The complex interplay between depression and multimorbidity in late life: risks and pathways

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ABSTRACT

Multimorbidity and depression are complex multifactorial conditions with major implications for older individuals, their families, and healthcare providers. In this scoping review, we aimed to 1) review findings from longitudinal epidemiological studies investigating the association between multimorbidity and depression; 2) identify potential mechanisms linking multimorbidity and depression; and 3) discuss challenges to advance the research field. Overall, evidence emerging from longitudinal studies supports a bidirectional association between the two conditions, although studies are methodologically heterogeneous in terms of design, inclusion criteria, measurement of multimorbidity and depression, and length of follow-up. A variety of biological, psychosocial, and care-related drivers may regulate the transition from multimorbidity to depression, and the other way around, although these mechanisms are yet to be explicitly verified. Further research is required to unravel the intricate interplay between multimorbidity, depression, their common drivers, and precipitating factors underlying the relationship between the two conditions. Understanding these processes will inform strategies aimed at promoting mental and physical health during aging.

1. Introduction

Multimorbidity and depression represent two critical challenges for the aging societies. Multimorbidity, defined as the co-occurrence of multiple chronic diseases in the same person, affects the majority of older individuals, vastly impairing functional status, quality of life, and contributing to mortality (Calderon-Larranaga and Fratiglioni, 2019; Nunes et al., 2016; Vetrano et al., 2018). Depression, on the other hand, is a common mental health condition, with a heterogenous clinical presentation and a strong negative impact on several aspects of the lives of older people and their caregivers (Alexopoulos, 2005, 2019). Epidemiological research consistently shows that multimorbidity and depression often coexist; their co-presence seems to trigger a cascade of disturbances that culminates into an even greater strain in terms of disability and mortality (Koyanagi et al., 2018; Quíñones et al., 2016, 2018). Thus, both conditions are high priority targets for aging research and clinical practice.

From a geroscience perspective, the aging process involves the disruption of several biological processes acting at cellular and molecular levels, such as mitochondrial dysfunction, oxidative stress, telomere shortening and cellular senescence (Ferrucci et al., 2020). In the face of depleted compensatory mechanisms, these pro-aging factors have been linked with accelerated disease development, suggesting that multimorbidity may be viewed as one of the phenotypic hallmarks of biological aging (Fabbri et al., 2015b). Similarly, studies employing various measures of biological age suggest that depression may be one of the expressions of the accelerated deterioration of neuronal structures (Brown et al., 2018; Verhoeven et al., 2014). Indeed, depression in late life has been viewed as the most common clinical manifestation of dysfunctions occurring in neural networks involved in the regulation of mood (Alexopoulos, 2019; Andreescu et al., 2019; Gonio et al., 2020; Naismith et al., 2012). Thus, late life multimorbidity and depression...
April 31, 2020. We performed the following search common for both multimorbidity and depression that may regulate the (multiple chronic disease OR multimorbidity OR somatic disease OR depression). A diversity of factors, ranging from inflammation to sedentary behavior, as well as social deprivation have been independently associated with the onset of both conditions, likely amplifying the effects of accelerated aging (Dekhtyar et al., 2019; Dugravot et al., 2020; Kivimaki et al., 2017). These individual and environmental influences, grouped into broader domains comprising biological, psychosocial, and care-related factors during the entire life-course, may be also relevant for regulating the bidirectional feedback loops between multimorbidity and depression in the context of advancing disturbances associated with accelerating aging (Patel and Chatterji, 2015).

The literature on multimorbidity and depression has witnessed an expansion in the past two decades. A recent meta-analysis of 40 cross-sectional studies has shown that depression is more likely in those with multimorbidity, compared to those with one or no physical diseases (Read et al., 2017). Evidence from longitudinal studies, however, is needed not only to enable a more robust assessment of the temporal relationship between these conditions, as well as the direction of any potential causal link between them, but also to take a full account of predisposing and facilitating influences of biological, psychosocial, and care-related factors, potentially governing the conversion from multimorbidity to depression and the other way around. Unfortunately, such evidence has been insofar less consistent, leaving open several questions surrounding directionality and mechanisms between depression and somatic diseases. Nonetheless, it is particularly important to critically appraise the literature on the association between multimorbidity and depression, as existing inconsistencies may be due to the heterogeneity of study populations and methodological approaches, including the length of follow-up, and the operationalization of both multimorbidity and depression.

Given these premises, the overarching objective of this scoping review is to assess the bidirectional association between multimorbidity and depression. Specifically, we aim to: i) summarize and critically evaluate the most relevant epidemiological evidence from longitudinal studies on the association between multimorbidity and depression; ii) present a framework of biological, psychosocial, and care-related factors common for both multimorbidity and depression; iii) propose future directions for research on multimorbidity and depression that would advance the understanding of underlying biological mechanisms, prevention, and treatment of both multimorbidity and depression.

2. Methods

The epidemiological evidence provided in this scoping review is based on articles published in PubMed between January 1, 2000 and April 31, 2020. We performed the following search “depress” AND (multiple chronic disease OR multimorbidity OR somatic disease OR multiple chronic condition) AND (prospective OR cohort OR longitudinal OR follow up)”, which yielded 2021 hits at the time of the search. In addition, studies were also retrieved from unstructured searches in online databases, or by consulting bibliographies of relevant articles. To be included in the section on the epidemiological evidence on the association of multimorbidity and depression, we considered the following inclusion criteria: 1) longitudinal design; 2) operationalization of multimorbidity as co-occurrence of multiple chronic conditions; 3) depression as diagnosed with standardized criteria or validated symptom rating scale cut-offs; 4) articles in English. Articles were selected in the final reference list based on their relevance to the topic. A flowchart of the study selection process is available as supplementary material (Supplementary Figure).

3. Summary of epidemiological evidence on bidirectional associations

Epidemiological evidence from prospective studies investigating the association between multimorbidity and depression is summarized in Table 1. To our knowledge, no study has simultaneously investigated both hypotheses, i.e. multimorbidity leading to depression and depression leading to multimorbidity. Thus, the evidence presented in this review stems from studies investigating the depression-multimorbidity association in one direction at a time.

3.1. From multimorbidity to depression

The first part of Table 1 (see Supplementary Table for details) summarizes 14 selected longitudinal studies on the relationship between multimorbidity and the development of depression. Eleven studies included individuals from population-based cohorts aged 55 years or older, while three investigated mid-life samples. Follow-up time ranged considerably, from three months to 11 years in all studies. A variety of operationalizations of depression were employed, including clinical diagnosis with standardized criteria (e.g. DSM-V or ICD-10), or multiple validated cut-offs of depressive rating scales (e.g. CES-D). Similarly, several definitions of multimorbidity were observed, such as the count or the presence of two or more chronic diseases, as well as the use of clusters of conditions based on the pathophysiological background (e.g. cardiovascular). A variety of study designs were used, which further hinders any direct comparison between studies. Despite considerable methodological heterogeneity, the evidence suggested that individuals with a higher somatic disease burden were more likely to experience depression later in life. In particular, the presence of multiple chronic diseases was associated with higher incidence of depressive disorders (Beckman et al., 2001; Chang et al., 2016; Patten, 2001; Schoevers et al., 2006; Wang et al., 2010; Yao et al., 2020), as well as worse depressive trajectories, although the latter result was supported by fewer findings (Fonda and Herzog, 2001; Hsu and Hsu, 2013; Lai et al., 2018). Interestingly, some studies also investigated multimorbidity in individuals with depression, suggesting that a detrimental trajectory of depression’s clinical course may be partly due to a higher somatic disease burden (Beckman et al., 2001; Geerlings et al., 2000; Gerrits et al., 2013; Hegeman et al., 2017). Studies investigating the role of specific clusters of diseases seemed to indicate that cardiovascular and musculoskeletal multimorbidity can particularly impact the development and the course of depression (Gerrits et al., 2013; Hegeman et al., 2017; Hsu and Hsu, 2013). However, a recent study operationalizing multimorbidity with exploratory factor analysis suggested that multiple disease patterns may be associated with an increased risk of incident depression, possibly suggesting a complex interaction among diseases and the underlying pathophysiology of depression (Yao et al., 2020).

3.2. From depression to multimorbidity

Fewer studies have prospectively explored the relationship between depression and the development of multimorbidity. As presented in Table 1, all 7 were characterized by younger populations, ranging from young adulthood to midlife. This is consistent with the epidemiology of depression, where first onset typically affects individuals between the third and fourth decade (Malhi and Mann, 2018). Both depression diagnoses and depressive rating scales were used to operationalize depression. Similarly, the co-occurrence of chronic conditions was defined with multiple operationalizations from lists of self-reported diseases. Follow-up time for the studies spanned from 6 to 20 years. Of note, two studies stemming from the same cohort involved only women (Xu et al., 2019a, b). Overall, the presence of depression or
depressive symptomatology was associated with higher rates of incident somatic multimorbidity over the follow-up (Gaspersz et al., 2018; Holahan et al., 2010; Karakus and Patton, 2011; Momen et al., 2020; Poole and Steptoe, 2018; Xu et al., 2019a, b). Early life mental wellbeing seemed to affect later development of multimorbidity, as women in their 20’s with worse psychological trajectories experienced higher rates of somatic diseases in their 30’s (Xu et al., 2019b). Using the same cohort, another study showed that the incidence of multimorbidity dramatically increased after the onset of a depressive episode in middle aged women (Xu et al., 2019a). Two studies explored the development of specific clusters of multimorbidity in relation to depression. A recent large study representative of the Danish population reported an increased risk of developing several groups of medical conditions in individuals diagnosed with mood disorders, a finding also suggested by a previous smaller study (Momen et al., 2020; Poole and Steptoe, 2018). Last, depressive burden, even in the absence of clinical depression, appeared to be linked with the development of multimorbidity, especially in individuals presenting mood and somatic symptoms (Gaspersz et al., 2018).

### 4. Putative drivers of multimorbidity and depression

Oftentimes, the same biological, psychosocial, and care-related drivers are commonly implicated in both depression and multimorbidity: their interacting influences likely disrupt multiple biological systems, contributing to the onset of each condition. Furthermore, the very same biological, psychosocial, and care-related factors may also precipitate the multimorbidity–depression relation, promoting the transition from one syndrome to another (Fig. 1). Here we present some of the potential mechanisms underlying the bidirectional association between multimorbidity and depression.

#### 4.1. Biological factors

**Inflammation.** An imbalanced immune system in favor of proinflammatory cytokines has been identified as one of the key axes to...
phenotypic aging and multimorbidity (Fabbrì et al., 2015a; Franceschi et al., 2018). Most chronic diseases are in fact characterized by a high inflammatory burden, which is detrimental for both physical and cognitive functions (Lai et al., 2017; Verghese et al., 2011), and further accelerates disease accumulation (Burman et al., 2019). Chronic inflammation may be further promoted by early psychosocial stress, poor diet and physical inactivity, factors that often co-occur in both multimorbidity and depression (Berk et al., 2013). Several lines of evidence suggest that inflammation may cause depression. First, diseases characterized by increased inflammatory markers, including metabolic syndrome or autoimmune diseases, have been linked with an heightened risk of developing depression (Dregan et al., 2019; Repoussi et al., 2018). Moreover, signs of dysregulated immune functions are also consistently found in depressed subjects, even at younger ages, both in peripheral systems and in the central nervous system, generally indexed by altered cytokines levels (Miller et al., 2009). Hence, (neuro)inflammation is increasingly considered a putative causative factor of depression (Enache et al., 2019), mainly through negative pleiotropic effects on neurogenesis function, neurogenesis and neuroplasticity, especially at the level of neural networks that underlie the regulation of mood (Alexopoulos and Morimoto, 2011; Miller and Raison, 2016). Most importantly, anti-inflammatory agents have shown some efficacy against depression, although this effect may be limited to those subtypes characterized by heightened inflammation (Köhler-Forsberg et al., 2019; Köhler et al., 2014; Leighton et al., 2018).

Vascular burden. The vascular depression theory was developed upon observation of a higher prevalence of cardiovascular risk factors and vascular brain lesions in older patients with mood symptoms and poor response to antidepressants (Alexopoulos et al., 1997, 2008). Nearly two decades later, the vascular depression hypothesis has been largely confirmed: several markers of peripheral and cerebral vascular dysfunction have been consistently associated with late life depression (van Agtmaal et al., 2017), particularly hyperintensities in subcortical gray matter, deep white matter, or periventricular areas (Alexopoulos, 2019). Likewise, high cardiovascular burden due to atherosclerosis, vascular stiffness, and endothelial dysfunction is linked to the onset and progression of most chronic diseases, thus contributing substantially to multimorbidity (Ferrucci and Fabbri, 2018). Control of vascular risk factors through medication and health-promoting behaviours such as physical activity has been proposed as a key target for prevention of both depression and somatic diseases (Murri et al., 2015; Marengoni et al., 2018).

Metabolic burden. Impairments in multiple endocrine systems are also intimately linked to depression and accumulation of chronic conditions. For instance, dysregulation of hypothalamic-pituitary-adrenal (HPA) axis function is one of the most studied explanatory links between chronic stress, allostatic load, and brain-body alterations (McEwen, 2007). Hyperactivity of the HPA axis has been demonstrated to cause brain structural changes which may translate into mood alterations and cognitive symptoms (Belvederi Murri et al., 2014; Geerlings and Gerritsen, 2017; McEwen, 2003). Similarly, exaggerated stress responses can exert detrimental effect on nearly all body systems, facilitating the onset of several chronic diseases (Martocchia et al., 2016). Diabetes and visceral obesity, in particular, are two key components of metabolic syndrome that could follow chronic HPA axis hyperactivity, and may further increase the risk of developing depression and chronic physical diseases (Moulton et al., 2015; Penninx et al., 2013).

4.2. Psychosocial factors

Socio-economic status (SES). Low SES consistently predisposes to poor health. Among individuals with lower SES, the co-occurrence of multimorbidity and depression is particularly high (Ashworth et al., 2019; Barnett et al., 2012; Charlton et al., 2013). Individuals with low SES are more likely to live in deprived neighbourhoods, where the quality of healthcare may be lower, crime may be higher, and housing may be poorer (Diez Roux and Mair, 2010; Mercer and Watt, 2007). Manual occupations typically involve more psychosocial and emotional demands, whereas physical work may increase the risk of chronic pain, injuries and chronic diseases (Pekala et al., 2017; Piha et al., 2012; Schütte et al., 2015). Conversely, higher education is correlated with health literacy, enabling greater engagement in healthy behaviours such as physical exercise, avoidance of smoking, appropriate management of disease and help-seeking behaviour, which has implications for both depression and multimorbidity (Mirovsky and Ross, 2003).

Psychosocial stress. Stressful life events have been linked with subsequent depression and multimorbidity, with evidence pointing to the relevance of critical windows of stress in childhood, as well as over prolonged life periods (Brodbeck et al., 2018; England-Mason et al., 2018; Henchoz et al., 2019; Sinnott et al., 2015; Triolo et al., 2020). In addition to the effect on the brain previously described, exposure of prolonged stress on the HPA axis can lead to epigenetic changes that can alter genetic expression and cellular regulation (Caniliffe, 2016). This has been implicated in the accelerated aging and faster development of diseases associated with chronic stress (Gassen et al., 2017). Further, chronic stress often co-exists with lower SES and unhealthy behaviours, such as smoking, alcohol or drug use, as well as physical inactivity (Gilson et al., 2017; Hiscock et al., 2012; O’Donoghue et al., 2018; Probst et al., 2014), which may further promote poor mental and somatic health. Last, prolonged stress can lead to sleep problems (Lo Martire et al., 2019), which have been associated with both later onset of depression and several chronic conditions such as cardiovascular disease and diabetes (Ituni et al., 2017; Zhai et al., 2015).

4.3. Care-related factors

Complex clinical management. The healthcare systems are often fragmented and not set up to provide holistic care to individuals with multiple somatic conditions, and the addition of depression may further complicate care. Diagnostic overshadowing, whereby symptoms of depression are unidentified and attributed to other conditions, can precipitate the burden associated with depression and multimorbidity (Goldberg, 2010). While the overall healthcare use is likely greater in the presence of multimorbidity, depression may severely compromise care quality for chronic conditions. Furthermore, the co-presence of depression and multimorbidity makes clinical management particularly challenging. Having multiple medical conditions and depression entails a substantial workload both on clinicians’ and patients’ part, in terms of handling multiple treatments, procedures, visits, and adhering to multiple, possibly conflicting, behavioural prescriptions (Buffel du Vaure et al., 2016).

Polypharmacy. Individuals with multimorbidity and depression are also more likely to exhibit greater concurrent use of medications (usually 5 or more), i.e. polypharmacy (Holvast et al., 2017). Hence, these patients may be more prone to side-effects and inadequate adherence which in turn may lead to further need for care (Marengoni et al., 2016). In addition, it has been shown that prescription of antihypertensive drugs and statins, as well as access to preventive screening programs appear to be lower in people with psychiatric disorders (Mitchell et al., 2012; Peytremann-Bridevaux et al., 2008), which may further predispose to the development of other diseases.

5. Discussion and future directions

The link between multimorbidity and depression has attracted growing attention over the last two decades. Despite heterogeneous findings, the evidence emerging from longitudinal studies points towards a bidirectional association between the two conditions, even after accounting for several potential confounders. This supports the notion that multimorbidity may constitute a risk factor for later depression, and that depression may predispose to the development of multimorbidity. Further, experimental and observational studies suggest that
multimorbidity and depression may result from a multifaceted interplay between biological, psychosocial, and care-related factors that promote the accumulation of abnormalities and depletion of compensatory mechanisms associated with accelerated aging. However, a detailed characterization of the relation between multimorbidity and depression remains elusive, and further research is needed to address several core issues, starting from their definitions.

Studies have so far employed multiple operationalizations of multimorbidity, which stem from different definitions and describe the health status at varying levels of complexity. For instance, the widely used definition based on disease count (i.e. presence of ≥2 diseases) may be overly simplistic and lack discriminatory power, as up to 89% of a population over 60 years would be considered multimorbid under such classification (Calderon-Larranaga et al., 2017). Whereas other definitions based on the rate of disease accumulation over time, may be better suited to capture the dynamic process of accelerated aging (Calderon-Larranaga et al., 2018), but are less readily translatable into the clinical setting. In addition, definitions based on the aggregation of specific types of physical diseases (e.g. musculoskeletal or cardiovascular) may highlight further differential association with depression by characterizing specific mechanisms that link disease burden and depression (Marengoni et al., 2020; Vetrano et al., 2020). This might ultimately ease the identification of at-risk groups, which may be targeted for specific interventions.

Similarly, the assessment of depression needs to be carefully considered. Late-life depression has heterogeneous pathogenesis and clinical presentation, including somatic and neurovegetative symptoms (Alexopoulos, 2019; Hegeman et al., 2012; McKinney and Sible, 2013). Thus, a reliable clinical assessment of depression among older patients with multimorbidity would need to take into account the specific complex interactions that may occur in each individual patient, likely dependent on age (Alexopoulos et al., 2002; Belvederi Murri et al., 2018; McKinney and Sible, 2013). It remains debated, in fact, whether depression in late life is characterized by more severe neurovegetative or somatic symptoms than among younger individuals, possibly requiring diagnostic instruments that are specifically developed for older people (Haigh et al., 2018; Hegeman et al., 2015, 2012). This issue would deserve particular consideration among those with multiple, interacting physical conditions.

Whereas the assessment of depression in epidemiological studies is generally based on self-rated symptom rating scales (Balsamo et al., 2018), the studies included in this review used widely accepted operational criteria to define the presence of depression (i.e. clinically validated cut-off scores). Still, the variability in rating scale content, population characteristics and clinical presentation might partly limit the direct comparison of findings, especially between younger and older adults (Fried, 2017). The issue of age differences deserves special attention. Accumulating somatic diseases from mid-or late-life increase the incidence of depression in late-life, partly because of age-related brain structural and functional changes that predispose to depressive states in older individuals (Alexopoulos, 2005, 2019). Conversely, depression occurring in physically healthy younger individuals seems also to favor the development or exacerbation of physical morbidity, again through a complex interaction of psychosocial, care-related and biological mechanisms (Gold et al., 2020). Both multimorbidity and depression in late life appear to be the end products of chronic life-long processes, although further research is needed to highlight the relative contribution of underlying biopsychosocial mechanisms (Colman and Ataullahjan, 2010; Marengoni et al., 2011).

Recently, a case has been made whether focusing on individual symptoms or symptom clusters, rather than maintaining a categorical perspective on depression, might contribute to address the clinical heterogeneity of depression across age groups (Belvederi Murri et al., 2018; Cramer et al., 2010; Robinaugh et al., 2020). This approach could prove particularly fruitful among multimorbid patients, considering the differential impact that specific diseases might have on the clinical facets of depression (Belvederi Murri et al., 2020; Hartung et al., 2019; Schuler et al., 2018). Similarly, the Hierarchical Taxonomy Of Psychopathology and Research Domain Criteria initiatives have been proposed to address the heterogeneity of clinical and pathophysiological mechanisms of mental disorders, respectively, using a transdiagnostic, hierarchical approach (Cuthbert and Insel, 2013; Kotov et al., 2018). These frameworks may also shed further light on the reciprocal pathophysiological and psychosocial mechanisms that underlie the link between depression and multimorbidity.

Finally, the mechanisms underlying the relationship between multimorbidity and depression remain to be elucidated. It needs to be underlined that the account of biological, psychosocial and care-related drivers we provided has been mainly derived in accordance with findings from studies investigating multimorbidity or depression separately. Thus, the conceptual and methodological endeavor towards empirical validation of this framework and translation into clinically useful insights is just at the beginning. To further advance the understanding on the underlying mechanisms, the following challenges need to be addressed: (1) to develop a shared account of distal and proximal factors that predispose to the onset of multimorbidity and depression in the same population; (2) to characterize the complex interactions of such drivers. Addressing such complexity requires large, community-based cohort studies with extensive, cross-domain information over a long timeframe, where the association of depression and multimorbidity can be examined across a broad range of age groups. Only then will we be able to confirm the bidirectional association, assess multiple interacting pathways, and eventually identify at-risk groups, who could benefit from tailored interventions to break the multimorbidity-depression vicious cycle.

6. Conclusion

Epidemiological evidence is increasingly pointing towards a bidirectional relationship between depression and multimorbidity, two highly disabling conditions. This finding bears clinically relevant implications for the treatment and management of patients displaying multimorbidity and depression. Further research is needed to disentangle the mechanisms linking these two conditions, especially in the context of the framework of biological, psychosocial and care-related drivers presented here. A better understanding of such pathways is critical to describe not only the aging trajectories of individuals with multimorbidity and depression, but also to potentially develop effective interventions aimed at limiting the burden of these two highly debilitating conditions.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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