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Social Isolation or Loneliness? Distinct associations with Multimorbidity among adults from the EPIPorto cohort

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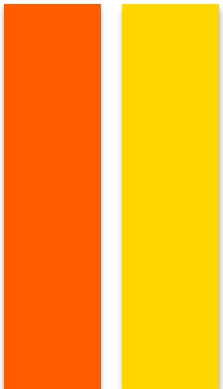

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Social Isolation or Loneliness? Distinct associations with Multimorbidity among adults from the EPIPorto cohort

Dissertation submitted in partial fulfilment of the requirements for the degree of Master's in Health Education, presented to the Faculty of Medicine and to the Faculty of Psychology and Educational Sciences of the University of Porto, supervised by Doctor Ana Henriques and co-supervised by Doctor Milton Severo

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This dissertation has one manuscript as a foundation:

Social Isolation or Loneliness? Distinct associations with Multimorbidity among adults from the EPIPorto cohort

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To my mother and brothers, with deep appreciation.

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List of Abbreviations and Acronyms

Introduction

COPD	Chronic Obstructive Pulmonary Disease
GNR	Guarda Nacional Republicana
MeSH	Medical Subject Headings
NASEM	National Academies of Sciences, Engineering, and Medicine
UNDESA	United Nations Department of Economic and Social Affairs
WHO	World Health Organization

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aRR	Adjusted Relative Risk
CI	Confidence Intervals
MAR	Missing at Random
MICE	Multivariate Imputation by Chained Equations
MM	Multimorbidity
NASEM	National Academies of Sciences, Engineering, and Medicine
PCA	Principal Component Analysis
WHO	World Health Organization

Resumo

Introdução: Com o envelhecimento da população mundial, a prevalência de doenças crónicas em adultos tem aumentado, levando a uma prevalência mais elevada de multimorbilidade - a coexistência de duas ou mais doenças crónicas num indivíduo -, particularmente entre adultos mais velhos. A multimorbilidade está associada a um aumento da mortalidade, limitações funcionais e uma redução da qualidade de vida, tanto para os indivíduos afetados como para os seus cuidadores, o que apresenta desafios consideráveis para os sistemas de saúde, tradicionalmente centrados na gestão individual de doenças. O isolamento social e a solidão são determinantes sociais da saúde inter-relacionados, mas distintos, que influenciam uma série de *outcomes* na saúde. No entanto, os seus efeitos independentes sobre a multimorbilidade continuam pouco explorados.

Objetivos: O principal objetivo deste estudo foi investigar as associações independentes entre isolamento social e solidão com a multimorbilidade em adultos portugueses. Especificamente, pretendemos avaliar de que forma estes fatores psicossociais influenciam o número e o tipo de doenças crónicas.

Métodos: Este estudo utilizou dados da coorte EPIPorto, composta por 2.485 adultos recrutados entre 1999 e 2003, com o último seguimento em 2022. Para responder à existência de heterogeneidade na medição da multimorbilidade, este estudo seguiu os critérios do consenso internacional de Delphi para a definição e avaliação da multimorbilidade. Foram criados diferentes *outcomes* de multimorbilidade: 1) a contagem total de doenças crónicas; 2) um subgrupo específico de doenças que envolvem os sistemas cardiovascular, metabólico/endócrino, mental/comportamental e musculoesquelético, identificado por análise de componentes principais; e 3) a contagem de doenças dentro de cada um destes subgrupos. O isolamento social foi determinado pelo tamanho do agregado familiar, categorizado como viver sozinho, viver com 1 pessoa ou viver com ≥2 pessoas, enquanto a solidão foi medida com recurso à Escala de solidão da UCLA, incluindo as suas diferentes dimensões (isolamento social e afinidades). Utilizámos Modelos Lineares Generalizados com uma distribuição de Poisson para explorar as associações entre isolamento social, solidão e *outcomes* de multimorbilidade. Foram calculados os riscos relativos ajustados (aRR) com intervalos de confiança (IC) de 95%.

Resultados: O isolamento social não apresentou associação com a contagem total de doenças, mas os agregados familiares maiores (viver com ≥2 pessoas) mostraram-se associados a um risco

aumentado de doenças metabólicas/endócrinas (aRR=1,50, IC 95%: 1,11-2,02). A solidão não se mostrou significativamente associada à contagem total de doenças, mas mostrou associação com um maior risco de desenvolvimento de multimorbilidade no subgrupo específico de doenças (aRR=1,13, IC 95%: 1,05-1,21), especificamente em condições mentais/comportamentais (aRR=1,25, IC 95%: 1,11-1,40). A dimensão de isolamento social da escala UCLA demonstrou associação com o subgrupo específico de doenças (aRR=1,20, IC 95%: 1,08-1,35), especificamente com um aumento do risco de doenças cardiovasculares (aRR=1,17, IC 95%: 1,05-1,32), metabólicas/endócrinas (aRR=1,20, IC 95%: 1,05-1,37) e mentais/comportamentais (aRR=1,29, IC 95%: 1,07-1,56).

Conclusão: Este estudo sugere que o isolamento social e a solidão estão associados de forma distinta à multimorbilidade, com efeitos que variam consoante o tipo de doenças crónicas e o método de medição. Estes resultados realçam a necessidade de intervenções de saúde pública baseadas em evidência e desenhadas de modo a abordar as formas específicas através das quais os fatores sociais influenciam os *outcomes* de saúde em adultos mais velhos. Os programas de educação para a saúde devem sensibilizar os profissionais de saúde, as comunidades e os decisores políticos para os efeitos prejudiciais do isolamento social e da solidão.

Abstract

Background: As the global population ages, the prevalence of chronic conditions in adults has increased, leading to a higher prevalence of multimorbidity - the coexistence of two or more chronic conditions within one person -, particularly among older adults. Multimorbidity is associated with increased mortality, functional limitations, and a reduced quality of life for both affected individuals and their caregivers, posing significant challenges for healthcare systems, traditionally focused on managing single diseases. Social isolation and loneliness are related, yet distinct, social determinants of health that influence a wide range of health outcomes. However, their independent effects on multimorbidity remain underexplored.

Objectives: The main objective of this study was to investigate the independent associations between social isolation and loneliness with multimorbidity among Portuguese adults. Specifically, we aimed to assess how these psychosocial factors influence the number and type of chronic conditions.

Methods: This study used data from the EPIPorto cohort, comprising 2,485 adults recruited between 1999 and 2003, with the latest follow-up in 2022. To address the heterogeneity in multimorbidity measurement, the research followed the international Delphi consensus criteria for multimorbidity definition and assessment. Different multimorbidity outcomes were computed: 1) the total count of chronic conditions; 2) a specific subgroup of conditions involving cardiovascular, metabolic/endocrine, mental/behavioural, and musculoskeletal systems, identified by principal component analysis; and 3) the count of conditions within each of these subgroups. Social isolation was determined by household size, categorized as living alone, living with 1 person, or living with ≥2 persons, while loneliness was measured using the UCLA Loneliness Scale, including its different dimensions (social isolation and affinities). We employed Generalized Linear Models with a Poisson distribution to explore the associations between social isolation, loneliness, and multimorbidity outcomes. Adjusted relative risks (aRR) with 95% confidence intervals (CI) were calculated.

Results: Social isolation did not show an association with the total disease count, but larger households (living with ≥2 persons) were linked to an increased risk of metabolic/endocrine conditions (aRR=1.50, 95% CI: 1.11-2.02). Loneliness was not significantly associated with the total disease count but was associated with a higher risk of developing multimorbidity from the specific subgroup of conditions (aRR=1.13, 95% CI: 1.05-1.21), specifically mental/behavioural conditions (aRR=1.25, 95% CI: 1.11-1.40). The social isolation dimension of the UCLA scale was associated with the specific subgroup of conditions (aRR=1.20, 95% CI: 1.08-1.35), specifically

with an increased risk of cardiovascular (aRR=1.17, 95% CI: 1.05-1.32), metabolic/endocrine (aRR=1.20, 95% CI: 1.05-1.37), and mental/behavioural (aRR=1.29, 95% CI: 1.07-1.56) conditions.

Conclusion: This study suggests that social isolation and loneliness are distinctly associated with multimorbidity, with effects varying according to the type of chronic conditions and the measurement method. These findings stress the need for evidence-based public health interventions to address the specific ways in which social factors influence health outcomes. Health education programs should raise awareness about the detrimental effects of social isolation and loneliness among healthcare providers, communities and public decision-makers for an efficient allocation of resources.

Introduction

1. A world growing older: what is changing?

Global population dynamics are changing rapidly due to rising life expectancy and declining fertility rates, resulting in a steadily aging population (1). According to the United Nations Department of Economic and Social Affairs (UNDESA) (2), the proportion of the world population aged 60 and above has grown significantly, increasing from 7.9% in 1950 to 14.2% in 2023. This demographic change is most pronounced in Europe, the region with the highest concentration of older adults, and Southern Europe leads the way, with Italy and Portugal at the top, where 31.4% and 31.1% of their populations, respectively, are aged 60 or older. Looking forward, the World Health Organization (WHO) (3) projects that the global population of individuals over 60 will more than double by 2050, surpassing 2 billion.

This demographic shift is primarily driven by significant advancements in healthcare, improved living conditions, better nutrition, the implementation of informed public health policies, and better education (4). Together, these factors have extended life-spans and led to a global restructuring of population demographics. This evolution also marks an epidemiological transition: while infectious diseases, once widespread and deadly, have been significantly reduced and are now largely confined to specific regions due to improved prevention and disease control strategies, chronic diseases such as heart disease, diabetes, and cancer have become increasingly prevalent worldwide. This rise in chronic diseases reflects changes in lifestyle and environmental factors and is expected to continue following this trajectory (5).

2. Multimorbidity: shifting to a new norm

As a consequence of population ageing and the rising prevalence of chronic diseases, the prevalence of multimorbidity - the coexistence of two or more chronic conditions in the same individual - is also increasing (6).

A recent systematic review and meta-analysis (7) estimated that 37.2% of the global population is affected by at least two chronic conditions, with females being most affected (39.4%), and geographical prevalence ranging from 45.7% in South America to 35% in Asia. Importantly, it is more frequent in populations aged over 60 years (51.0%), which indicates that multimorbidity among older populations is not only pervasive but has become the norm, posing a burden to a

significant part of the population. In Portugal, 38.3% of adults experience multimorbidity. This prevalence increases sharply among adults aged 65 to 74, where 74% present multiple chronic conditions. The prevalence for this age range is higher in women, at 82.3%, compared to 65.5% in men (8). A recent study has projected a 13.1% growth in the prevalence of multimorbidity in Portugal by 2050 (9).

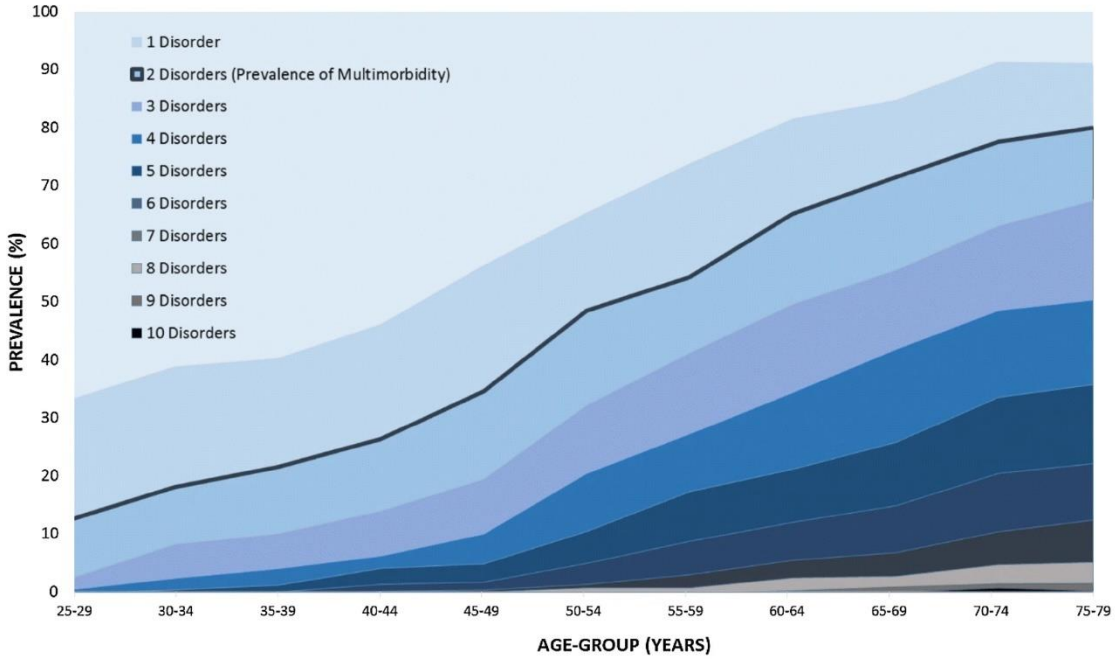

Figure 1. Prevalence of Multimorbidity by age group in Portugal (2014)

Reproduced from Laires & Perelman, 2018 (9)

A relevant conceptual distinction must be made: while 'multimorbidity' and 'comorbidity' are often incorrectly used as synonyms to describe the presence of multiple chronic conditions in one person, 'comorbidity' refers to additional conditions occurring alongside a primary illness, whereas 'multimorbidity' considers any co-occurrence equally, with no single condition being the focus of either the patient or the healthcare professional (10, 11). Multimorbidity focuses on the individual as a whole, allowing patient-centred care by addressing the patient's overall experience and treatment burden (12). From a research perspective, studies that aim to assess outcomes related to a single primary condition align more closely with the comorbidity framework. In contrast, research focused on studying the broader implications of multiple chronic conditions without a dominant illness is better suited to the multimorbidity framework. This distinction is important because the inappropriate use of terminology in both clinical and academic contexts can lead to confusion and inadequate treatment strategies. The recent

creation of a distinct Medical Subject Headings (MeSH) term for *multimorbidity* in 2018 reflects the importance of maintaining clarity between these concepts in both research and practice (13)

While this formal distinction is expected to bring clarity and promote consistency in the use of terminology within the field, the measurement of multimorbidity remains highly heterogeneous across studies, which can lead to considerable variability in reported prevalence rates and hinder the comparison of results across different populations and settings. This heterogeneity arises from differences in the definitions of multimorbidity, the number and types of conditions considered, and the methods used to identify these conditions (6, 14, 15). For example, some studies limit their scope to a narrow list of chronic conditions, while others take a wider approach, incorporating chronic, acute conditions, or risk factors.

2.1. The impact of multimorbidity

Multimorbidity significantly impacts the quality of life of the affected individuals, with multiple studies over the past decades consistently showing a negative correlation between multimorbidity and quality of life (16). This is attributable to several key factors:

(i) Functional limitations: they refer to restrictions in an individual's ability to perform basic activities, and often lead to reduced self-efficacy, which is the belief in one's ability to manage and control various aspects of their life (17). These limitations can hinder a person's capacity to perform necessary self-management tasks and impact one's health behaviours (18);

(ii) Polypharmacy: The use of multiple medications is common among these patients, which can lead to adverse drug interactions and increased risk of medication non-adherence (19, 20);

(iii) Complexity of associated treatments: Since healthcare systems are configured to address singular conditions, patients with multimorbidity often experience fragmented care. This leads to significant illness burdens, frequent medical visits, and complex treatment plans (21);

(iv) Employment and financial instability: complex health management makes it challenging for patients to maintain regular employment and remain active in the job market; older working individuals with multiple chronic conditions are more likely to partially or fully retire compared to their counterparts without multimorbidity, affecting their financial stability and subsequent life decisions (22);

(v) Increased mortality risk: a higher risk of mortality has also been reported for certain multimorbidity clusters. This can be explained by physiological mechanisms similar to those that raise the risk of death from specific diseases, aggravated by interactions between morbidities and interactions between their treatments (23).

Multimorbidity also burdens the caregivers of frail adults, increasing families' burden due to the extensive time commitment and high care demands of dependent individuals. This burden is exacerbated by the stress of financial responsibilities, life role changes, and managing behavioural issues. Consequently, caregivers often experience psychological strain, anxiety, and decreased quality of life, highlighting the need for comprehensive support systems (24) for patients managing more complex multimorbidity.

Previous research indicates that managing multiple chronic conditions often leads to fragmented and poorly coordinated care, largely because healthcare systems are traditionally designed to address single diseases (25). This fragmentation results in duplicative and inefficient use of services, which strains healthcare resources by significantly increasing both inpatient and outpatient demands, ultimately leading to the unsustainability of the system (26).

In addition to these structural challenges, primary care systems often lack the necessary training and resources to manage these patients effectively. Training for primary care providers is often inadequate, especially in geriatrics and chronic disease management, because most clinical guidelines typically exclude patients with multimorbidity. This gap in training and guidance leaves clinicians, health managers, and policymakers without sufficient evidence-based strategies for managing multimorbidity, leading to inadequate care that can be potentially harmful to patients, while also placing an excessive burden on care providers. As a result, there is an urgent need to rethink health systems to better address the complexities of multimorbidity (6, 27).

National studies consistently show that each additional chronic condition significantly increases healthcare expenditures. For instance, in Ireland, per annum, each additional chronic disease had a cost of €513 (28), supporting the findings from other authors who estimated that, in Singapore, the annual cost per additional condition was SGD$2,265 for healthcare and SGD$3,177 for social care (29). Expanding on this, a systematic review and meta-analysis highlighted that not only the global prevalence of multimorbidity is increasing, as managing multimorbidity is more complex and resource-intensive than treating single diseases, with costs varying widely based on disease combinations, population demographics, and healthcare contexts (30).

Given the public health significance of the severe and multi-levelled impact of multimorbidity, it is unsurprising that this issue has spurred extensive research efforts, including a pressing need to explore its lesser-known determinants (31).

2.2. Contributing factors to chronic disease development and accumulation

2.2.1. Genetic and biological factors

Genetic factors play a crucial role in the development of chronic diseases, independent of ageing. Specific genetic predispositions can significantly increase the likelihood of developing conditions, such as cardiovascular diseases (32). However, ageing, while a natural developmental process, is inherently linked to a decline in biological functions, marked by several key hallmarks. These include: (i) genomic instability, where accumulated DNA damage elevates cancer risk; (ii) telomere attrition, leading to cellular ageing; (iii) epigenetic changes, disrupting gene expression; (iv) proteostasis, or impaired protein homeostasis; (v) deregulated nutrient sensing, impacting metabolic health; (vi) mitochondrial dysfunction, reducing energy production; (vii) cellular senescence, affecting cell division; (viii) stem cell exhaustion, compromising tissue repair; and (ix) altered intercellular communication, driving inflammation (33-35). These biological mechanisms drive the onset and progression of chronic age-related diseases, and these conditions rarely occur in isolation: as individuals age, the risk of developing multiple chronic conditions simultaneously increases. For instance, chronic low-grade inflammation, frequently termed "inflammaging," is an important mechanism linking various age-related diseases. Inflammation contributes to the development of both cardiovascular disease and diabetes, creating a common biological pathway that ties these diseases together (36). Consequently, addressing one condition in isolation may fail to capture the interdependent nature of these diseases.

2.2.2. Environmental and behavioural factors

Environmental conditions play an important role in determining health outcomes, both directly and indirectly. The physical environment impacts health not only through exposure to harmful agents but also by shaping the behaviours of individuals and communities. For instance, long-term exposure to air pollution around industrialized areas has been clearly linked with cardiovascular disease (37). Similarly, substandard housing conditions, such as crowding, poor

sanitation, or inadequate heating, increase the risk of chronic diseases, particularly respiratory conditions (38).

In addition to their direct effects on health, environmental conditions also influence health-related behaviours. Exposure to air pollution can discourage outdoor activities (39), leading to physical inactivity, which is a major behavioural risk factor for chronic diseases such as obesity, diabetes, and cardiovascular disease (40) The opposite - higher practice of physical exercise - happens when the population has access to green, walkable areas (41).

Beyond the impact of environmental conditions, individual behaviours also significantly influence the development of chronic diseases. Along with physical inactivity, poor diet, smoking, and excessive alcohol consumption - collectively known as lifestyle factors - are some of the most well-documented behavioural risk factors. Diet influences chronic conditions like diabetes, hypertension and some cancers. Moreover, these conditions often act as catalysts for the development of additional diseases, such as the influence of hypertension on cardiovascular disease (42). Smoking, particularly heavy smoking, has a strong association with an increased risk of developing multiple chronic diseases. It was the strongest modifiable lifestyle risk factor among those examined in different studies, including cohort, case-control and meta-analyses studies undoubtedly linking smoking to important chronic conditions like chronic obstructive pulmonary disease (COPD), lung cancer and laryngeal cancer (43). Harmful alcohol consumption ranks as the seventh leading global risk factor for death and disability, and is recognized as a potent carcinogen, contributing to 4.1% of all new cancer cases in 2020 (44). Recent research has shown that no level of alcohol consumption can be considered safe for health (45), challenging the guidelines that suggest moderate drinking may be harmless (46). In addition to cancers and other neoplasms, alcohol is linked to neuropsychiatric, cardiovascular, circulatory, and digestive diseases. Furthermore, its cognitive impairment effects can interfere with adherence to medication regimens for pre-existing conditions (47).

2.2.3. Psychosocial factors

Psychosocial factors are emotional, social, and cognitive influences impacting health, like stress, anxiety, family support, peer relationships, and health beliefs; together, they directly affect treatment adherence and patient well-being (48). However, feelings of alienation and mediating factors like loneliness and stress have been directly linked to inflammation and chronic disease outcomes (49). The psychosocial aspects of chronic disease accumulation remain underexplored, particularly in vulnerable populations, such as children, persons with disability,

or older individuals living alone (31). Social isolation and loneliness are important, yet overlooked determinants for all, especially considering an ageing population (50).

3. The specific case of Social Isolation and Loneliness

Humans are inherently social beings, a characteristic rooted in our evolutionary history. This is supported by a wide body of research demonstrating the role of social connections in survival and well-being (51). However, modern life in industrialized nations led to a decline in meaningful social connections, resulting in more people experiencing loneliness and solitary living (52). Though social isolation and loneliness are often used interchangeably, they represent different phenomena.

Social isolation is typically defined by the absence or near absence of social interactions or engagement with others (53). Epidemiological studies often operationalize social isolation through objective criteria, such as lacking a spouse, infrequent contact with family or friends, and lack of participation in organizations or groups (54).

Recently, a systematic review and meta-analysis reported that social isolation affects on average 26% of older community-dwelling adults aged, globally, with significant geographical variations (55). In Europe, as many as 22% of older adults are socially isolated, although the Americas region is the most affected, with 30% of older adults lack social contacts. In Portugal, *Guarda Nacional Republicana* (GNR) [National Republican Guard] conducted the "*Censos Sénior*" operation, aimed at identifying older individuals isolated and identified 44.511 individuals in this situation, in 2022 (56).

Historically, conceptualizations of loneliness as a significant psychological issue began in the 1950s with Fromm-Reichmann describing loneliness as the longing for interpersonal intimacy (57). This early work laid the foundation for subsequent theories aiming to differentiate between different forms of loneliness. Weiss, in 1973, argued that loneliness is fundamentally about unmet social needs and distinguished between emotional loneliness, which arises from the absence of a close, intimate figure, and social loneliness, which results from the absence of a broader social network (58). Building on these ideas, Perlman and Peplau described loneliness as the distressing experience that arises when social relationships of an individual are perceived to be lacking either in quantity or in quality (59). This perspective led to the development of the *cognitive discrepancy theory* of loneliness, which explains that loneliness results from the subjective evaluation of one's relationships relative to personal expectations for an ideal social

network. This theory has become one of the most widely employed in loneliness research (60) and helps to explain why some individuals with limited social contacts may still feel content and not experience loneliness and, conversely, why others with vast social connections may still feel lonely (61). John Cacioppo and colleagues have further expanded our understanding of loneliness by integrating biological, psychological, and social dimensions into their research. However, Cacioppo's work is distinctive since it frames loneliness as not only a psychological state but also a condition with significant physiological consequences. His research has shown that loneliness can trigger specific biological processes, including increased cortisol levels and inflammation, which contribute to health issues, such as cardiovascular disease and impaired immune function (62). This approach brings attention to the evolutionary significance of loneliness, suggesting that loneliness serves as a signal to reconnect with others, an essential mechanism for survival in ancestral environments - the *evolutionary perspective* (63).

Systematic reviews have reported the global prevalence of loneliness among adults, with particular emphasis in the second half of life (64), found that loneliness is a widespread issue, with prevalence rates among older adults (≥60 years) ranging from 20% to 30% globally, and 10-15% of older adults experiencing loneliness frequently. In Europe, the prevalence of loneliness varies significantly, with Eastern Europe reporting the highest levels at 40%, while Northern Europe reports the lowest at 10-20%. In Portugal, it is estimated that 14.9% of the population over 60 years of age experiences frequent feelings of loneliness, but these levels were shown not to be significantly associated with age (65).

Even though social isolation and loneliness affect individuals across all age groups, adults with more severe health conditions are especially vulnerable to their adverse effects, particularly those experiencing transitions such as retirement, change of residence, and the loss of partners and friends (66-69), common at this life stage. The impact of social isolation and loneliness on health is increasingly recognized as a major public health concern. Research has demonstrated that these social factors are not only detrimental to well-being but also have a significant bearing on mortality, with effects comparable to established risk factors like obesity and smoking (70, 71). Both conditions are associated with increased risks of neurological conditions, such as impaired cognition (51), and cardiovascular diseases (72). Loneliness is particularly associated with adverse psychological outcomes such as depression and anxiety, while social isolation seems to be more heavily related to increased mortality risk (73). These distinctions suggest that while social isolation and loneliness are related, they impact health in different ways (74). This may be due to their operation through different pathways, including their varying impacts on

health behaviours. For instance, social isolation is associated with smoking, while loneliness is more strongly linked to physical inactivity (75).

The interplay between social isolation, loneliness, and multimorbidity remains underexplored, particularly in how these social determinants might synergistically exacerbate chronic conditions in older adults (6). Though recent research has begun to focus more attention on the relationship between loneliness or social isolation and health outcomes, their distinct associations with multimorbidity, particularly in relation to social isolation, remain underexplored (76).

Objectives

The increasing prevalence of chronic conditions due to global aging has led to higher rates of multimorbidity, particularly among older adults. Multimorbidity is associated with adverse outcomes, including increased mortality, reduced quality of life, and new challenges to healthcare systems, traditionally oriented toward single-disease management. Loneliness and social isolation are critical social determinants of health, yet their independent specific effects on multimorbidity are yet to be well understood.

The main objective of this study is to investigate the independent association of loneliness and social isolation with multimorbidity among Portuguese older adults. Specifically, we seek to determine how these social factors influence both the overall number of chronic conditions, and specific types of chronic conditions present with the goal of informing targeted health intervention programs.

We aim to raise awareness among healthcare professionals about the nuanced impact of the social isolation and loneliness on multimorbidity, leading to a better identification of at-risk individuals and the implementation of effective prevention strategies.

Manuscript

Social Isolation or Loneliness? Distinct associations with Multimorbidity among adults from the EPIPorto cohort

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Abstract

Objective: To investigate the independent association of social isolation and loneliness with different outcomes of multimorbidity among Portuguese adults using data from the EPIPorto cohort.

Methods: EPIPorto encompasses 2,485 adults evaluated from 1999-2003 until 2022. Multimorbidity was assessed based on the Delphi international consensus criteria; different variables were computed: 1) a count of all chronic conditions; 2) based on principal component analysis, a count of a subgroup of chronic conditions (cardiovascular, metabolic/endocrine, mental/behavioural, and musculoskeletal body systems); and 3) a count of conditions separately for each one of these body systems. Loneliness was measured using the UCLA Loneliness Scale, with separate analyses for the total score and its two dimensions: social isolation and affinities. Social isolation was assessed through the household size. Missing data was handled through multiple imputation by chained equations. Generalized linear models with Poisson distribution were estimated and adjusted relative risks (aRR) and 95% confidence intervals (95%CI) were computed.

Results: An increase in household size was not associated with the count of all chronic conditions, after adjusting for confounders. In contrast, a larger household size (living with ≥2 persons) was associated with an increased risk of metabolic/endocrine conditions (aRR=1.50, 95%CI: 1.11-2.02), but not loneliness. Loneliness significantly increased the risk of MM when focusing on a specific subgroup of conditions (aRR=1.13, 95%CI: 1.05-1.21), in particular the risk of mental/behavioural conditions (aRR=1.25, 95%CI: 1.11-1.40). Additionally, a higher UCLA social isolation dimension score significantly increased the risk of MM when considering a specific subgroup of conditions (aRR=1.20, 95% CI: 1.08-1.35), cardiovascular (aRR=1.17, 95% CI:

1.05-1.32), metabolic/endocrine (aRR=1.20, 95% CI: 1.05-1.37) and mental/behavioural conditions (aRR=1.29, 95% CI: 1.07-1.56) conditions.

Conclusions: Loneliness and social isolation have distinct impacts on MM, and this association varies depending on how MM is measured. Public health interventions should consider these specificities to design more effective strategies aimed at improving the health of an ageing population, leading to better resource allocation and more sustainable healthcare systems.

Keywords

Ageing; Chronic disease; Loneliness; Multimorbidity; Social Isolation

Abbreviations

MM, Multimorbidity;

Introduction

Global population dynamics are changing significantly due to increased life expectancy and declining fertility rates, translating into an aged population. The percentage of people aged 60 and above worldwide has risen from 7.9% in 1950 to 14.2% in 2023. Moreover, projections suggest that the global population over 60 will double by 2050, exceeding 2 billion (1). Europe has the highest proportion of older adults, with Southern Europe in the lead. Italy and Portugal are at the forefront, with 31.4% and 31.1% of their populations aged 60 or above, respectively (2).

This demographic shift marks an epidemiological transition characterized by a decline in infectious diseases and a rise in chronic diseases (3). Thus, the coexistence of two or more chronic conditions within the same person – multimorbidity (MM) - is increasingly common in older populations: more than a third of the global population lives with MM, with a prevalence of 51.0% among those aged over 60 years (4).

The consequences of MM are diverse: multimorbid individuals are more likely to die prematurely (5), face a higher risk of functional limitations (6), and more frequently manage polypharmacy, treatment complexity, and associated interactions (7, 8) As a result, they have a poorer quality of life (9). Those of working age are also more likely to anticipate partial or full retirement (10), with related financial burden. Furthermore, when combined with frailty, MM may place a burden on carers, causing them significant psychological strain (11). Since MM is associated with high healthcare services utilization (12), health managers and policymakers need guidance on redesigning systems to address this condition (13). To design effective interventions, research is needed on MM and its modifiable risk factors.

Loneliness and social isolation are recognized as important social determinants of health (14). Though they affect individuals across all age groups, older adults are especially vulnerable to

adverse effects due to a natural decline in their social networks (15). The impact of loneliness and social isolation on an individual's quality of life, physical and psychological morbidity, and mortality are comparable to major risk factors such as obesity, and the equivalent to smoking 15 cigarettes a day (16, 17).

Social isolation and loneliness are related but distinct phenomena. Social isolation refers to the absence or near-absence of social contacts or interactions (18). In contrast, loneliness is the subjective and distressing feeling of being alone, independent of the presence of other people (19), representing a personal perception of lacking desired social connections.

The existing research on loneliness and social isolation presents mixed findings regarding their distinct impacts on health. For example, both social isolation and loneliness have been associated with increased risks of mental health conditions (20) and mortality (16). However, recent systematic reviews suggest that loneliness is more strongly tied to psychological outcomes, while social isolation is more closely linked to a higher risk of mortality (21).

Although research on the distinct impacts of social isolation and loneliness on complex outcomes like MM is generally limited, existing studies suggest that the relationship between social isolation and MM is less frequently explored, possibly due to the challenges in objectively measuring social isolation (22, 23).

Multimorbidity is characterized by significant heterogeneity in its definition, the choice of conditions counted, and the measures used, with many authors failing to report these in their studies (24, 25) This variability greatly affects MM prevalence estimates, which range from 3.5% to 100% (26), making it more difficult to reproduce studies.

Thus, this study aims to better clarify the independent association of loneliness and social isolation with different measures of MM among Portuguese older adults, following an international Delphi consensus on MM research.

Methods

Study design and participants

This study is based on data from the EPIPorto cohort (27), a population-based prospective closed cohort recruited between 1999 and 2003 (baseline) encompassing 2,485 adults from Porto, Portugal. The main aim of this cohort was to study the determinants of health in the adult population of Porto, with participants selected by random digit dialling. Participants were evaluated throughout time at five follow-ups: 2005-2008 (follow-up 1; proportion of participation: 68%), 2013-2015 (follow-up 2; proportion of participation: 40%), 2017-2018 (follow-up 3; proportion of participation: 39%), 2020 (follow-up 4; proportion of participation: 35%), and 2022 (follow-up 5; proportion of participation: 34%), allowing a longitudinal analysis of adult's health over time. From this point onwards, we will refer to the evaluations as *baseline* and *follow-up 1* through *follow-up 5*.

For this study, we have used information from baseline, follow-up 1, follow-up 2, and follow-up 5, since the other follow ups did not provide information within the scope of the current study. In all evaluations, trained professionals administered a structured questionnaire in face-to-face interviews to gather data on participants' sociodemographic, behavioural, and health characteristics.

Due to variations in individuals' participation, data availability and completeness across different follow-ups, the sample size for each variable of interest varied. The sample ranged from 781 to 2485 participants. Further information regarding the respondents for each study variable can be found in Table 1.

The Joint Ethics Committee of Hospital S. João and University of Porto Medical School approved this study protocol (CES-320/2016).

Multimorbidity

Information on the presence of chronic conditions was collected and analysed at follow-up 5. This information was gathered through responses to questions regarding past and present self-reported diagnosis of diseases done by a physician.

Chronic conditions were identified using the Delphi international consensus criteria (28), which recommend including 24 mandatory conditions in MM measures and the additional 35 conditions that the consensus recommend including unless there are justified reasons for exclusion. None of these 59 conditions were excluded.

Conditions were first counted and then categorized according to body systems (e.g., cardiovascular, circulatory) using the International Classification of Diseases 10th Revision (ICD-10), as advised by the Delphi consensus guidelines. Six MM outcomes were then computed: 1) a discrete variable was created by counting the total *number of chronic conditions* each participant presented at follow-up 5; 2) using principal component analysis (Supplementary material 1), a subgroup of types of conditions (cardiovascular, metabolic/endocrine, mental/behavioural, and musculoskeletal) was identified and then it was computed a discrete variable counting the presence of the mentioned *subgroup of conditions*; 3) each of these four body systems was then analysed separately, and the number of diseases in each subgroup was considered, to facilitate the examination of their individual relationships with social isolation and loneliness.

Social Isolation

Social isolation was assessed based on household size, determined by the number of persons the participant lived with, and categorized into three groups: living alone (often considered a marker of social isolation) (16), living with one person, and living with two or more persons. Since this information was collected at various follow-ups, a sensitivity analysis was conducted to identify which time point in household size was the best predictor of MM at follow-up 5, and based on a Poisson regression model, household size at follow-up 1 has shown to be the most important, with the strongest association with MM. It can be hypothesized that this household

size reflects what participants had for most of their lives and at a time when events like widowhood were less common.

Loneliness

Loneliness was measured only at follow-up 5 using the UCLA Loneliness Scale (29), a well-established 20-item instrument that assesses two different dimensions of loneliness and has been validated for the Portuguese older population. The Portuguese version of this scale (30) contains 16 items, with four items having been removed from the original to enhance reliability. It is specifically designed to evaluate loneliness, assessing both feelings of social isolation – which corresponds to a social disintegration by a breakdown in social bonds (the *Social Isolation Dimension; UCLA-SI*) and feelings of affinity - the perception of being welcomed (the *Affinities Dimension; UCLA-A*). The items allow participants to indicate the extent of their loneliness feelings and experiences using a Likert-type scale with responses ranging from 1 to 4, where a score of 1 indicates 'never,' 2 represents 'rarely,' 3 signifies 'sometimes,' and 4 indicates 'frequently.' Consequently, the total score spans from 16 to 64, with a cutoff point of 32. Participants scoring 32 or above reveal the presence of negative feelings of loneliness. The scale with the dimensions of the Portuguese version of UCLA is available in the supplementary material (Supplementary material 2).

Sociodemographic and behavioural characteristics

Several sociodemographic and behavioural characteristics were used to compare participants and non-participants at follow-up 5, integrated into the missing data imputation process. Sex, age, education, and marital status were self-reported by participants and were retrieved from the baseline evaluation. Education, recorded as complete years of schooling (from 0 to 21), was categorized into elementary (0 to 9), secondary (10 to 12) or graduate level (13 to 21). Lifestyle behaviours (physical exercise, tobacco smoking, and alcohol consumption) were obtained from responses to closed questions (“Do you usually engage in any physical activity?”, "Do you smoke,

or have you ever smoked?" and “Do you drink or have you ever consumed alcoholic beverages?”), and recorded as 'yes' or 'no'. Marital status was collected with the question "What is your marital status?", with responses pre-categorized as “married/in a civil union”, “single”, “widowed”, and “divorced/separated”.

Statistical Analysis

Continuous variables are expressed as means (standard deviations), or as medians (interquartile ranges), and compared using two independent samples t-test. Categorical variables were described as counts and percentages, and comparisons were made using Chi-Square or Fisher tests. For comparing means among three or more groups, Analysis of Variance (ANOVA) was used.

Generalized linear models (GLM) with a log-link function and a Poisson distribution were used to analyse the impact of various exposures (household size, UCLA total score and its dimensions) on different health outcomes (number of chronic conditions, presence of a specific subgroup of chronic conditions, and the existence of cardiovascular, metabolic/endocrine, mental/behavioural, and musculoskeletal conditions) at follow-up 5. Unadjusted and adjusted models were constructed, and results were reported as relative risks (RR) with 95% confidence intervals (95% CI). Adjusted models included the covariates *sex*, *age* and *education* to control for potential confounding factors (31-33). For the sake of interpretation, UCLA scores were divided by 10; therefore, the relative risks are referring to a change of 10 points in the UCLA scale.

To address missing data, multivariate imputation by chained equations (MICE) was used relying on *missing at random* (MAR) assumption. For continuous, dichotomous, polytomous, and ordinal variables, we employed linear regression, logistic regression, multinomial logistic regression, and ordinal logistic regression, respectively, to impute the missing values. We performed 10 multiple imputations.

To estimate the RR and their respective confidence intervals, we applied Rubin's rules, a set of statistical principles used to combine parameter estimates and associated variances across multiple imputed datasets.

All variables in the study (exposures, outcomes, sociodemographic and behavioural data) were included in the imputation process. Data analyses were performed by R versions 4.3.1 and 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria), and IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

Results

Table 1 shows the sociodemographic and health-related characteristics of the EPIPorto cohort, comparing participants (n=836) and non-participants (n=1649) at follow-up 5. When comparing to non-participants, participants were generally younger, were more likely to be married or in a civil partnership, to hold a graduate degree, less likely to smoke, more likely to practice physical exercise, less likely to have any chronic conditions and less likely to live alone.

The median score for loneliness among participants was 22, with an interquartile range (IQR) of 18 to 29, on a scale ranging from 16 to 64 (Table 1). Additionally, as a sensitivity analysis, no significant differences in loneliness scores were found between those who were living alone, living with 1 person, and with 2 or more persons in the same household (Supplementary Material 3).

At follow-up 5, 28.8% of participants had at least two chronic conditions, and 56.0% of these participants had at least one condition encompassing at least one of four body systems, namely cardiovascular, metabolic/endocrine, mental/behavioural, or musculoskeletal. Among these participants, 41.6% had at least one cardiovascular condition, 17.4% had at least one metabolic/endocrine condition, 9.8% had at least one mental/behavioural condition, and 6.5% had at least one musculoskeletal condition (Table 2).

After imputing missing data and adjusting for sex, age, and education, no significant associations were found between social isolation or loneliness and the risk of having a higher number of total chronic conditions. However, larger household sizes (living with ≥2 persons) were associated with a higher risk of metabolic/endocrine conditions (aRR=1.50, 95% CI: 1.11-2.02) (Table 3).

Loneliness was not significantly associated with the total number of chronic conditions but was linked to a specific subgroup of diseases (RR=1.13, 1.05-1.21). In particular, loneliness was associated with an increased risk of mental/behavioural conditions (RR = 1.25, 95% CI: 1.11–1.40), independent of age, sex, and education level. Regarding UCLA-SI and UCLA-A dimensions,

the former was associated with a higher risk of disease from the subgroup of specific chronic conditions (RR=1.20, 95% CI: 1.08-1.35), namely cardiovascular (RR=1.17, 95% CI: 1.05-1.32), metabolic/endocrine (RR=1.20, 95% CI: 1.05-1.37) and mental/behavioural conditions (RR=1.29, 95% CI: 1.07-1.56), while the latter was not significantly associated with any of the MM outcomes considered (Table 3).

Discussion

Our study explored the complex relationship between loneliness, social isolation, and MM among older adults. We found that while these factors were not associated with the simple counts of chronic conditions - typically used to identify MM - larger household sizes were related to a significantly higher risk of having more metabolic/endocrine conditions. In comparison, loneliness was associated with higher risk of specific conditions, specifically mental/behavioural conditions. Regarding UCLA Loneliness scale specific dimensions, the UCLA-SI, as opposed to the UCLA-A, was linked to higher risks of cardiovascular, metabolic-endocrine, and mental health conditions.

Multimorbidity research is characterized by significant heterogeneity in definitions and measurement methods, which can make comparisons between studies difficult (24). To ensure comparability with similar studies, our work adhered to the guidelines established by an international Delphi consensus on how to define and measure MM (28). To our knowledge, research on this topic has not consistently adhered to these international guidelines.

Multimorbidity has been linked to several unfavourable health outcomes. Specific types of chronic conditions, rather than just an overall count, may play a crucial role in understanding how MM affects health and mortality (34). However, most of the research on MM only sums up all the conditions an individual presents. In this study, by categorizing MM according to body systems, we were able to identify associations between these systems using principal component analysis, ultimately identifying four key systems: cardiovascular, metabolic/endocrine, mental/behavioural, and musculoskeletal. These findings align with the most common patterns described in MM literature focused on older adults, such as cardio-respiratory, metabolic, and mental-articular conditions (35), or cardio-metabolic, mechanical-obesity-thyroidal, psychogeriatric, and depressive patterns (36), with slight variations according

to sex. Regarding social isolation, the present study suggests an association between larger households and the presence of metabolic/endocrine conditions.

Previous studies have generally shown that individuals experiencing social isolation are more prone to worse health and well-being outcomes, and premature mortality. However, some individuals thrive in isolated conditions due to personal preferences or lifestyle choices, meaning that the impact of social isolation is not uniformly negative across all individuals. Moreover, findings from a recent meta-analysis challenge the common assumption that older adults are more vulnerable to the adverse effects of social isolation than younger adults, with results indicating that middle-aged adults had a higher mortality risk from loneliness or living alone than older adults (16). Despite the scarcity of research on this topic, social isolation has been independently linked to higher odds of having been previously or newly diagnosed with Type 2 Diabetes Mellitus (T2DM) in men (37), and a higher risk of developing T2DM regardless of genetic predisposition (38). Similarly, a study involving two large cohorts found that social isolation is significantly associated with a higher risk of T2DM, through Mendelian randomization, indicating a likely causal rather than merely correlational relationship (39). Metabolic MM is associated with a higher likelihood of functional impairment, which can lead to limitations in activities of daily living (40). According to the same study, these conditions are more prevalent in adults over 75 years old. Consequently, this population tends to be more dependent on others and may have a higher contact with caregivers, family members, and healthcare professionals. Rather than being isolated, these individuals are often part of a supportive network, including a larger household. This may explain the associations observed in our study.

The social isolation measure used in the present study was solely based on the household size, which might not capture the full spectrum of this concept, since people can, for example, live alone and spend time with their friend outside the house. Future research should incorporate other dimensions of social isolation.

In our findings, loneliness was not associated with the overall number of chronic conditions. Instead, it is significantly associated with mental/behavioural health conditions, such as depression and anxiety. This is consistent with previous research linking loneliness to more mental health issues. The NASEM report on Social Isolation and Loneliness in Older Adults highlights the bidirectional relationship between loneliness and mental health disorders, emphasizing how loneliness and social withdrawal can exacerbate psychiatric conditions, while mental health issues may increase feelings of loneliness, creating a cyclical pattern (41). On the other hand, a 5-year cross-lagged analyses (42) found that loneliness predicted depression, but not the other way around. Additionally, a narrative synthesis and meta-analysis found that loneliness is linked to the subsequent development of depression, and that adults experiencing frequent loneliness have more than double chances of developing depression (43). Though our study design inhibits from inferring causality, these findings reinforce the importance of addressing loneliness as a risk factor for mental health.

Different dimensions of the UCLA scale have yielded different results in our study: while the UCLA-A did not show any association with MM outcomes, higher scores on UCLA-SI were associated with increased risks of having more cardiovascular, metabolic/endocrine, and/or mental/behavioural conditions. We infer that, considering a commonly used definition of loneliness as *perceived social isolation* (16, 44), items measuring the perception of social isolation (*Social Isolation Dimension*) inherently provide a strong assessment of loneliness. As UCLA-A relates to the perceived quality of relationships and belonging, this suggests that emotional satisfaction may not directly influence health outcomes, or other forms of support might compensate for emotional deficiencies. One explanation for the association between UCLA-SI and conditions related to several body systems is that, as this dimension involves more physical aspects of feeling alone, they can impact health by limiting practical support during illnesses or crises; for example, the perception that "*there is no one I can turn to*" may prevent an individual from seeking help, even in situations where assistance is needed.

Some strengths and limitations of this study should be discussed. One of the main strengths is the use of a detailed classification system based on the Delphi international consensus criteria to define and measure MM. This approach enhances consistency, comparability and reproducibility of MM research, addressing a key issue in this field (7, 28). Additionally, we controlled for important sociodemographic variables such as age, gender, and education level, increasing the rigor of our finding. The use of the UCLA Loneliness Scale, a well-established and validated measure for our population, further added reliability to the assessment of loneliness. While our study is primarily of a cross-sectional nature, the use of data from multiple time points offered an advantage over typical cross-sectional studies, enabling a more complete exploration of data, which we hope has enhanced the robustness of our findings. We addressed participation bias, often a challenge due to systematic attrition (45), by using *multiple imputation by chained equations,* a robust method for handling missing data that strengthens the validity of our results (46). While the assumption that data are *missing at random* is central to our imputation strategy, there is still a possibility that unmeasured variables in our cohort could have affected our results. Nevertheless, by focusing our imputation on the most relevant variables, we have minimized the potential bias to a reasonable extent. Finally, certain limitations should also be acknowledged. First, the use of disease count variables assumes a linear relationship between the number of diseases and their cumulative impact, which may not accurately reflect the true burden of each additional disease. Second, the study's geographical focus on Porto, Portugal, may limit the generalizability of the findings to other populations or cultural contexts. Future research should explore these phenomena in more diverse settings to validate and extend our conclusions.

This study contributes to the existing literature by confirming the significant role of loneliness in influencing MM and highlighting the need for integrated care models that address both psychological and physical health dimensions. Previous research demonstrated that chronic illnesses exacerbate mental health issues (47). However, according to the stress-buffering

hypothesis (48), social support can mitigate these effects by providing emotional and cognitive resources. Recognizing these modifiable social factors as crucial components in developing effective prevention and intervention strategies is vital for better managing the accumulation of chronic diseases and mitigating their adverse effects, particularly in an ageing population.

Our findings further contribute to the literature by differentiating the impacts of loneliness and social isolation on MM, despite their intertwined nature. This distinction is important not only for improving patient outcomes but also for addressing broader implications for healthcare systems. The rising prevalence of MM and its challenges need a comprehensive approach to healthcare delivery that involves multiple sectors and levels of intervention. Effective resource allocation is essential to managing the increased demand for healthcare services due to the management of multiple chronic conditions. Investing in preventive measures, early detection, and timely intervention can help reduce the burden on healthcare systems.

Currently, interventions for individuals with MM are under-researched, partly because these patients are frequently excluded from clinical trials (49). Moreover, medical education and care often focus on managing single-disease patients, despite the growing need for healthcare professionals to support patients with MM through personalized, coordinated care.

Conclusion

This study highlights the complex relationship between loneliness, social isolation, and MM in middle-aged and older adults, emphasizing the importance of understanding social determinants in the context of chronic disease. While social isolation, represented by household size, is not consistently linked to all forms of MM, it seems to play a role in the accumulation of metabolic/endocrine diseases. Loneliness, particularly the perception of social isolation captured by the UCLA Social Isolation Dimension, is particularly related with cardiovascular, metabolic-endocrine, and mental and behavioural conditions. This study emphasizes the need for tailored interventions that not only address both the psychological and physical aspects of health in prevention and management of MM, as also differentiates between related yet different psychosocial aspects. A comprehensive approach that integrates social support into chronic disease management could help healthcare systems better manage MM, enhance quality of life, and promote more sustainable healthcare systems.

Declarations

Author contributions: Conception and design: AH; data analysis: SB and MS; data interpretation: SB, AH and MS; writing - original draft preparation: SB; writing - review and editing: SB and AH and JAdT; supervision: AH.

Ethical statement: The Joint Ethics Committee of Hospital S. João and University of Porto Medical School approved this study protocol (CES-320/2016).

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Data availability: Data from the EPIPorto cohort are not publicly available due to privacy or ethical restrictions. The data can be made available for research proposals on request to the EPIPorto Executive Committee (epiporto@med.up.pt). Further information about EPIPorto cohort can be obtained through this website: https://ispup.up.pt/coorte/epiporto/

Conflicts of interests: The authors declare no competing interests.

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Table 1. Sociodemographic and health-related characteristics of EPIPorto cohort (overall and by participation status at Follow-up 5)

	N	%	Overall (N=2485)	Non-participants at Follow-up 5 (N=1649)	Participants at Follow-up 5 (N=836)	*p*
Sex, n (%)	2485	100				0.110
Female			1539 (61.9)	1003 (60.8)	536 (64.1)	
Male			946 (38.1)	646 (39.2)	300 (35.9)	
Age at baseline, Mdn (IQR)	2485	100	53 (42.0-65.0)	58.0 (46.0-69.0)	47 (38.5-54)	<0.001
Marital status, n (%)	2484	99.9				<0.001
Married/Civil union			1682 (67.7)	1080 (65.5)	602 (72.0)	
Single			349 (14.0)	220 (13.3)	129 (15.4)	
Widow			285 (11.5)	237 (14.4)	48 (5.7)	
Divorced/Separated			168 (6.8)	111 (6.7)	57 (6.8)	
Education level, n (%)	2482	99.9				<0.001
Primary or lower			1513 (61.0)	1134 (68.7)	379 (45.3)	
Secondary			320 (12.9)	186 (11.3)	134 (16.0)	
Graduate			649 (26.1)	327 (19.8)	322 (38.5)	
Tobacco consumption, n (%)	2422	97.5				0.060
No			1337 (55.2)	898 (56.6)	439 (52.6)	
Yes			1085 (44.8)	689 (43.4)	396 (47.4)	
Alcohol consumption, n (%)	2422	97.5				0.040
No			440 (18.2)	270 (17.0)	170 (20.4)	
Yes			1982 (81.8)	1317 (83.0)	665 (79.6)	
Physical activity, n (%)	2425	97.6				0.030
No			1576 (65.0)	1058 (66.5)	518 (62.0)	
Yes			849 (35.0)	532 (33.5)	317 (38.0)	
NCC at baseline, n (%)	2479	99.8				<0.001
0			1257 (50.7)	724 (44.1)	533 (63.8)	
1			759 (30.6)	548 (33.4)	211 (25.2)	
2			350 (14.1)	271 (16.5)	79 (9.4)	
3			83 (3.3)	73 (4.4)	10 (1.2)	
≥ 4			30 (1.2)	27 (1.6)	3 (0.4)	
Household composition, n (%)	1680	67.6				<0.001
Living alone			229 (13.6)	158 (17.3)	71 (9.3)	
Living with 1 person			619 (36.8)	402 (43.8)	217 (28.4)	
Living with ≥2 persons			832 (49.6)	354 (38.9)	477 (62.3)	
Loneliness, Mdn (IQR)	781	31.4	-	-	22 (18-29)	
Social Isolation dimension			-	-	15 (12-19)	
Affinities dimension			-	-	7 (5-10)	

Note: Percentages may not sum to 100 due to rounding
Mdn: Median; IQR: Interquartile range; NCC: Number of chronic conditions

Table 2. Prevalence of chronic conditions at follow-up 5 (number of chronic conditions; subgroup of chronic conditions; conditions by body system)

Number of conditions	Sum of conditions n (%)	Subgroup of conditions* n (%)	Cardiovascular conditions n (%)	Metabolic/endocrine conditions n (%)	Mental/behavioural conditions n (%)	Musculoskeletal conditions n (%)
0	296 (35.0)	365 (44.0)	491 (59.0)	691 (83.0)	754 (90.0)	781 (93.0)
1	302 (36.0)	300 (36.0)	298 (36.0)	142 (17.0)	78 (9.3)	53 (6.3)
2	165 (20.0)	132 (16.0)	40 (4.8)	3 (0.4)	3 (0.4)	2 (0.2)
3	49 (5.9)	29 (3.5)	6 (0.7)	-	1 (0.1)	-
≥4	24 (2.9)	10 (1.2)	1 (0.1)	-	-	-

Note: Percentages may not sum to 100% due to rounding

***** Cardiovascular, Metabolic/endocrine, Mental/behavioural, Musculoskeletal

Table 3. Association between Social isolation and Loneliness with different multimorbidity outcomes (number of chronic conditions; subgroup of chronic conditions; conditions by body system)

	Adjusted Relative Risk - aRR (95% CI) *					
	Number of chronic conditions	Subgroup of chronic conditions**	Cardiovascular conditions	Metabolic and endocrine conditions	Mental and behavioural conditions	Musculoskeletal conditions
Social Isolation						
Living alone	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)	1 (REF)
Living with 1 person	1.01 (0.91-1.12)	1.12 (0.96-1.32)	1.04 (0.90-1.20)	1.27 (0.96-1.68)	1.23 (0.94-1.61)	1.11 (0.87-1.41)
Living with ≥2 persons	1.06 (0.92-1.21)	1.21 (0.97-1.50)	1.12 (0.93-1.34)	**1.50 (1.11-2.02)**	1.12 (0.75-1.68)	1.28 (0.78-2.08)
Loneliness* **						
Total score	1.04 (0.99-1.08)	**1.13 (1.05-1.21)**	1.08 (0.99-1.17)	1.11 (1.00-1.23)	**1.25 (1.11-1.40)**	1.14 (0.99-1.32)
UCLA-SI	1.06 (1.00-1.13)	**1.20 (1.08-1.35)**	**1.17 (1.05-1.32)**	**1.20 (1.05-1.37)**	**1.29 (1.07-1.56)**	1.19 (0.99-1.42)
UCLA-A	0.99 (0.91-1.07)	0.97 (0.74-1.26)	0.87 (0.68-1.11)	0.95 (0.71-1.29)	1.32 (0.81-2.14)	1.14 (0.72-1.79)

* Mutually adjusted for loneliness, social isolation, age, sex, and education

** Cardiovascular, metabolic and endocrine, mental and behavioural and musculoskeletal conditions

*** Measured with the UCLA Loneliness Scale. For the sake of interpretation, UCLA scores were divided by 10; therefore, the relative risks are referring to a change of 10 points in the UCLA scale.

UCLA-SI: UCLA social isolation dimension

UCLA-A: UCLA affinities dimension

Supplementary material 1. Table with Principal Component Analysis loadings and communalities by body system, for each evaluation moment

Evaluations	Body Systems	PC1	h2	u2
Baseline	Cardiovascular	**0.73**	0.53248	0.47
	Metabolic and Endocrine	**0.52**	0.27033	0.73
	Respiratory	0.23	0.05434	0.95
	Neurological	0.02	0.00026	1.00
	Cancer	-0.11	0.01167	0.99
	Mental and Behavioural	-0.02	0.00041	1.00
	Musculoskeletal	**0.56**	0.31166	0.69
	Digestive	-0.13	0.01734	0.98
	Urogenital	0.10	0.00905	0.99
	Eye	0.14	0.01914	0.98
	Ear	0.05	0.00252	1.00
	Congenital	0.10	0.01023	0.99
Follow-up 1	Cardiovascular	**0.57**	0.33	0.67
	Metabolic and Endocrine	0.37	0.13	0.87
	Respiratory	0.32	0.10	0.90
	Neurological	0.18	0.034	0.97
	Cancer	0.23	0.053	0.95
	Mental and Behavioural	**0.49**	0.24	0.76
	Musculoskeletal	**0.70**	0.49	0.51
	Digestive	0.19	0.036	0.96
	Urogenital	0.21	0.046	0.95
	Haematological	0.11	0.012	0.99
	Eye	0.22	0.050	0.95
	Ear	0.00	0.000012	1.00
	Congenital	0.01	0.00015	1.00
Follow-up 2	Cardiovascular	**0.69**	0.48143	0.52
	Metabolic and Endocrine	**0.48**	0.22748	0.77
	Respiratory	0.26	0.06843	0.93
	Neurological	0.14	0.01952	0.98
	Cancer	0.20	0.04188	0.96
	Mental and Behavioural	**0.43**	0.18831	0.81
	Musculoskeletal	**0.64**	0.40535	0.59
	Digestive	0.05	0.00295	1.00
	Urogenital	0.14	0.01864	0.98
	Haematological	-0.05	0.00252	1.00
	Eye	0.02	0.00048	1.00
	Ear	0.18	0.03412	0.97
Follow-up 5	Cardiovascular	**0.52**	0.27051	0.73
	Metabolic and Endocrine	**0.58**	0.33412	0.67
	Respiratory	0.34	0.11712	0.88
	Neurological	0.30	0.08918	0.91
	Cancer	-0.19	0.03735	0.96
	Mental and Behavioural	-0.04	0.00157	1.00
	Musculoskeletal	0.04	0.00176	1.00
	Digestive	-0.02	0.00049	1.00
	Urogenital	0.12	0.01363	0.99
	Haematological	0.32	0.10207	0.90
	Eye	0.36	0.13165	0.87
	Ear	**0.45**	0.20647	0.79
	Congenital	0.05	0.00222	1.00

PC1: Principal component 1 loading; h^2: communality; u^2: uniqueness

Supplementary material 2. UCLA loneliness scale - 16 item - Portuguese version (Pocinho M, Farate C 2005)

	Frequently	Sometimes	Rarely	Never	
1 – I am unhappy doing so many things alone	4	3	2	1	UCLA-A
2 – I have nobody to talk to	4	3	2	1	UCLA-A
3 – I lack companionship	4	3	2	1	UCLA-A
4 – I feel as if nobody really understands me	4	3	2	1	UCLA-A
5 – There is no one I can turn to	4	3	2	1	UCLA-SI
6 – I am no longer close to anyone	4	3	2	1	UCLA-SI
7 – My interests and ideas are not shared by those around me	4	3	2	1	UCLA-SI
8 – I feel left out	4	3	2	1	UCLA-SI
9 – I feel completely alone	4	3	2	1	UCLA-A
10 – I am unable to reach out and communicate with those around me	4	3	2	1	UCLA-SI
11 – My social relationships are superficial	4	3	2	1	UCLA-SI
12 – No one really knows me well	4	3	2	1	UCLA-SI
13 – I feel isolated from others	4	3	2	1	UCLA-SI
14 – I am unhappy being so withdrawn	4	3	2	1	UCLA-SI
15 – It is difficult for me to make friends	4	3	2	1	UCLA-SI
16 – I feel shut out and excluded by others	4	3	2	1	UCLA-SI

UCLA-A: UCLA affinities dimension
UCLA-SI: UCLA social isolation dimension

Supplementary material 3. Loneliness scores by household size categories

Variable	N	Living alone Median (IQR)	Living with 1 person Median (IQR)	Living with ≥2 persons Median (IQR)	*p*
UCLA - total score	714	22.0 (9.5)	23.0 (11.2)	22.0 (10.0)	0.39
UCLA - SI	715	15.0 (6.0)	15.0 (8.0)	14.0 (6.0)	0.34
UCLA -A	732	7.00 (3.00)	8.00 (5.00)	7.00 (5.00)	0.72

UCLA-total score: UCLA loneliness scale total score
UCLA-SI: UCLA social isolation dimension
UCLA-A: UCLA affinities dimension

Conclusion

The findings of this dissertation highlight the significant role that social isolation and, particularly, loneliness play in shaping multimorbidity, suggesting that they may influence the onset and development of multiple chronic conditions. Multimorbidity is consistently associated with other unfavourable health outcomes, including higher mortality rates, diminished quality of life, and increased healthcare utilization. While much existing research focuses on the total number of chronic conditions, our study emphasizes the importance of understanding the specific types of conditions involved in multimorbidity and how they intertwine with different aspects involving interpersonal relationships. The findings show an independent influence of both social isolation and the subjective experience of loneliness.

One of the main challenges in multimorbidity research is the lack of standardized definitions and measurement methods, complicating comparisons between studies and limiting the development of targeted interventions. This variability emphasizes the need for standardized methodologies to create more effective strategies. Recognizing that multimorbidity is not a random aggregation of diseases but a set of patterns influenced by biological, psychological, and social factors opens opportunities for personalized interventions. As populations age and the burden of chronic diseases increases, addressing modifiable risk factors like loneliness and social isolation as related but associated with different outcomes, can improve health and quality of life. Addressing social isolation and loneliness separately in healthcare protocols has the potential to reduce healthcare costs and enhance system efficiency by implementing more effective interventions.

Health education plays an essential role in managing social isolation and loneliness at different levels. On the individual level, besides informing patients that social connection benefits their health, individuals must also be equipped with the tools to act on this knowledge. Self-management education, an essential component of health education, empowers individuals with multimorbidity to take an active role in managing their conditions. By improving self-efficacy, patients are better positioned to create and maintain meaningful relationships, which is essential for mitigating the psychological and emotional impact of loneliness.

Engaging families is equally important. Raising awareness among family members about the physical and psychological health benefits of their presence and support can improve patient outcomes. Additionally, the use of eHealth tools provides individuals with access to online

community groups and resources, particularly benefiting those with smaller social networks. Since socially isolated individuals are less likely to adhere to treatment plans or engage in preventive health behaviours, healthcare professionals must play a key role in helping patients recognize the impact of loneliness on their health. Professionals should also guide patients in adopting strategies to overcome these challenges.

Ultimately, by integrating psychosocial aspects such as social isolation and loneliness into the prevention and management of multimorbidity plans, preventive strategies and better healthcare protocols can improve health outcomes. This approach is essential for promoting healthier aging, enhancing quality of life, and creating more sustainable healthcare systems.

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