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Multimorbidity and functional impairment—bidirectional interplay, synergistic effects and common pathways

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Abstract

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This review discusses the interplay between multimorbidity (i.e. co-occurrence of more than one chronic health condition in an individual) and functional impairment (i.e. limitations in mobility, strength or cognition that may eventually hamper a person's ability to perform everyday tasks). On the one hand, diseases belonging to common patterns of multimorbidity may interact, curtailing compensatory mechanisms and resulting in physical and cognitive decline. On the other hand,

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physical and cognitive impairment impact the severity and burden of multimorbidity, contributing to the establishment of a vicious circle. The circle may be further exacerbated by people's reduced ability to cope with treatment and care burden and physicians' fragmented view of health problems, which cause suboptimal use of health services and reduced quality of life and survival. Thus, the synergistic effects of medical diagnoses and functional status in adults, particularly older adults, emerge as central to assessing their health and care needs. Furthermore, common pathways seem to underlie multimorbidity, functional impairment and their interplay. For example, older age, obesity, involuntary weight loss and sedentarism can accelerate damage accumulation in organs and physiological systems by fostering inflammatory status. Inappropriate use or overuse of specific medications and drug–drug and drug–disease interactions also contribute to the bidirectional association between multimorbidity and functional impairment. Additionally, psychosocial factors such as low socioeconomic status and the direct or indirect effects of negative life events, weak social networks and an external locus of control may underlie the complex interactions between multimorbidity, functional decline and negative outcomes. Identifying modifiable risk factors and pathways common to multimorbidity and functional impairment could aid in the design of interventions to delay, prevent or alleviate age-related health deterioration; this review provides an overview of knowledge gaps and future directions.

Keywords

multimorbidity; physical function; cognitive function; ageing

Introduction

In recent decades, multimorbidity – the co-occurrence of more than one chronic health condition in an individual – has emerged as a major challenge for healthcare systems [1], both in high-income countries and in low- and middle-income countries, where populations are ageing fastest [2]. In high-income countries, up to 20% of the population experiences multimorbidity before the age of 40 years [3]. Prevalence then sharply increases, reaching 75% at 70 years, after which it remains relatively stable, probably because of selective mortality [4]. The absolute number of people affected by multimorbidity is expected to double by 2035, and at least two-thirds of the gain in life expectancy above 65 years will be spent with four or more chronic conditions [5].

Both the number of people with multimorbidity and the prevalence of multimorbidity seem to have increased in recent years [6], and greater increases are documented in more recent birth cohorts [7]. The rise has been mainly driven by population ageing and longer survival of people with chronic conditions. The mortality rate from conditions such as stroke, myocardial infarction and diabetes is lower than in the past. Thus, more diseases accumulate in those who survive. The use of more sensitive diagnostic procedures, better control of risk factors like hypertension and improvements in detecting and recording chronic disorders may also have contributed to the increasing prevalence of multimorbidity [6].

Multimorbidity leads to physical decline, and people with more conditions, more severe disease and specific disease patterns experience steeper deterioration [8]. People with

multimorbidity are also more likely to have poorer cognitive status [9] and worse quality of life in both midlife [10] and old age [11] than those without multimorbidity. In a meta-analysis conducted in 2016, older adults with multimorbidity were 44% more likely to die during follow-up than those with no or only one chronic disease [12]. According to a large collaborative study involving 1.2 million participants, any combination of co-occurring cardio-metabolic conditions was associated with a multiplicative mortality risk [13]. The impact of multimorbidity on individuals' health profiles surpasses the impact we would expect from the summed effect of single conditions. This nonlinear pattern may be further exacerbated by a continuous imbalance between illness and treatment burden and the ability/resources of people with multimorbidity to cope with such burden, which leads to a vicious cycle of breakdowns in care, self-care and health outcomes [14].

Limitations in physical and cognitive function due to multimorbidity decisively affect people's illness and treatment burden and their response capacity, which may further increase multimorbidity [15, 16]. Thus, assessing their health requires considering not only specific medical diagnoses and functional status, but also the interaction between the two. This approach is likely to provide more information about people's baseline risk for poor outcomes, responsiveness to treatment and vulnerability to the adverse effects of treatment [17]. Moreover, because the same mechanisms are likely to underlie multimorbidity and functional deficits, the traditional idea of a causal pathway that leads from multimorbidity to functional impairment is somewhat misleading. Instead of a simple linear pathway, a multimorbidity-functional impairment circle is probably a better representation of the health and social care needs of adults, particularly older adults.

The objective of this review was to summarize the scientific evidence on: (i) the interplay between multimorbidity and impairment in both physical and cognitive function, as well as potential synergistic effects of the interplay on health-related outcomes, and (ii) the major risk factors shared by multimorbidity and functional impairment. The ultimate goal is to provide a solid rationale for integrating and measuring both constructs in research and clinical practice.

Methodological considerations

This narrative literature review is based on the authors' knowledge of the current literature, their expertise in the field and a discussion panel on the latest major findings on multimorbidity and functional decline that took place during a 2-day meeting in Stockholm in May 2018. The meeting included a symposium at which the background to the topic was elucidated and a workshop with 18 multidisciplinary experts from North America and Europe with backgrounds in geriatrics, primary care, public health and health services research, epidemiology, and pharmacy/pharmacology. The authors surveyed the literature published over the last two decades, making sure that key results from population-based longitudinal studies were included. As the aim was to summarize main findings and suggest new research avenues, the definitions of multimorbidity, physical function and cognitive function were not restricted. Table 1 provides an overview of the definitions and measurements of multimorbidity and functional impairment encountered in the cited literature.

Interplay between multimorbidity and function

Multimorbidity and physical function

In the general adult population, multimorbidity often predicts decline in physical function and loss of independence, which suggests a causal link between these phenomena [18]. With few exceptions, both cross-sectional and longitudinal studies have shown that multimorbidity is associated with poor physical function in older adults [19–21]. In the Maastricht Aging Study (MAAS), the poorer physical functioning that accompanied multimorbidity persisted and seemed to increase over time in older adults [22]. The Kungsholmen Project, which included people 78 years and older living in central Stockholm, showed that on average, those with multimorbidity spent 81% of their remaining years of life with disability [23].

Walking speed and handgrip strength, two measures of physical performance commonly used in geriatric medicine, decrease in the presence of multimorbidity, and older age further strengthens this association [24–26]. This finding highlights the reduced resilience to morbidity in older adults. However, multimorbidity does not fully explain observed age-related differences in physical performance, which suggests that morbidity, as described by the current nosological definition of diseases, is not the only determinant of functional decline [27]. Although studies have not found gender differences in walking speed, multimorbidity seems to have a greater effect on muscle strength and number of impaired ADL in women than men [28, 29]. Women's greater vulnerability to the negative effects of multimorbidity is still not well explained. The results of some studies support the idea that symptom severity and the presence of geriatric syndromes (e.g. falls, urinary incontinence, pain) – independent of multimorbidity – are associated with the development of functional impairment and disability [30, 31]. In fact, multimorbidity may be a mediator between pathophysiological processes and negative health outcomes such as impaired physical function [32].

Rapid accumulation of chronic diseases may be an indicator of accelerated ageing [33]. In line with this finding, analyses of data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) showed that the risk of developing new ADL impairments was more than twice as high in older adults who more rapidly developed multimorbidity than those who accumulated diseases more slowly [34]. Interestingly, women and those with a poorer social network were more susceptible to the detrimental consequences of a fast accumulation of diseases [34].

Diseases that share similar aetiology and pathophysiology can be associated with specific profiles of functional impairment and disability [11, 35]. There is evidence that diseases belonging to common patterns of multimorbidity may interact, curtailing compensatory mechanisms and resulting in more severe functional limitation [36, 37]. According to analyses of data from the SNAC-K population-based study, neuropsychiatric diseases, alone or in association with each other, are major determinants of disability and slow walking speed in older adults, whereas isolated cardiovascular multimorbidity is associated only with a decline in walking speed [38]. Other longitudinal study results support these findings [39–42].

Several parameters of physical function are embedded in the concept of physical frailty, a condition of increased susceptibility to negative events that is characterized by the presence of at least three of the following disorders: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed and weak grip strength [43]. According to a systematic review and meta-analysis, community- dwelling older adults with multimorbidity have twofold higher odds of being frail than those without multimorbidity [44]. That study also showed that more than two-thirds of older adults with frailty have multimorbidity, but less than one-fifth of those with multimorbidity are frail [44]. Once again, multimorbidity appears to be an important – but not the only – determinant of poor functioning.

Although the majority of studies support the idea that multimorbidity plays a causal role in the development of functional impairment and disability, recent findings suggest that the association could be bidirectional. Unfortunately, only a few studies have specifically addressed this hypothesis. According to findings from the Irish Longitudinal Study on Ageing (TILDA), walking speed and handgrip strength are inversely associated with developing multimorbidity and, in general, with accruing new diseases [45]. The idea that better physical fitness may slow the accumulation of chronic diseases is also supported by studies that have observed a link between physical activity and multimorbidity [46–49]. However, because none of these studies was longitudinal, they may be biased by reverse causality; that is, people with multimorbidity could be less physically active because of low fitness. Nevertheless, secondary analyses of data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) showed that a multi-domain intervention that included but was not limited to physical exercise and cognitive training was associated with a reduced risk of developing chronic diseases during a 2-year follow-up [50].

Several studies show that diseases and functional status interact to determine the risk for multiple outcomes. In SNAC-K, the coexistence of multiple cardiovascular, and to a lesser extent, of multiple neuropsychiatric diseases, was associated with an increased risk for all-cause mortality and cardiovascular mortality, but only in older adults with slow walking speed *(D. L. Vetrano, D. Rizzuto, A. Calderon-Larranaga, G. Onder, A. K. Welmer, C. Qiu, R. Bernabei, A. Marengoni, & L. Fratiglioni, under review).* Similarly, in a study from the United States that included older adults with heart failure, those with both functional limitation and multimorbidity were at higher risk for mortality, emergency department visits, hospitalizations and outpatient visits than people free from these conditions or those who only had multimorbidity [51]. In that study, the association between multimorbidity and number of outpatient visits was stronger than the association between functional impairment and number of outpatient visits [51]. Another study from the United States, which used administrative data, showed that older adults with both multimorbidity and mobility limitations used healthcare resources more frequently and intensively than those with only multimorbidity or only mobility limitations [52]. Three longitudinal studies that examined co-occurring multimorbidity and functional impairment have reported that only functional impairment is associated with higher mortality [20, 53, 54]. However, only one study formally tested and showed that functional decline mediates the impact of multimorbidity on

mortality [55]. Finally, two studies suggest that physical activity may mediate the association between multimorbidity and mortality [56, 57].

Multimorbidity and cognitive function

Evidence that multimorbidity can contribute to dementia and cognitive decline has emerged from animal models and from clinical and epidemiological studies [58]. Brain autopsies of people with dementia have identified significant comorbidities [59]. Furthermore, studies show that lower cognitive function is associated with an increased burden of multimorbidity [60, 61], and longitudinal trajectories of cognitive decline and rising multimorbidity seem to co-occur in older adults without dementia [62]. Indeed, multimorbidity and cognition seem to be bidirectionally correlated. The FINGER trial, the first large-scale intervention consisting of diet, physical exercise, cognitive training and vascular risk monitoring to prevent cognitive decline in older adults, was effective not only in preventing cognitive decline in at-risk older adults [63], but also in lowering the risk of developing new chronic diseases during the 2-year follow-up [50].

Observational studies have shown that multimorbidity is associated with all the stages of the cognitive dysfunction continuum, from the preclinical phase [64] to cognitive decline [65], mild cognitive impairment [66] and established dementia [67]. It is even associated with early-onset Alzheimer's disease [68]. One study has reported a dose-dependent relationship between the number of diseases and subjective cognitive impairment [9], a finding consistent with the hypothesis that multiple aetiologies may contribute to cognitive impairment and dementia [69].

Multimorbidity occurs frequently in people with dementia [70]. Data from more than 30 000 patients included in the Swedish National Quality Registry for Dementia (SveDem) show that several cardiovascular comorbidities are typically present at the time of the dementia diagnosis [71], and that one- quarter of patients with dementia are treated with antidepressants [72]. Interest in understanding the relative contribution of comorbid conditions to the development of cognitive impairment and dementia has increased, as this research has the potential to reveal shared mechanisms and provide insight into dementia pathogenesis [73]. Such research might also contribute to improving the prognosis of people with dementia via adequate treatment of comorbidity [73]. Exploratory analyses using diagnostic register data have shown that dementia is part of a pattern of multimorbidity that includes other neurological disorders (e.g. Parkinson's disease, insomnia and mental health problems), cardiovascular diseases (e.g. congestive heart failure, cerebrovascular disease, cardiac arrhythmia) and other diseases (e.g. anaemia, chronic skin ulcers, osteoporosis, thyroid disease, retinal disorders, prostatic hypertrophy) [74–76]. Some of these conditions have an aetiological link (e.g. cerebrovascular disease, thyroid disease), others are likely to be complications (e.g. skin ulcers, insomnia), and others, at least apparently, are not pathophysiologically correlated (e.g. osteoporosis, prostatic hypertrophy) [77].

The coexistence of multimorbidity and cognitive impairment makes it particularly challenging to provide health care, as multimorbidity may speed dementia progression. A recent systematic review provided evidence that somatic comorbidities are associated with a worsening of cognitive, functional and neuropsychiatric symptoms in people with late-onset

Alzheimer's disease [78]. At the same time, the presence of dementia may adversely affect and complicate the clinical care of other conditions in several ways. First, detecting comorbid conditions is especially difficult in people with dementia, as they may be less likely to attend regular appointments or to express discomfort sufficiently. Second, clinicians may focus predominantly on the behavioural and psychological symptoms associated with dementia, and by doing so may fail to diagnose other conditions. In fact, there is some evidence that particular conditions are likely to remain untreated or even undiagnosed in people with dementia, such as vision and hearing problems, diseases of the musculoskeletal system, lipoprotein disorders, hypertension and atrial fibrillation [79, 80]. Finally, cognitive decline and dementia may remain undetected in older adults with severe multimorbidity [81].

Cognitive impairment and multimorbidity interact to impact older adults' health status, quality of life and survival. In a cross-sectional study undertaken in residential care settings in Spain, people with dementia and high comorbidity reported the most compromised health status, especially when vision, oral and genitourinary problems coexisted [82]. The extent of comorbidity was even more important than severity of dementia in precipitating the onset of disability in nursing home residents in western Canada [83].

Additionally, co-occurring multimorbidity and dementia contribute to increased mortality rates. A retrospective population-based cohort study in Canada found that in people with dementia, comorbidity increased the risk for death by 1.5–6.4 [84]. High levels of comorbidity even cancelled the effect of dementia type or severity in predictions of long-term mortality amongst very old patients discharged from a Swiss acute geriatric hospital unit [85].

When multimorbidity and limitations in cognitive function co-occur, people's self-management abilities, their engagement in health-promoting activities and their use of health care might be suboptimal. In a Canadian home care cohort of over 30 000 people with dementia, the risk for hospitalization and emergency department visits increased as the level of multimorbidity rose [86]. Hospital and emergency department visits are particularly detrimental for people with dementia because they are at heightened risk for cognitive and functional decline during and after hospitalization [87]. Increasing numbers of comorbidities were also associated with more primary care visits and prescriptions in a retrospective cohort of incident dementia patients diagnosed in primary care in the United Kingdom [88]. All of this adds to the cost of health care for older adults with multimorbidity and dementia [89].

Main risk factors common to multimorbidity and functional impairment

Biological factors

Chronological ageing is the major risk factor for multimorbidity; both the prevalence and severity of multimorbidity increase exponentially as the body ages [90, 91]. Epidemiological studies, especially those with a longitudinal design, have identified several risk factors for the development and progression of multimorbidity that are independent of chronological age. For example, studies have shown that obese men and women are more likely than those

who are not obese to be affected by multimorbidity and to develop it earlier in life [7, 92]. Overweight and obesity may lead to multimorbidity through multiple mechanisms such as reduced functional capacity and fitness and/or stimulation of inflammation and insulin resistance, all of which are shared risk factors for cardiovascular and non cardiovascular disease and for functional impairment [93, 94]. Counterintuitively, in obese older adults, loss of weight is also associated with increasingly severe multimorbidity [95]. In obese older adults who lose weight, the increase in multimorbidity is mostly accounted for by the development of anaemia and chronic kidney disease [95], which together with weight loss are typical features of the frailty phenotype.

This is consistent with the hypothesis that loss of weight in late life is a consequence and not the cause of quickly deteriorating health status and progressing multimorbidity.

Many studies also report that sedentarism is a risk factor for multimorbidity. The mechanisms behind this association are still uncertain, but sedentarism is a risk factor for all age-associated diseases, from cancer to cardiovascular disease and depression [96, 97]. Whether increasing one's level of physical activity may inhibit the vicious cycle of disease accumulation and prevent or slow the progression of multimorbidity is unknown and should be tested in appropriately designed clinical trials [98–101].

Insight into the possible biological substrate of multimorbidity is provided by emerging evidence that high circulating levels of inflammatory markers, a condition referred to as 'inflammaging', is cross sectionally associated with multimorbidity and predicts steeper rates of multimorbidity development over time [33, 102]. Researchers have proposed that both inflammaging and multimorbidity result from damage that accumulates in organs and physiological systems with age, which challenges organismal reserve capacity and resilience [91, 103–105]. Consistent with this hypothesis, higher resting metabolic rate per kilogram of lean body mass, a recognized biomarker of active resilience and accelerated ageing in animals and in humans, predicts future multimorbidity in older adults [106, 107]. Two additional observations indirectly support this hypothesis: first, weight loss is a strong prognostic factor for mortality in old age [108], and second, the majority of people who die very old experience a substantial decline in weight already in the 3 to 8 years prior to death [109]. The research outlined above suggests that people who develop multimorbidity earlier in life are ageing biologically faster than the general population, a hypothesis that could be tested and may provide information useful to preventing and clinically managing multimorbidity [107].

A small but growing body of evidence suggests that specific mechanisms of biological ageing (i.e. hallmarks of ageing) may impact both global susceptibility to disease and physical functional decline [110–112] (Fig. 1). Recent studies also connect the basic biology of ageing with cognitive decline and late-onset dementia as well as with mobility loss, which suggests that multimorbidity and physical and cognitive decline have a common causal route [113] Common shared mechanisms would be consistent with epidemiological reports suggesting substantial heterogeneity in the rate at which older adults develop and accumulate age-related diseases [114] Thus, some people may develop a susceptibility to multiple diseases and functional impairment earlier than others [90]. Of note, the existence

of shared mechanisms is not contrary to but rather complements the traditional view that diseases, and especially coexisting multiple diseases, cause functional impairment and disability, although their effects may be delayed by redundancy and compensatory strategies (see arrows on the right of Fig. 1) [115].The finding that physical activity protects against both multimorbidity and physical and cognitive functional impairment is also consistent with the hypothesis that biological ageing lies at the root of both. In fact, physical activity is the only intervention that has direct beneficial effects on the mechanisms of biological ageing and on the physical and cognitive deterioration that occur with ageing [116, 117].

Gathering direct evidence of a link between the biology of ageing and the risk for multimorbidity and functional impairment remains problematic, however. Even if the putative biological mechanisms that underlie the ageing process have been identified, measuring them in humans is challenging. Efforts are underway. Recently, researchers have developed an epigenetic biomarker of phenotypic ageing, the DNAm PhenoAge. This biomarker tracks biological ageing and is sensitive to phenotypic deviation from normal ageing [118]. Similarly, the epigenetic age of the prefrontal cortex has been associated with pathology, cognitive impairment and even dementia [119]. Premature changes in these biomarkers are associated with more severe multimorbidity, although the strength of the association is modest, possibly because the effect of specific methylation sites relevant to this outcome is buried by the complexity of the index [119].

Care-related factors

Despite the acknowledged impact of other care-related factors such as hospitalization on functional decline in people with multimorbidity [120], the following section focuses on drug-related problems, which both result from and lead to multimorbidity.

Medications can help preserve function by treating symptoms (e.g. low back pain [121]) and by preventing, stabilizing or slowing the progress of chronic conditions (e.g. hypertension, Parkinson’s disease, dyspnoea, COPD, ischaemic heart disease, osteoporosis, diabetes [122–125]). However, drugs can also promote multimorbidity and functional impairment. First, the coexistence of multiple diseases and symptoms may lead to polypharmacy – the use of multiple medications. More than 50% of people 65 years or older receive five or more medications concomitantly [126]. Polypharmacy increases the risk for drug-drug interactions, especially in older adults [127]. The more coexisting diseases a person has and the more drugs they are prescribed, the more likely drug-drug interactions are to occur [128]. Such interactions increase the risk for adverse drug reactions, which in turn can lead to worse physical and cognitive function.

Second, multiple medications can also lead to drug–disease interactions, which occur when a medication used to treat a disease or symptom has a negative effect on another coexisting health problem [127]. For example, some beta-blockers prescribed for heart disease or hypertension can worsen asthma and mask hypoglycaemia in people with diabetes. In addition, specific diseases may alter medication metabolism. Typical examples are kidney and liver diseases that lead to reduced drug clearance and therefore to a higher risk for adverse drug reactions. The risk for adverse reactions may be further intensified by changes in body composition that are frequently observed in older people (e.g. sarcopenia,

sarcopenic obesity) [129]. Heart failure may also cause changes in pharmacokinetics, including diminished renal and hepatic blood flow, reduced splanchnic blood flow and liver metabolic capacity, hepatic venous congestion, and a reduction in the volume of distribution. A relevant phenomenon related to the complex relationship amongst polypharmacy, adverse drug effects and drug-disease interactions is the prescribing cascade, the process whereby the side effects of medications are misinterpreted as a symptom of a new disease, resulting in further prescriptions [130]. Examples of this phenomenon are the use of anti-Parkinson medications to treat extrapyramidal symptoms caused by antipsychotics and the use of anticholinergic medications to manage urge incontinence due to treatment with cholinesterase inhibitors [131, 132].

Third, several medications can have a direct negative impact on physical or cognitive function, in particular in older adults. The use of anticholinergic drugs is associated with falls, hip fractures, ADL limitations and impaired cognition [133, 134]. Inappropriate medication use is in fact another pathway through which medications might cause functional and cognitive deficits. For example, the inappropriate use of proton pump inhibitors in older adults can cause vitamin B12 deficiency. Vitamin B12 is known to impact cognition, and deficiency reduces calcium absorption, increases fracture risk and is associated with increased mortality [135]. Finally, overtreatment of chronic conditions, often because of excessively strict therapeutic goals, might also lead to negative health outcomes. For example, overtreatment of diabetes in older adults is associated with disability and increased risk for mortality [136].

The relationship between impaired physical and cognitive function and pharmacological treatment of multimorbidity may be bidirectional [137] (Fig. 2). On the one hand, medications might influence the onset of physical and cognitive deficits, as described above; on the other, physical and cognitive function may influence therapeutic choices and medication effects [125]. For example, physical dysfunction can make it hard to manage pill containers, which can lead to reduced adherence to treatment and increased risk for medication errors [138]. Cognitive impairment and dementia can affect decision-making capability, alter treatment benefit and burden, impact medication adherence and cause communication difficulties, including a decreased ability to report adverse effects [139]. Finally, both functional and cognitive impairment are associated with reduced life expectancy, which may limit the beneficial effect of some preventive drugs (e.g. statins, antihypertensives, antiosteoporotics) given that their time-to-benefit might exceed individuals' actual life expectancy [125].

Psychosocial factors

The term 'psychosocial' refers to the influence of social factors on people's minds or behaviours and to the relationship between behavioural and social factors.

Multimorbidity is more common and starts some 10–15 years earlier in people who live in areas of high socioeconomic deprivation than in those who live in more affluent communities [140]. The authors of a 2018 systematic review of 24 studies confirmed this effect [141]. In their meta-analysis, they also found that people with a low level of education had 64% higher odds of multimorbidity than those with a high level of education [141]. The

social patterning of multimorbidity has several important implications. First, it means that multimorbidity contributes to the broad inequalities that exist in many countries and to the high level of premature mortality in people of lower socioeconomic status (SES) [142]. The high prevalence of multimorbidity also contributes to the high levels of prefrailty and frailty seen in deprived areas [143]. Second, health-related quality of life is worse in people of lower SES who have multimorbidity than those of higher SES who have multimorbidity, and this is apparent at a younger age [142]. Third, healthcare use – and hence, healthcare costs – are higher in people with multimorbidity and low SES [144].

As the number of physical conditions a person has increases, so does the person's chance of having a common mental health disorder [141, 145]. There is, however, an important interaction between social factors and psychological factors in this association. People of low SES are substantially more likely to have multimorbidity that includes mental and physical conditions than those of higher SES [141, 146]. This is apparent in all age groups but more pronounced in those of younger age [146]. Such mental-physical multimorbidity exacerbates the effect of SES on service use. For example, unplanned and potentially avoidable hospital admissions rise with increasing levels of physical multimorbidity, and low SES intensifies this rise at all levels of multimorbidity. Mental health problems further increase admissions at all levels of multimorbidity [144]. Moreover, the association between mental health and physical multimorbidity is known to be bidirectional [147]. Not only do increasing numbers of somatic health problems raise the risk of developing mental health problems, but people with mental health problems also have a higher risk of developing multimorbidity over time than those without such problems.

Traditional risk factors, such as smoking, alcohol and diet, are of some importance in the aetiology of multimorbidity, but a recent analysis of data from a longitudinal cohort study in Scotland found that traditional risk factors only explained around 40% of the excess multimorbidity in people of low SES [148]. The remaining 60% is still unexplained but might be attributable to the direct or indirect effects of psychosocial factors such as adverse childhood experiences [149]. Factors such as negative life events, weak social networks and an external locus of control also predict the development of multimorbidity [150–152]. Conversely, a high sense of coherence protects against adverse health outcomes in older adults with multimorbidity [153] and can help mitigate the negative effects of low SES on health [154]. SES also affects brain development and function, which may have implications for the future development of multimorbidity and poor outcomes in people in deprived areas [155].

Psychosocial factors such as social connectedness protect against age-related decline in cognitive function, probably through multiple neurobiological mechanisms. In the Rush Memory and Aging Project, an ongoing longitudinal clinical-pathologic cohort study that began in 1997, a wide array of psychosocial behaviours were independently associated with the subsequent rate of cognitive decline and/or risk for incident cognitive diagnoses [156]. These include trait and state measures of psychological distress, social isolation, social capital, emotional isolation and purpose in life. Using data from the MacArthur Study of Successful Aging, researchers found connections between a range of psychosocial factors and decline in physical function in older adults with different chronic diseases [157]. In that

study, greater emotional support was associated with less decline in physical function in people with cardiovascular disease, and greater social conflict was associated with greater decline in people with hypertension or diabetes. Interestingly, social and psychological factors were unrelated to changes in functioning in those with no chronic conditions.

Conclusion

To date, most studies of the relationship between multimorbidity and functional impairment have focused on the former as a pre condition for the incidence of the latter. Researchers have aimed at identifying risk or protective factors for either multimorbidity or function, but rarely considering both simultaneously. This review summarizes evidence suggesting that using an integrated model will support better framing open questions about the origin and consequences of multimorbidity. In such a model, lifelong biological, care-related and psychosocial factors operate as determinants of the interaction between multimorbidity and both physical and cognitive function (Fig. 3).

Although certain aspects of the topics of multimorbidity and function have been widely investigated (e.g. prevalence, patterns of disease combinations, consequences, effect on healthcare use and costs), information on the common causes of and risk factors for both health constructs is very scarce. Studies that incorporate multimorbidity and function as coexisting and interacting outcomes are even rarer. Thus, we also provide an overview of knowledge gaps and future directions that might help improve our understating of common risk factors upon which interventions can be built (Table 2). We believe the following research questions deserve priority: Is it possible to identify shared modifiable risk factors for multimorbidity and functional impairment? If so, what would be the impact of addressing them in vulnerable people? Should multimorbidity, or a certain level of it, systematically prompt screening for physical and cognitive impairment? What else can we learn from the biology of ageing that may contribute to delaying, preventing, alleviating or reversing age-related multimorbidity and functional impairment?

In the meantime, the integrated assessment of multimorbidity and function – already embedded in instruments like the Health Assessment Tool [158] – should remain the basis of the overall clinical decision-making process, allowing physicians to more easily weigh treatment benefits and risks and patients to make properly informed choices. However, both constructs need to be considered as means towards the goal of patient-centred medicine rather than end goals in and of themselves [159]. We should avoid taxonomic simplification and/or routinization whereby both constructs become simple labels added to patients' medical records, and no subsequent action is taken by healthcare professionals. Instead, such an integrated assessment should lead to measuring each patient's improvement potential and establishing an individualized therapeutic or palliative plan of social and medical care.

From a health policy perspective, the reorganization and reinforcement of primary care will be essential to optimize health outcomes in people with multimorbidity and functional impairment, as it is person-focused and continuous over time. Primary care physicians are well prepared to appraise the interactions between multimorbidity and both physical and cognitive function whilst considering the lifelong effect of biological, care-related and

psychosocial factors, as depicted in our circular diagram in Fig. 3. General practitioners may also play a major role in increasing awareness of the bidirectional interplay and synergistic effects of multimorbidity and functional impairment during their clinical encounters with older patients and their caregivers. Moreover, primary care is ideally suited to orchestrate the multidisciplinary care needed by older people with coexisting multimorbidity and functional limitations, given that it is embedded within local communities, where other social and public health agents coexist.

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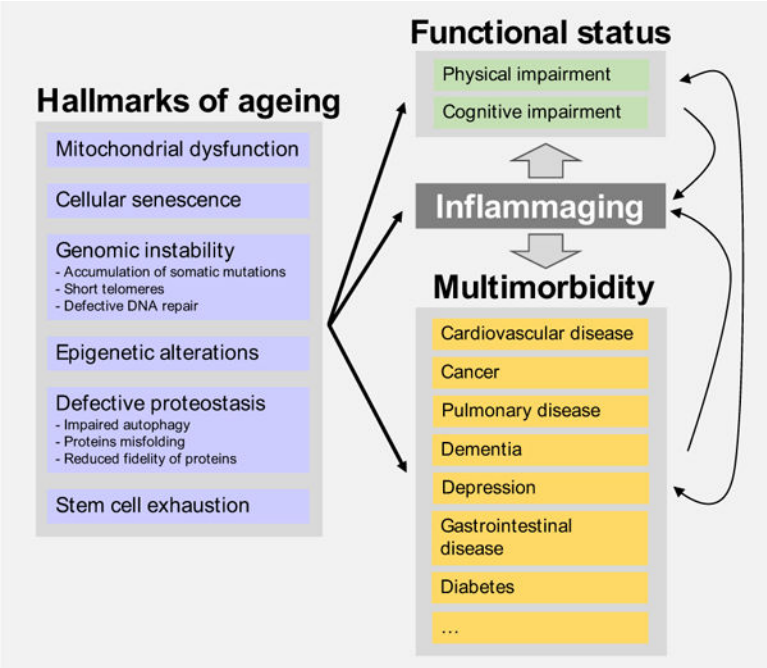

Fig. 1.

Biological mechanisms underlying the bidirectional association between multimorbidity and functional impairment.

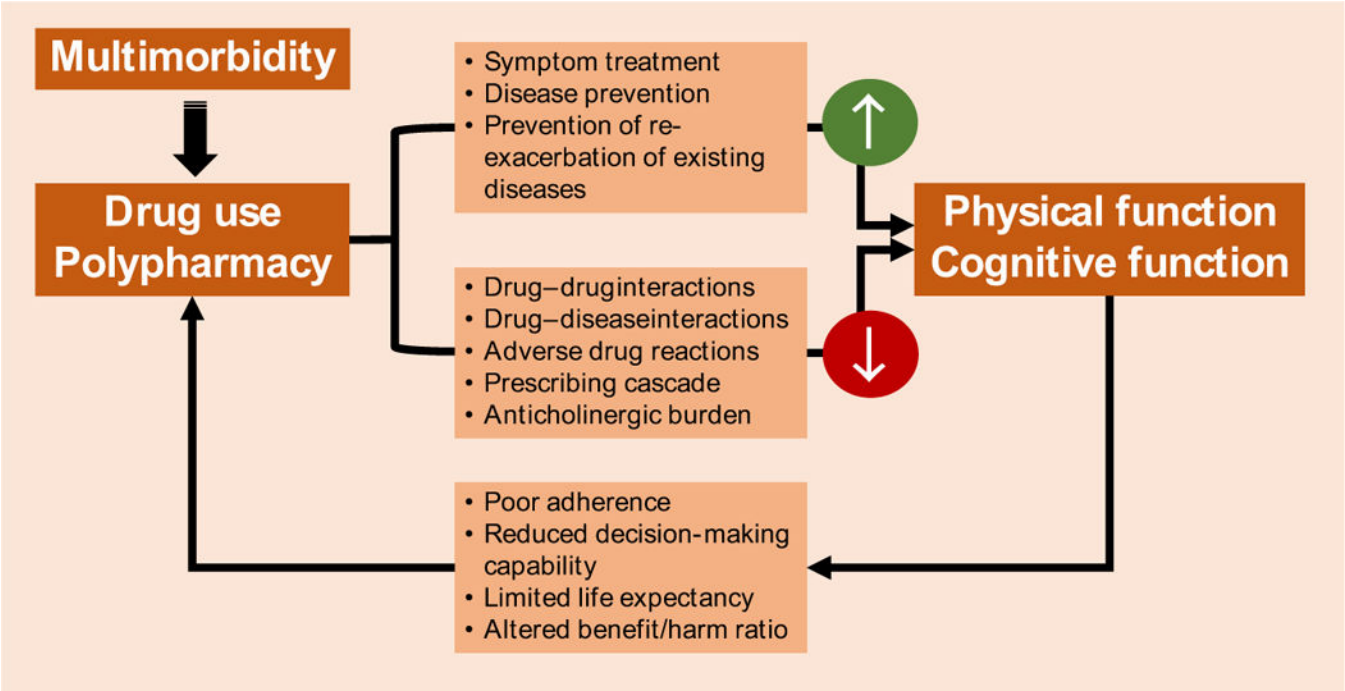

Fig. 2.

Drug-related problems underlying the bidirectional association between multimorbidity and functional impairment.

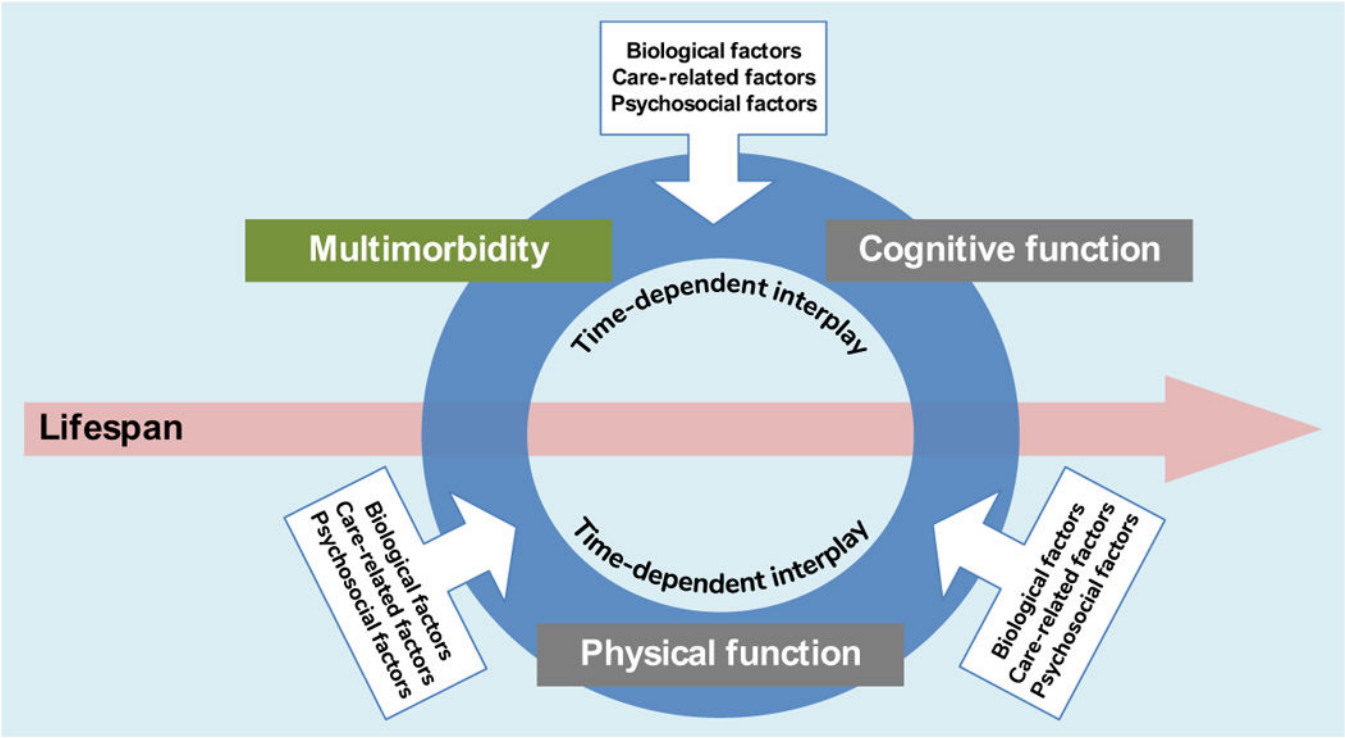

Fig. 3.

Integrated framework for the development of multimorbidity and functional impairment: a proposal for future research.

Table 1

Measures, definitions and operationalizations of multimorbidity, physical function and cognitive function in the cited literature

Measures and definitions	Differences in operationalization
Multimorbidity	
(1) Disease counts Number of diseases on a continuous scale or categorized in accordance with specific cut-offs **(2)** Patterns of diseases Systematic associations amongst diseases defined on the basis of expert criteria or statistical associations **(3)** Weighted indices Scores derived from disease weights obtained for specific outcomes (e.g. Charlson, CIRS) **(4)** Speed of disease accumulation Rate of change in the number of diseases in a given observation period **(5)** Comorbidities of an index disease Combinations of diseases that occur together with the index disorder	Diseases may include: • Chronic or acute and chronic conditions • Symptoms, syndromes and/or risk factors • Conditions selected from specific existing lists or on the basis of a priori criteria such as the prevalence or predictability of specific outcomes • Conditions that were self-reported, diagnosed by a physician or inferred from medication use
Impairment of physical function	
(1) Mobility limitations Limitations in the ability to move around that may eventually impair a person's ability to accomplish daily activities **(2)** Strength limitations Limitations in upper or lower limb muscle strength as defined by specific thresholds **(3)** Limitations in the activities of daily living (ADL) Number of activities that a person can only accomplish with the help of another person	• Mobility may be assessed with objective tests (e.g. usual walking speed) or via self-report (e.g. SF-36) Strength may be objectively measured or inferred from the self-reported ability to perform specific tasks • ADL may include personal ADL (PADL) and instrumental ADL (IADL), counted sepa rately or grouped in an overall score • Measures of mobility and strength may be embedded in a more comprehensive test (e.g. SPPB, frailty phenotype)
Impairment of cognitive function	
(1) Dementia Loss of cognitive function that interferes with daily life and ADL **(2)** Cognitive impairment Difficulty with global cognitive function or specific domains of cognitive function (e.g. memory, decision-making, concentration, learning) that does not interfere with daily life and ADL **(3)** Cognitive decline Decline of global or specific domains of cognitive function over time	• Diagnosis of dementia may be based on neuropsychological assessment by direct clinical examination (e.g. NIA-AA, DSM) or derived from hospital registries • Dementia can be further classified by age of symptom onset (early/late onset), symptom severity (mild/moderate/severe) or demen tia subtype (vascular/mixed/Alzheimer's/ secondary) • Cognitive impairment and decline may be assessed by face-to-face neuropsychological assessment, by telephone interview (e.g. TICS) or reported by the affected person or a proxy • Cognitive impairment and decline may be assessed with global cognitive measures (e.g. MMSE, MOCA, CDR, GDS) or domain specific tests (e.g. digit symbol test for evaluating attention)

ADL, activities of daily living; CDR, Clinical Dementia Rating; CIRS, Cumulative Illness Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Global Deterioration Scale; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging and Alzheimer's Association; PADL, personal activities of daily living; SF-36, 36-Item Short Form Health Survey; SPBB, Short Physical Performance Battery; TICS, Telephone Interview for Cognitive Status.

Table 2

Pathways and risk factors common to multimorbidity and functional impairment: current knowledge

What we know	Knowledge gaps
Biological factors	
• Old age, obesity, involuntary weight loss and sedentarism Pathway: All are risk factors for the burden and severity of multimorbidity, probably because of their effect on levels of circulating inflammatory mediators (i.e. inflammaging) and thus on accelerated damage accumulation in organs and physiological systems	• Specific biological mechanisms of ageing in single individuals have not yet been identi fied
• Ageing-related factors Pathway: Intrinsic biological mechanisms of ageing (e.g. mito-chondrial dysfunction, cellular senescence, defective proteostasis) could be the basis of the bidirectional association between multimorbidity and functional impairment	• Criteria to identify those forms of multi morbidity caused by accelerated biological ageing are lacking, which hampers the development of targeted therapeutic and management interventions
• Epigenetic markers Pathway: Premature changes in epigenetic biomarkers (sensitive to phenotypic deviations from normal biological ageing) are associated with the severity of multimorbidity, providing further support for the hypothesis that there is a link between the biology of ageing and the risk for multimorbidity and functional impair-ment	• Specific clinical trials with outcomes related to the development and progression of mul timorbidity are still rare. An exception is the future TAME study on chronic use of met formin [160]
Care-related factors (i.e. drugs)	
• Polypharmacy Pathway: Drug-drug and drug-disease interactions and the pre scribing cascade (e.g. use of anti-Parkinson medication to treat extrapyramidal symptoms caused by antipsychotics)	• The need for and added value of preventive medicines in people with shortened life expectancy due to multimorbidity and/or functional impairment is poorly understood
• Inappropriate use (e.g. anticholinergic drugs, proton pump inhibitors) or overuse (e.g. antidiabetics) of specific drugs	• The effectiveness of individual drugs in people with multimorbidity and/or func tional impairment, based on numbers needed to treat, is little understood
• Lack of adherence to drug treatment Pathway: Multimorbidity and functional deficits may limit	

What we know	Knowledge gaps
patients' ability to take medications accurately because of prob lems with pill handling. They may also affect decision-making and reporting of adverse effects	• There is wide uncertainty about the impact of drug treatment on functional outcomes (both physical and cognitive) • Few studies have addressed the bidirec tional association between sarcopenia and adverse drug events
Psychosocial factors • Socioeconomic status Pathway: Less than half of the excess multimorbidity in deprived populations is explained by lifestyle; the rest may be due to factors such as adverse childhood experiences, negative life events, weak social networks and an external locus of control • Psychological distress, social isolation, social conflict, emotional isolation and lack of purpose in life Pathway: The association between these factors and decline in physical and cognitive function in old age could be due to poor self-management; amotivation; risk factors such as smoking, alcohol, poor diet and low exercise levels; and/or direct effects on inflammation	• The role of psychosocial factors in multi morbidity, functional impairment and neg ative outcomes needs to be better delineated. Specifically, little is known about the direction of the associations and potential moderating or mediating effects • Although there is some evidence that social interventions such as social prescribing may improve anxiety, depression and phys ical activity [161], the influence of such approaches on functional impairment or mortality is unknown • Clinical trials performed specifically on people living in deprived areas and incor porating modifiable psychosocial factors are rare. Recent primary care-based complex interventions focusing on priority goal set- ting [162] and patient-centredness [163] could serve as examples