of people who never developed the disease throughout the study (Figure 6., 95% CI overlap).

For all other disease groups, where an association at baseline had been demonstrated (Table 3.), significantly higher lagged loneliness scores were observed in people reporting disease, when compared to the mean loneliness scores of people not reporting that specific disease.

Nevertheless, many factors could explain these differences and lead to higher loneliness scores, namely, more advanced age in specific disease groups, socioeconomic status, and previous illness.

3.4 Modelling chronic disease development and loneliness

To fully examine the effect loneliness may have on disease development, and to test if other factors may impact this hypothetical longitudinal association, multivariate logistic regressions were used for each of the diseases, as described in the Methods section. The tested outcomes were development of new disease throughout the follow-up period. We carried out additive models, to assess loneliness individually (adjusted for sex and age), plus prior illness (multimorbidity at baseline) or specific disease risk-factor, plus social and individual context components (time-varying), plus socioeconomic factors (time-varying), plus European welfare group (Figures 2 and 3., Methods).

For each regression model, reference groups were as follows: being between 50-64 years old, always or now living with someone/ having an occupation / engaging in activities; low education; never having financial issues or not having them any longer (*i.e.* ability to make ends meet). Bismarckian countries are used as the reference European welfare region.

Additionally, logistic regression models with all variables considered at baseline were also carried out; odds ratios of loneliness at baseline of the fully adjusted model were included in Figure 7 for comparison.

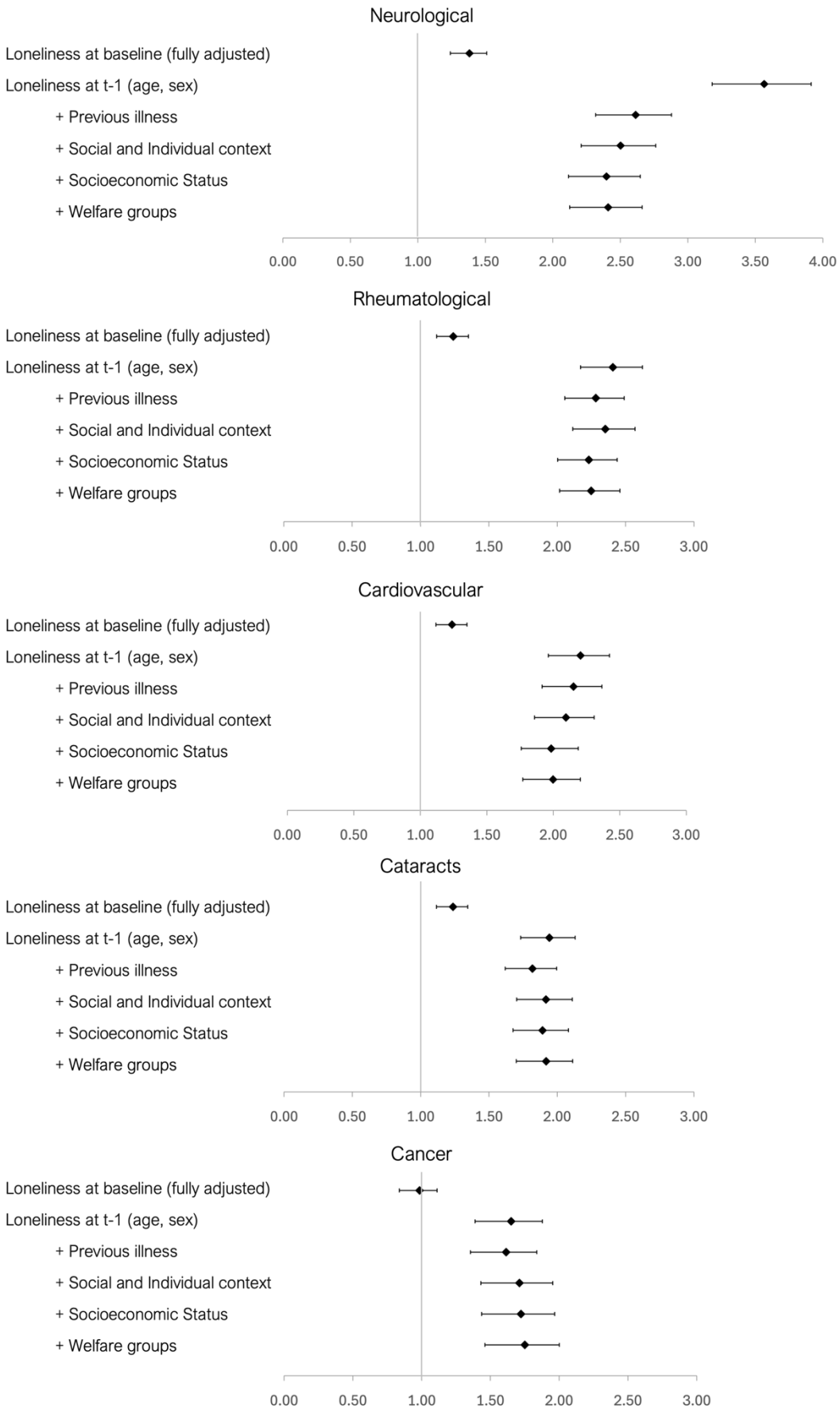


Figure 7. Multivariate regression models on each disease group: loneliness ≥6pt AOR (95%CI).

Figure 7 shows forest plots of the odds ratios (95%CI) of loneliness at baseline on new disease development during the study period (adjusted for all variables), and compares it with the AOR of the additive longitudinal models, where loneliness is measured before disease development (t_{-1}) and changes in social and individual context, age and socioeconomic status before disease development are also considered.

Similarly to the cross-sectional analyses (Table 3.), loneliness at baseline, when fully adjusted for all variables, did not show a significant association with cancer development throughout the study (Figure 7, bottom plot). In all other tested diseases, loneliness at baseline was significantly associated with disease development, albeit with a significantly lower AOR 95% confidence interval than in the time-varying models.

For neurological and psychiatric diseases, the odds of developing at least one of the diseases for people with a score of 6 points or higher in the loneliness scale were, when only adjusted for sex and age, were between 3.22 – 3.95 times higher (95% CI) than people with a mean loneliness below 6 throughout the study. These odds were significantly reduced (2.35 – 2.91) when adjusted for prior depression.

In all other disease groups, sequential adjustment for prior illness or disease risk-factor, social and individual components, socioeconomic status and welfare group did not have a significant impact in the effect of loneliness on disease development.

The computed odds ratio and 95%C.I. for all included variables in the fully adjusted models are presented in Supplementary Tables 3 and 4. Age had the largest effect on cataracts development (AOR=5.96 for 80+, AOR=3.60 for 65-74 y.o., $p<0.001$), followed by loneliness (AOR=1.92, $p<0.001$). For cancer, loneliness had the largest effect size, increasing the odds of development by 75%. As with cataracts' development, age also had the largest effect on cardiovascular disease development (AOR=3.58 for 80+, AOR=2.17 for 65-74 y.o., $p<0.001$), also followed by loneliness at the preceding interview (AOR=2.00, $p<0.001$); in this sample, prior hypertension or high blood cholesterol increased the odds of cardiovascular disease by 52%. For all other disease groups, loneliness at t_{-1} had the largest effect size in the outcome.

The social and individual context components varied in their observed effect on disease outcomes; when adjusted for all other factors in the models, living alone was associated with a reduction in odds of neurological and psychiatric diseases, as well as rheumatic. For other

diseases, it did not have a significant effect. Not engaging in activities (negative change or never) was associated with the outcome by 37-42% (respectively) in neurological diseases and 12-16% in cardiovascular diseases, not having any significant effect in rheumatic disease development. Not having an occupation was also not associated with rheumatic diseases but was so in neurological (35%) and cardiovascular (20-21%, Supplementary Table 3.). Having children did not have a significant effect on any of the observed outcomes (except cancer development, p=0.049).

Regarding socioeconomic status, having difficulty in making ends meet in the wave where disease was reported (t0) and the wave before that (t-1), i.e. 'always had financial issues', was associated with disease development in all groups, except cancer (p=0.050, Supplementary Table 4.), ranging from 4% (cataracts) to 54% (cardiovascular, Supplementary Table 3.) increase in odds. Educational levels revealed similar effects, albeit non-significant for cataracts, showing a socioeconomic gradient in cardiovascular and rheumatic diseases. Interestingly, we observed a possible U-shape in the odds of developing neurological and psychiatric diseases: medium level education showed a 9% reduction in developing these diseases, whereas no difference was observed with high educational level when compared to the reference category (low education level). Additionally, we observed a positive correlation between higher levels of education and developing cancer (14% and 19% higher chance for medium and high levels, respectively).

Significant differences were also observed between welfare regions. Most strikingly, Southern countries had reduced odds of disease development in all groups, except neurological diseases (where no difference was observed), when compared to Bismarckian countries. Likewise, Eastern countries also showed reduced odds of all disease development when compared to the reference welfare group, except in cardiovascular diseases.

Discussion

Key findings

Our analyses show loneliness is a strong longitudinal predictor of various chronic conditions, in a sample of 38 983 people living in Europe above the age of 50. Specifically, having a loneliness score equal to or above 6 points in the R-UCLA scale, measured in the 2-4 years before disease development, significantly increases the chance of developing cardiovascular diseases (stroke or heart attack), neurological and psychiatric conditions (Alzheimer's, Parkinson or other affective disorders), rheumatism (rheumatoid arthritis, osteoarthritis or other type of rheumatic disease), cancer and cataracts. We saw this strong effect independently of age before diagnosis, sex, changes in social context and socioeconomic status and European welfare region.

Interpretation of results

Our results are in line with current evidence; loneliness is significantly associated with the onset of chronic diseases, in particular, with high-morbidity and high-mortality related diseases.[16]

A recent, very comprehensive study by Fawaz and Mira (2023), which also used the SHARE database, demonstrated social isolation (defined by living alone, not participating in activities and infrequent contact with children – or not having children) is a strong predictor of premature death. These authors postulated loneliness, health behaviours, and healthcare utilisation mediated the effect of social isolation on higher mortality; they conclude this association between mortality and social isolation is not solely mediated by these factors.[23] Here, we took a different approach; since it is well established that social isolation is not a necessary condition to experiencing loneliness, and direct physiological mechanisms between this emotional experience and disease have been described extensively (through chronic stress and inflammation)[9], we aimed to more precisely define a longitudinal link between *feeling* lonely and disease diagnosis, independently of social isolation components commonly defined in the literature.[21,23,25] Indeed, we see that recent negative changes in social and individual context do not reduce the impact of loneliness on disease development in all diseases groups here analysed. More specifically, we noted stopping engaging in activities and never having engaged had a similar (significant) effect in increasing the odds of disease development in cardiovascular, when compared to always engaging in activities, both in neurological and cardiovascular diseases. Similarly, never having an occupation and no

longer having an occupation also produced comparable effect sizes for these two disease groups. Conversely, the chance of developing rheumatic diseases was not affected by these factors. Furthermore, we observed that living alone (either negative change or always living alone) even reduced the odds of developing this group of diseases. Regarding cataracts and cancer development, we saw a larger effect of activity engagement and occupation, but not of living alone. It is possible the lack of effect observed in living alone is explained by the fact that it impacts disease mostly due to loneliness. The negative correlation observed specifically with neurological and rheumatological diseases can be explained by the loss of independence even prior to disease reporting (i.e. having to move in with children due to Alzheimer's type-symptoms, or severe arthritis that restricts mobility). Regarding the lack of effect of having children in most models, a more refined version of this variable would be to consider the frequency of contact with children, and grouping those without children with those with little to no contact reported, as in Fawaz and Mira.[23]

Crucially, we did not find a significant difference between the 'always negative' and 'became negative (negative change)' categories for each of the time-varying variables. Unlike with loneliness, these produced different effects on the outcome (or no effect) depending on the disease group; a more refined approach into these changes, for example, considering answers of the two preceding (and sequential) waves and not the wave of diagnosis reporting, would potentially yield more robust effects. It is also possible the effect of these social components is mainly mediated by loneliness, nevertheless, studies show an independent effect of social isolation and loneliness on some of the diseases here examined.

For example, Golaszweski and colleagues have recently demonstrated an independent association between loneliness (using the same R-UCLA scale) and cardiovascular disease (CVD) and between social isolation and major CVD (including death), but saw a larger magnitude of the combined effect of both components, in a cohort of elderly U.S.A females.[25] Similarly, Christiansen *et al*. also saw an independent effect of social isolation and loneliness in CVD and type 2 diabetes diagnosis in the Danish general population, but no association between loneliness or social isolation and cancer diagnosis was reported. These authors conclude the observed effects were mostly mediated by baseline psychological and behavioural factors.[39] Three critical aspects may help explain the differences between the present work and these two studies: both use medical records/ patient diagnosis registry crossed with survey data, allowing for a more precise indication of time of diagnosis; nevertheless both loneliness and social isolation are measured at the

beginning of the study, and thirdly, their study populations differ from ours (Danish general population[39] and elderly (65+) women in North America[25]).

The observed differences between welfare group effects on disease development warrant further investigation; given the sample is not fully representative of each country (and subsequently, of each welfare region), it is not possible to infer from these results – a sample adjusted for longitudinal weights would allow for a more refined assessment.

Interestingly, we did not expect to find an effect an effect of loneliness on cataracts development. Literature has focused on feelings of loneliness upon diagnosis, not before (*i.e. do people who have untreated or developing cataracts feel lonelier*?). One possible explanation is that visual acuity may be impaired before the disease is diagnosed and that may lead to feelings of social isolation, less enjoyment in activities, and other psychosocial changes that are not captured in our model.

We saw a gradual effect of loneliness on disease when changing the threshold on the loneliness scale from 5 to 7 points in our sensitivity analyses (data not shown); the higher the threshold, the larger the magnitude it has on disease development (as well as wider confidence intervals, due to lower percentage of people affected). This suggests chronic / persistent loneliness (from 7 points on the R-UCLA scale, implying at least one answer as "Often" – please refer to Methods for more details) has a stronger effect on disease onset.

The sample used in this study shows similar characteristics to multiple reports on loneliness and its association with increased age, female gender, lower socioeconomic status and predominance in Southern and Eastern European welfare regions. Additionally, some studies which have also examined loneliness as a separate dimension to social context (being alone *versus* feeling alone) also report similar associations to those we have found, although the strength of these associations may differ in different populations: people in Southern countries tend to co-habit with family members (not necessarily the spouse or partner), whereas it is more common that Scandinavians live by themselves, which does not translate to higher levels of loneliness.[23] Not engaging in activities was positively correlated with loneliness in our sample, which has been shown to be a better indicator than living alone on negative health outcomes, as we also observe in our sample (independently of loneliness).[55] Moreover, by investigating loneliness by gender (Figure 4), we confirm the well-established observation that women feel lonelier at a higher proportion than men, throughout the study, although they engage more in activities, and are more

likely to have an occupation (Figure 5), This latter observation is probably influenced by the fact that “homemaker” was included in this category as an occupation, a role predominantly held by women. Furthermore, we observe a significant increase in loneliness levels from wave 8 (pre-covid) to wave 9 (post-covid), as well as between wave 6 (2015) and 7 (2017) in both genders (Figure 3); no conclusions can be drawn from these observations, apart from the natural association of ageing and loneliness, as well as variations in the sample.[9] Notably, we did not explore the potential impact of COVID-19 in this work, nor did we include SHARE corona surveys. Nevertheless, current evidence indicates this group was not disproportionally affected when compared to others during lockdowns.[56–58]

Strengths and limitations

This study adds to current literature on an essential public health concern, by using recent longitudinal data, spanning from 2013 to 2022. Crucially, it includes a large sample population from different countries and European welfare regions, and dissects the effect of loneliness on new disease development in five different disease groups. Results are consistent with current literature, albeit with a larger magnitude than most studies, which we believe can be mainly explained by two factors: 1. in our models, we include recent social changes and loneliness measurements just before disease development (2-4 years) for each individual, and 2. we are not adjusting for all possible psychosocial and behavioural changes that may impact (and mediate) the observed effect, such as physical activity, personality traits, social support, amongst others.

Another crucial aspect which has not yet been addressed is correction for attrition bias. The submission of the present work to a scientific journal will include this adjustment, to ensure losses between waves are considered in the models, as well as weights of the different countries per welfare region.

Nevertheless, we may not be able to correct for participants who have been lost to follow up due to death, which may work as a robustness test in our models; the association between loneliness and premature mortality has been demonstrated,[23,48] which means it is possible that people that were lost to follow-up due to loneliness-related premature death are not accounted for here.

Another limitation of this study is the self-reporting bias, which can be even more problematic when reporting illnesses. Surveys are very useful tools of large data collection; however, individuals may not always provide accurate assessments. Factors such as social desirability bias,

where individuals may offer socially acceptable responses rather than truthful ones, or the tendency to under- or overestimate their health and psychosocial status may vary based on their socio-demographic characteristics.[59] Ideally, cross-referencing electronic health records with survey data would provide an even more powerful and refined model to examine several questions in public health.

Many other factors could contribute to disease development were not explored here; at a larger scale: healthcare system and public health policies, and at a more individual level: unmet clinical needs, feeling of safety (living arrangements), rural and urban living and health behaviours. Other upstream psychosocial factors (having meaning in one's life, satisfaction with life, personality traits) were not specifically addressed, but may have an impact on internal perception of loneliness and *feeling* isolated from others.

Crucially, although we have established a temporal association, this study does not show a causal mechanism between loneliness and disease. Arezzo & Giudici have used an instrumental variable method (using personality traits and being born in the country) to demonstrate a causal relationship between social capital (mainly focused on engaging in social activities) and self-assessed health[22]; although it is an interesting approach, it would be difficult to find such a variable which would fit all the necessary assumptions to provide a robust model for our hypothesis on loneliness, especially since we have demonstrated that the most common "social isolation" indicators do not impact significantly the temporal effect of loneliness on disease, and are, indeed, only moderately associated in some studies.[26]

Policy implications

Eliminating loneliness in older adults, particularly the elderly (65+) may be extremely difficult, due to the subjective and personal nature of this experience itself, allied with the evidence that it may act independently of social isolation components, which would be the easier targets for public health interventions.

A recent systematic review and meta-analysis has evaluated several different types of interventions to reduce both loneliness and isolation in the elderly (which are more often the selected target group), which included psychological support (counselling, cognitive behavioural therapy, among others), animal therapy, exercise, music therapy and other social and technological interventions.[60] These authors found most interventions to have a small effect size,

and the highest – animal therapy and use of technology, in long-term care settings – also showed high heterogeneity and overall low quality evidence. Similar results had been reported in a previous review, where authors recognise the difficulty in finding a "one-size-fits-all" type of solution.[61,62] Still, public policies (rather than specific programmes) can have a significant impact on reducing loneliness in the elderly; a quasi-experimental study in England showed free bus passes for over 65 (based on state pension) caused a reduction in loneliness, which was explained by increased engagement in activities (volunteering) and higher frequency in contact with children.[63]

Nevertheless, several social programmes specifically targeting this issue have been developed, which can, at a local level, have an impact on community life (including all actors, from police departments to local commerce), and instead of eliminating loneliness and isolation, perhaps could prevent newer generations from going through this experience, or at least, minimise its impact on health.[64] Given the cultural and social nature of this issue, local evaluations could provide more robust results, considering specific context and demographic factors. Notably, most interventions focus on the 65+, rather than starting their interventions earlier on (50+, for example); considering preventing loneliness rather than trying to reverse it, may be more effective,

Expanding on available evidence, we show loneliness significantly increases the odds of development of several types of chronic diseases, with varied aetiologies, when measured 2-4 years prior to reporting of its diagnosis. A simpler, albeit more downstream, potential solution, could be the application of loneliness scales (R-UCLA, as used in this study) in primary health services or social care in the most vulnerable population, serving as a powerful tool to predict disease. In an integrated health system, centred in patients and focused on the general population, individually targeted interventions such as this one, aligned with social care, could help mitigating the impact of loneliness on health in older adults and the elderly.

Future work

New lines of investigation which examine changes in health-seeking behaviour during the COVID years, already shown to differ in this population in pre-pandemic times[36,65], could be worth pursuing, in particular due to possible delays in diagnosis caused by saturation of health services. Preliminary data using SHARE indicates medication use, seeking doctors' advice or consults and

hospitalisations in this vulnerable population may have significantly differed between loneliness levels and welfare groups, when considering age, sex and number of diseases (*data not shown*).

Additionally, preliminary data also showed physical activity may play a role in the impact of loneliness on disease; we saw that moderate to vigorous activity are inversely correlated with loneliness, even when adjusting for all disease types, sex and age, in a cross-sectional sub-sample. Conversely, having smoked daily, currently or in the past, as well as binge-drinking behaviour was inversely correlated with loneliness, suggesting these behaviours in the elderly may not be mediating the observed effect. Similar dynamics between social isolation and these health behaviours have been reported previously, suggesting physical activity may mediated isolation's (perceived and objective) effect on health, making it an avenue worth pursuing.[23]

Crucially, more refined models of disease development, and more precise definitions of time and intensity of loneliness required to produce an effect on health would be necessary to answer the question *"how lonely does one need to feel, and for how long, for their health to be irreversibly affected?".* Another important point is to consider established associations between different types of disease; Kivimaki and colleagues developed a multi-cohort study to characterise *disease cascades* in a data-driven approach, to examine the association between socioeconomic status and times of several diseases' onset.[66] Even though we corrected our models for prior multimorbidity and well-known risk factors of disease, a similar approach would provide a more refined model to study the consequences of loneliness on specific diseases and their association (*i.e. cascade*). Lastly, cross-referencing the SHARE dataset with the recently released dried blood spot samples, which provide analytical data on circulating levels of specific proteins and inflammatory biomarkers, could allow for a longitudinal identification of a biological mechanism between loneliness and disease.

Conclusion

Loneliness is an intrinsic part of human experience, a feeling potentially developed through time to seek others and ensure our survival within a community.[9] However, similarly to other physiological mechanisms evolved to protect us, its maladaptation has had clear nefarious consequences on our health. Another example of a maladaptive mechanism is food consumption and (excessive) fat storage; signals are sent to maintain us alive, only to overcompensate and ultimately harm us.

The present work explores the effect of loneliness prior to disease onset in older adults, controlling for ageing-associated life changes, as well as socioeconomic and demographic factors, in different European regions. We found loneliness is strongly associated with developing specific diseases, however, the commonly used indicators of social isolation have shown little to no effect on mitigating its impact on all the examined groups of disease: neurological, rheumatic, cardiovascular, cancer and cataracts.

Our final goal as public health researchers should be to identify policy areas where harmful exposures can be reduced at best, and / or decrease its negative consequences through known co-factors and potential mediators. The complexity of this exposure, in its subjective and individual nature, makes it challenging to design either specific social programmes or public policies that can have a significant impact. However, using a loneliness score questionnaire in healthcare or social settings could be a powerful tool to identify at-risk individuals, and be able to provide specific-disease prevention when considering the person in their whole context.

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Appendix

Supplementary Table 1. Variables descriptions and recoding information

variable	type	label	categories / scale	description/ recoding
Exposure	TV	loneliness score	R-UCLA scale between 3 and 9 pts	
	TV	loneliness above 6 pts	(0) not lonely (3 - 5 pts on the scale)	dichotomised >= 6 as previously validated in Steptoe *et al*. 2013[48]
			(1) lonely (6-9 pts)	
Demographic	fixed	age (categories)	50 - 64	age at end of study period (no disease selected) or mean age before disease reported (each specific disease model), binned into 3 categories.
			65 - 79	
			80 +	
	fixed	gender	male (0)	
			female (1)	
	fixed	welfare groups	(1) Bismarckian	*country* recoded into these four categories (Supplementary Table 2).
			(2) Scandinavian	
			(3) Southern	
			(4) Eastern	

TV – Time-varying

Supplementary Table 2. Variables descriptions and recoding information (*continuation*).

variable	type	label	categories / scale	description/ recoding
Social and Individual Context	TV	household size	(0) living alone (1) living with someone	*hhsize* dichotomised into >=1 or 0
	fixed	has children	(0) no children (1) has at least one child	*ch001* dichotomised into 0 or >=1
	TV	activities	(0) fewer than two activities (1) at least two activities	aggregated 7 types of activities (ac module) dichotomised <2 or >=2: *voluntary or charity work, educational or training course; sport, social or other kind of club; taken part in a political or community-related organization; read books, magazines or newspapers, did word or number games, played cards or games such as chess.*
	TV	occupation	(0) no occupation (1) occupation	employment variable recoded: 1 = employed, self-employed, homemaker. all other situations were considered as "no occupation".
Socioeconomic Status	TV	ability to make ends meet	(0) difficult or somewhat difficult (1) easily or fairly easily	*co007* dichotomised from 4 categories to 2.
	fixed	education level	(1) low education (2) medium education (3) high education	ISCED 1997 variable re-coded into 3 categories.[52] People who reported “other” or “still in education” were excluded from sample (n=748).
Health	TV	number of chronic diseases	sum of all chronic diseases included in SHARE	*chronic_mod* from easySHARE (scale)
	TV	currently has or ever diagnosed	(0) not selected; (1) selected	Disease variables “Ever diagnosed/ currently having”, from ph module.
	fixed	depression	(0) not selected; (1) selected	EURO-D caseness scale, dichotomised in >= 4 points.
	fixed	multimorbidity	(0) not selected; (1) selected	Number of chronic diseases, dichotomised >= 2.[49]

TV – time-varying

Supplementary Table 3. Countries within each welfare group included in the sample.

Welfare group * country	N	% within wg	% within sample
Bismarckian			
Austria	2388	15%	6%
Germany	3525	23%	9%
France	2534	16%	7%
Netherlands	488	3%	1%
Switzerland	2158	14%	6%
Belgium	3603	23%	9%
Luxembourg	856	6%	2%
Total	15552		40.0%
Scandinavian			
Sweden	2888	51%	7%
Denmark	2787	49%	7%
Total	5675		14.6%
Southern			
Spain	3665	49%	9%
Italy	3110	42%	8%
Portugal	637	9%	2%
Total	7412		19.1%
Eastern and Post-Communist			
Czechia	3554	35%	9%
Poland	696	7%	2%
Slovenia	2140	21%	6%
Estonia	3864	38%	10%
Total	10254		26.4%

Supplementary Table 4. Fully adjusted multivariate regression models for each disease (Neurological, Rheumatic and Cardiovascular) – Loneliness ≥ 6.

	Neuro/Psychiatric				Rheumatic				Cardiovascular			
	AOR	(95% CI)		sig.	AOR	(95% CI)		sig.	AOR	(95% CI)		sig.
Loneliness at t-1	2.41	2.16	2.69	***	2.25	2.04	2.48	***	2.00	1.79	2.23	***
Female	1.47	1.36	1.60	***	1.67	1.57	1.77	***	0.63	0.59	0.68	***
65 – 79 y. o.	1.12	1.01	1.25	*	1.49	1.37	1.61	***	2.17	1.96	2.41	***
80+ y. o.	2.02	1.78	2.29	***	1.91	1.71	2.12	***	3.58	3.16	4.06	***
Has prior illness§	2.13	1.96	2.31	***	1.43	1.35	1.52	***	1.52	1.42	1.62	***
Started living alone	0.94	0.78	1.14	ns	0.74	0.63	0.87	***	0.89	0.74	1.06	ns
Always lived alone	0.84	0.76	0.92	***	0.85	0.79	0.91	***	0.94	0.86	1.03	ns
Stopped engaging in activities	1.37	1.21	1.55	***	0.92	0.83	1.01	0.087	1.12	1.00	1.26	*
Never engaged in activities	1.42	1.29	1.56	***	0.97	0.90	1.05	ns	1.16	1.06	1.27	**
Stopped having an occupation	1.17	1.00	1.38	0.055	1.05	0.93	1.17	ns	1.20	1.04	1.39	*
Never had an occupation	1.35	1.21	1.51	***	0.95	0.87	1.03	ns	1.21	1.09	1.35	***
Has children	0.98	0.87	1.11	ns	1.06	0.96	1.17	ns	1.08	0.97	1.21	ns
Started having financial issues	1.13	0.99	1.29	0.066	1.20	1.08	1.33	**	1.04	0.92	1.18	ns
Always had financial issues	1.38	1.25	1.51	***	1.39	1.28	1.50	***	1.41	1.29	1.54	***
Medium level Education	0.91	0.82	0.99	*	0.89	0.83	0.95	**	0.96	0.88	1.04	ns
High level Education	0.98	0.87	1.09	ns	0.80	0.73	0.87	***	0.88	0.80	0.97	*
Scandinavian	0.73	0.64	0.83	***	0.82	0.75	0.89	***	1.05	0.95	1.17	ns
Southern	0.96	0.86	1.08	ns	0.72	0.65	0.78	***	0.77	0.69	0.85	***
Eastern	0.68	0.62	0.75	***	0.72	0.67	0.78	***	1.01	0.93	1.10	ns

ns – not significant, *p<0.05, **p<0.01, ***p0.001

§ for neurological and psychiatric conditions, having depression was considered; for cardiovascular disease, hypertension and high blood cholesterol was considered; for rheumatic diseases, multimorbidity was considered.

Reference categories: Not lonely at t-1; Male; 50-64 y.o.; No prior illness, Never lived alone; Always engaged in activities (>2); Always had an occupation; Does not have children; Always able to make ends meet (no financial issues), Low level of education; Bismarckian welfare group.

Supplementary Table 5. Fully adjusted multivariate regression models for each disease (Cataracts and Cancer) - Loneliness ≥ 6.

	Cataracts				Cancer			
	AOR	(95% CI)		sig.	AOR	(95% CI)		sig.
Loneliness at t-1	1.92	1.72	2.13	***	1.75	1.50	2.04	***
Female	1.26	1.17	1.35	***	0.73	0.66	0.81	***
65 – 79 y. o.	3.60	3.20	4.04	***	1.57	1.36	1.81	***
80+ y. o.	5.96	5.20	6.83	***	1.69	1.42	2.02	***
Has prior illness*	1.52	1.42	1.63	***	1.14	1.03	1.25	**
Started living alone	0.90	0.75	1.07	ns	0.81	0.62	1.06	ns
Always lived alone	1.01	0.93	1.10	ns	0.91	0.80	1.02	ns
Stopped engaging in activities	0.82	0.72	0.92	***	0.99	0.84	1.16	ns
Never engaged in activities	0.76	0.69	0.83	***	0.82	0.72	0.94	**
Stopped having an occupation	1.02	0.87	1.20	ns	1.28	1.04	1.57	*
Never had an occupation	1.19	1.07	1.33	***	1.33	1.14	1.54	***
Has children	1.00	0.90	1.12	ns	0.86	0.74	1.00	*
Started having financial issues	1.06	0.94	1.20	ns	0.92	0.77	1.11	ns
Always had financial issues	1.14	1.04	1.25	**	1.14	1.00	1.30	*
Medium level Education	0.94	0.87	1.02	ns	1.14	1.02	1.29	*
High level Education	0.93	0.85	1.03	ns	1.19	1.04	1.36	*
Scandinavian	1.19	1.08	1.31	***	1.00	0.87	1.15	ns
Southern	0.85	0.76	0.95	**	0.76	0.65	0.89	**
Eastern	0.84	0.76	0.91	***	0.76	0.67	0.86	***

ns – not significant, *p<0.05, **p<0.01, ***p0.001
§ for neurological and psychiatric conditions, having depression was considered; for cardiovascular disease, hypertension and high blood cholesterol was considered; for rheumatic diseases, multimorbidity was considered.
Reference categories: Not lonely at t-1; Male; 50-64 y.o.; No prior illness, Never lived alone; Always engaged in activities (>2); Always had an occupation; Does not have children; Always able to make ends meet (no financial issues), Low level of education; Bismarckian welfare group.

Supplementary Table 6. Fully adjusted multivariate regression models for each disease (Neurological, Rheumatic and Cardiovascular) – Loneliness ≥ 5.

	Neuro/Psychiatric				Rheumatic				Cardiovascular			
	AOR	(95% CI)		sig.	AOR	(95% CI)		sig.	AOR	(95% CI)		sig.
Loneliness at t-1	2.02	1.85	2.21	***	1.83	1.70	1.97	***	1.64	1.50	1.78	***
Female	1.46	1.34	1.58	***	1.66	1.57	1.77	***	0.63	0.59	0.67	***
65 – 79 y. o.	1.12	1.00	1.24	*	1.49	1.38	1.62	***	2.17	1.96	2.40	***
80+ y. o.	1.99	1.76	2.27	***	1.92	1.72	2.13	***	3.57	3.15	4.05	***
Has prior illness*	2.08	1.91	2.25	***	1.42	1.34	1.51	***	1.51	1.41	1.62	*
Started living alone	0.93	0.77	1.12	ns	0.73	0.62	0.86	***	0.88	0.74	1.05	ns
Always lived alone	0.83	0.75	0.91	***	0.84	0.78	0.90	***	0.94	0.86	1.02	ns
Stopped engaging in activities	1.35	1.20	1.53	***	0.91	0.82	1.01	0.074	1.11	0.99	1.25	0.067
Never engaged in activities	1.42	1.29	1.56	***	0.97	0.90	1.05	ns	1.16	1.06	1.27	**
Stopped having an occupation	1.17	0.99	1.37	0.061	1.04	0.93	1.17	ns	1.20	1.04	1.40	*
Never had an occupation	1.34	1.20	1.50	***	0.94	0.87	1.02	ns	1.21	1.09	1.34	***
Has children	0.99	0.87	1.12	ns	1.06	0.97	1.17	ns	1.09	0.97	1.22	ns
Started having financial issues	1.13	0.99	1.29	0.061	1.20	1.08	1.33	**	1.05	0.93	1.18	ns
Always had financial issues	1.37	1.25	1.51	***	1.38	1.28	1.49	***	1.41	1.29	1.54	***
Medium level Education	0.90	0.82	0.99	*	0.89	0.82	0.95	**	0.96	0.88	1.04	ns
High level Education	0.98	0.88	1.10	ns	0.80	0.73	0.87	***	0.88	0.80	0.97	*
Scandinavian	0.72	0.64	0.82	***	0.82	0.75	0.90	***	1.05	0.95	1.17	ns
Southern	0.95	0.85	1.06	ns	0.71	0.65	0.78	***	0.77	0.69	0.85	***
Eastern	0.67	0.60	0.74	***	0.71	0.66	0.77	***	1.00	0.92	1.09	ns

ns – not significant, *p<0.05, **p<0.01, ***p0.001

§ for neurological and psychiatric conditions, having depression was considered; for cardiovascular disease, hypertension and high blood cholesterol was considered; for rheumatic diseases, multimorbidity was considered. Reference categories: Not lonely at t-1; Male; 50-64 y.o.; No prior illness, Never lived alone; Always engaged in activities (>2); Always had an occupation; Does not have children; Always able to make ends meet (no financial issues), Low level of education; Bismarckian welfare group.

Supplementary Table 7. Fully adjusted multivariate regression models for each disease (Cataracts and Cancer) - Loneliness ≥ 5.

	Cataracts				Cancer			
	AOR	(95% CI)		sig.	AOR	(95% CI)		sig.
Loneliness at t-1	1.54	1.42	1.68	***	1.46	1.29	1.65	***
Female	1.25	1.17	1.35	***	0.73	0.66	0.80	***
65 – 79 y. o.	3.59	3.19	4.03	***	1.57	1.36	1.80	***
80+ y. o.	5.95	5.19	6.81	**	1.69	1.41	2.02	***
Has prior illness*	1.52	1.42	1.63	**	1.14	1.03	1.25	*
Started living alone	0.90	0.75	1.07	ns	0.81	0.62	1.06	ns
Always lived alone	1.02	0.93	1.10	ns	0.91	0.80	1.03	ns
Stopped engaging in activities	0.81	0.72	0.92	**	0.98	0.84	1.15	ns
Never engaged in activities	0.76	0.69	0.84	***	0.83	0.72	0.95	**
Stopped having an occupation	1.02	0.87	1.20	ns	1.28	1.04	1.57	*
Never had an occupation	1.19	1.07	1.33	**	1.32	1.14	1.54	***
Has children	1.01	0.90	1.13	ns	0.87	0.75	1.00	0.055
Started having financial issues	1.06	0.94	1.20	ns	0.93	0.77	1.11	ns
Always had financial issues	1.14	1.04	1.25	**	1.14	1.00	1.30	*
Medium level Education	0.94	0.87	1.02	ns	1.14	1.01	1.29	*
High level Education	0.94	0.85	1.03	ns	1.19	1.04	1.36	*
Scandinavian	1.19	1.07	1.31	**	1.00	0.88	1.15	ns
Southern	0.85	0.76	0.95	**	0.76	0.65	0.89	**
Eastern	0.82	0.75	0.90	***	0.75	0.66	0.85	***

ns – not significant, *p<0.05, **p<0.01, ***p0.001

§ for neurological and psychiatric conditions, having depression was considered; for cardiovascular disease, hypertension and high blood cholesterol was considered; for rheumatic diseases, multimorbidity was considered. Reference categories: Not lonely at t-1; Male; 50-64 y.o.; No prior illness, Never lived alone; Always engaged in activities (>2); Always had an occupation; Does not have children; Always able to make ends meet (no financial issues), Low level of education; Bismarckian welfare group.