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Delirium and frailty in older adults: Clinical overlap and biological underpinnings

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Frailty and delirium are two common geriatric syndromes sharing several clinical characteristics, risk factors, and negative outcomes. Understanding their interdependency is crucial to identify shared mechanisms and implement initiatives to reduce the associated burden. This literature review summarizes scientific evidence on the complex interplay between frailty and delirium; clinical, epidemiological, and pathophysiological commonalities; and current knowledge gaps. We conducted a PubMed systematic search in June 2023, which yielded 118 eligible articles out of 991. The synthesis of the results—carried out by content experts—highlights overlapping risk factors, clinical phenotypes, and outcomes and explores the influence of one syndrome on the onset of the other. Common pathophysiological mechanisms identified include inflammation, neurodegeneration, metabolic insufficiency, and vascular burden. The review suggests that frailty is a risk factor for delirium, with some support for delirium associated with accelerated frailty. The proposed unifying framework supports the integration and measurement of both constructs in research and clinical practice, identifying the geroscience approach as a potential avenue to develop strategies for both conditions. In conclusion, we suggest that frailty and delirium might be alternative—sometimes coexisting—manifestations of accelerated biological aging. Clinically, the concepts addressed in this review can help approach older adults with either frailty or delirium from a different perspective. From a research standpoint, longitudinal studies are needed to explore the hypothesis that specific pathways within the biology of aging may underlie the clinical manifestations of frailty and delirium. Such research will pave the way for future understanding of other geriatric syndromes as well.

Keywords: delirium, frailty, hallmarks of aging, review

Introduction

Aging is associated with a gradual accumulation of biological deficits over the life span, ultimately resulting in a physiological decline [1–3]. Individuals experiencing accelerated aging may exhibit various phenotypes, sometimes known as geriatric syndromes, which are clinical conditions that extend beyond the boundaries of discrete disease categories and present as multifactorial health issues [4]. Frailty and delirium are two of the most frequent geriatric conditions in older people, and both pose significant challenges for affected

individuals, their families, and healthcare systems. Frailty refers to a typically age-related state of decreased functional reserve and biological homeostasis [5–10]. Because of this, it confers vulnerability to poor functional recovery after an acute event [5, 11]. Frailty can capture the discrepancy between chronological and biological aging, when individuals of the same age exhibit different responses to the same stressors. Indeed, an early definition of frailty treated it as a fixed factor yielding a greater rate of individual aging across the life course [12]. Delirium is an acute clinical condition characterized by cognitive dysfunction and a fluctuating course, which typically develops directly as a result of an acute medical illness such as pneumonia or stroke, or a stressor such as pain, metabolic disturbances, or medication side effects [13]. Delirium most commonly occurs in people with some existing risk factor—most notably dementia—when faced with acute triggers [13–15].

Epidemiological data indicate that frailty, depending on the assessment tools used, affects up to one in four community-dwelling older adults and is even more prevalent in clinical and long-term care settings [16]. Delirium affects one in every five hospitalized older adults [17, 18], so the likelihood that a patient would have both conditions is substantial. Moreover, frailty and delirium may be causally linked. Frailty—especially as an indicator of accelerated aging—is a predisposing factor for delirium, whereas delirium is a clinical manifestation of a dysfunctional response to stressors, another accelerated aging feature. Frailty and delirium are age-related, multiply determined, and increase the risk of adverse outcomes—including poor quality of life, and increased health and social care utilization [11, 19–23]. This further suggests that delirium and frailty are models to study accelerated aging, where there are likely to be shared mechanisms [24, 25], and insights may be generalizable to other health problems of older people, such as falls, sarcopenia, multimorbidity, or depression.

Despite commonalities, some still regard delirium and frailty as distinct and separate entities. Delirium is perceived as a primarily brain-related dysfunction, whereas frailty is still often viewed as primarily locomotor, or a nonspecific measure of accelerated aging. Moreover, the role of cognition—and thus delirium—in capturing frailty is less understood. Here, we propose that simultaneously investigating the strong interrelationship with aging in the appropriate settings—for example, where the prevalence of both conditions is expected to be high—would have benefits for both understanding the aging process and providing better care for older people. In this narrative literature review, we aim to summarize the scientific evidence on the interplay between delirium and frailty, describing the clinical, epidemiological, and pathophysiological commonalities and highlighting current knowledge gaps. In so doing, we provide a rationale for integration and measurement of both constructs in research and clinical practice to progress toward better treatments and effective prevention strategies.

Methodological considerations

This literature review is based on a systematic search of PubMed and synthesis of relevant results conducted by experts in the field. Keywords related to frailty and delirium—including Medical Subject Headings terms, synonyms, and variations—were searched in PubMed from its inception to June 30, 2023, yielding 991 results. Two reviewers independently screened these results, identifying 118 articles as relevant to the review's topic. These articles include both original studies—for example, research on the epidemiological association between frailty and delirium—and reviews—for example, analyses detailing mechanisms linking frailty and delirium. The selected articles were circulated among all co-authors, who further added relevant references based on their expertise and narratively synthesized the findings.

Overlapping risk factors, clinical phenotypes, and outcomes

Risk factors

Delirium and frailty share numerous risk factors, exhibit similar phenotypic characteristics, and are associated with common adverse clinical outcomes. Several non-modifiable and modifiable factors are predisposing conditions for both syndromes (Fig. 1). Older age increases the likelihood of delirium, especially within intensive care units and surgical settings [14], and also contributes to incident frailty in individuals living in the community [26]. Similarly, low educational attainment raises the risks of both delirium [27] and frailty [28]. Several sociodemographic and psychological characteristics are modifiable risk factors associated with both frailty and delirium. Loneliness is linked to frailty [29], and poor social and family networks elevate the risk of postoperative delirium [30, 31]. Depression is associ-

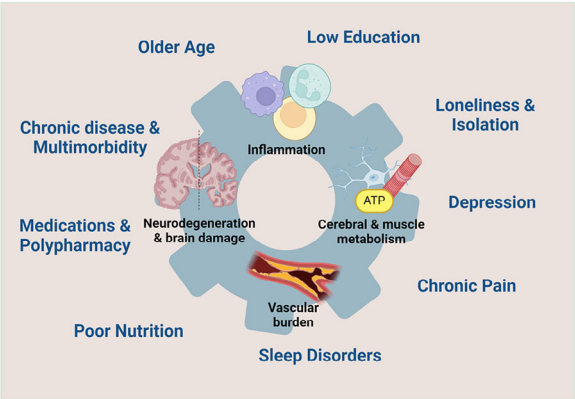

Fig. 1 *Common risk factors and pathophysiological pathways linking frailty and delirium.*

ated with more than a fourfold risk of frailty [32] and is also a well-recognized risk factor for delirium [15]. Chronic pain has been shown to nearly double the risk of developing frailty [33], and a systematic review and meta-analysis has shown that both pain at rest and pain with movement increase delirium risk in older inpatients by over twofold and by one third, respectively [34]. Insomnia and other poor sleep quality symptoms can also influence frailty occurrence [35]. Similarly, sleep disorders can predispose individuals to postoperative delirium following hip fracture surgery [36], elective arthroplasty [37], and cardiac surgery [38].

Many other conditions can be listed among the modifiable risk factors for both frailty and delirium. Undernutrition increases the odds of pre-frailty by nearly three times and frailty by four times over a 5-year follow-up [39]. The risk and presence of undernutrition are also risk factors for postoperative delirium in older individuals with hip fracture [40] and coronary artery bypass graft surgery [41]. Multimorbidity—that is, the co-occurrence of multiple long-term conditions—is twice as likely in older individuals with frailty compared to those without [42, 43], and specific multimorbidity patterns can predispose individuals to frailty [44]. Moreover, multimorbidity is a well-known predisposing factor for delirium [15, 45, 46], with individuals having an increased multimorbidity burden facing about a threefold increased risk of delirium [47].

Other factors and conditions have been associated with either frailty or delirium, but not definitively with both. Their exact role therefore remains uncertain, necessitating further evidence. Genetic predisposition has been found to be inconclusive in relation to delirium. A recent systematic review of 25 articles yielded mixed results regarding the association between the apolipoprotein E (ApoE) gene and delirium, with some studies identifying a lack of association and others a positive one [48]. However, 5 of these 25 studies were rated as having low genetic analysis quality. Similarly, evidence for associations between delirium and other genes—such as dopamine transporter gene SCL6A3, dopamine receptor 2 gene, glucocorticoid receptor, melatonin receptor, or mitochondrial DNA haplotypes—remains either inconclusive or absent [48]. There is also limited research regarding genetic predisposition to frailty. Some studies have explored the potential role of ApoE polymorphisms and other candidate genes, such as ApoE 9p21.3 variant and factor forkhead box O-3 (FOXO3A), in the development of frailty, but no definite association has been identified so far [49–52].

Specific medications—especially those with anticholinergic properties, opioids, neuroleptics, and benzodiazepines [53, 54]—are unequivocally linked with delirium occurrence. A systematic review reported that opioid treatment is associated with a 2.5-fold increase in the risk of delirium, whereas benzodiazepines are associated with a 3-fold increase [55]. Antipsychotics, antiparkinsonian drugs, and drugs for constipation, as well as increased anticholinergic burden, have also been associated with an increased risk of incident delirium [47, 53]. This association does not appear to be as clear for frailty [43]. Still, a longitudinal study found that sedative hypnotic use was associated with a 1.5-fold increase in the risk of frailty [56]. Sensory impairments—for example, visual and hearing impairments—are well-recognized risk factors for delirium [57]. However, there is insufficient evidence of a clear association with frailty [6]. A challenge in interpreting the relationship between sensory impairments and frailty arises from the inclusion of visual and hearing deficits in frailty assessment tools—as in the case of frailty indices—making it hard to determine their temporal relationship. However, it should be noted that sensory capacities are considered part of the intrinsic capacity construct proposed by the World Health Organization [58], and they are an integral part of a standard comprehensive geriatric assessment [59].

Clinical phenotypes

Frailty and delirium also share several clinical manifestations, with motor, cognitive, and affective domains being the most affected by both syndromes. Our synthesis reported in Table 1 is based on the international criteria for diagnosing delirium [13, 60–62] and on the most widely employed tools for assessing frailty [42], in the absence of an established reference standard [7, 63–72]. The clinical characterization of both frailty and delirium involves specific considerations—particularly regarding motor involvement—which are crucial for understanding their relationship. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition, Text Revision [13], the International Classification of Disease (ICD)-10 [60], and the ICD-11 criteria [61], delirium often presents with psychomotor disturbances. In particular, ICD-10 [60, 62] includes rapid shifts from hypoactivity to hyperactivity, altered speech flow, and enhanced startle reaction. These definitions implicate motor involvement as a core part of the syndrome. In line with these observations, recent studies indicate a reduced upright activity level in older patients with delirium, as measured with accelerometers [73] and other specific tests [74–78]. Another important consideration is that both frailty and delirium benefit from exercise and rehabilitation [79, 80], indirectly suggesting that physical activity may exert a pleiotropic effect on both locomotor and brain systems [81].

To understand its overlap with delirium, consider the different operational criteria used for frailty. These variations can make understanding the causal relationship between specific health conditions and frailty challenging. The phenotype model identifies muscle dysfunction and energy unbalance as drivers of physical frailty, and if considered independently, delirium could be a risk factor or an outcome. In contrast, the frailty index frames frailty as an accumulation of clinical, biological, and functional impairments reflecting the individual's biological age. Here, a history of delirium could be a component of the frailty definition [82]. A common way to overcome such a limitation in several studies is to recalculate the frailty index without specific features representing the exposure or partly defining it [83, 84].

Classically, delirium and frailty follow acute and chronic temporal patterns of onset [85]. However, the reality is more nuanced. Both have dynamic clinical courses [6, 45, 86–89]. Just as delirium may have incomplete resolution [90], even after several months, frailty can evolve rapidly, particularly after a major event such as a critical illness or emergency surgery [91, 92]. Moreover, degrees of frailty may recover in the near-term [93, 94]. The degree to which these variable trajectories imply that delirium or frailty are inherently modifiable is unclear.

Outcomes

Regardless of the operational criteria adopted to define it, frailty is consistently associated with increased risk of hospitalization, prolonged length of stay [95], complex discharge procedures [96], new-onset disability [97], heightened risk of institutionalization [98], and mortality [99]. Likewise, patients with delirium are at increased risk of prolonged hospitalization, functional decline, institutionalization, and mortality during and after hospitalization [17, 18, 100]. Finally, the heightened risk of falls associated with both syndromes may stem from the shared physical and cognitive disturbance—resulting in muscle weakness, impaired executive function, and increased reaction time [22, 74, 101]—ultimately leading to failure to remain upright in the face of environmental challenges. Healthcare expenditure and social burdens are substantial for both conditions [17, 42, 96].

A bi-directional relationship

From frailty to delirium

In the last years, a growing body of evidence has demonstrated the capacity of frailty to predict incident delirium across different clinical settings. A systematic review (eight studies included in the meta-analysis; $n = 5541$, mean age 77.8) reported a 2.19-fold increased risk of delirium in persons with frailty [102]. Yet another review showed that fewer than 10% of frailty studies considered delirium an outcome [103]. A more recent study documented the independent association between a frailty index and incident delirium in a sample of 218 hospitalized older persons [104]. In this case, the presence of pre-frailty was associated with a more than fivefold increase in the risk of developing incident delirium, whereas the presence of frailty was associated with nearly a sevenfold increase. Consistent findings were also reported in a large sample of 150,000 older persons admitted to intensive

Table 1. *Overview of diagnostic clinical signs and symptoms of delirium and frailty, highlighting commonalities between the two conditions.*

Delirium[a]	Frailty[b]
Motor domain	
• Hypoactivity or hyperactivity and unpredictable shifts from one to the other/mixed motoric activity level [13, 62] • Increased or decreased flow of speech [62] • Increased reaction time [62]	• Standing balance impairment [71]/difficulty in walking [7, 65, 67, 69–71] or climbing stairs [71]/gait slowness [63, 68, 69] • Weakness [63] (lack of strength in hands [66] or impaired repeated chair stands [64, 68, 71]/poor resistance [7]) • Physical tiredness [66, 71] or exhaustion [7, 64]/fatigue [63] • Low physical activity [63] • Falls in the past year/fear of falling while walking [71]
Cognitive domain	
• Disturbance of attention, orientation, and awareness developing within a short period of time [13, 60–62] • Impairment in multiple areas of neurocognitive functioning (e.g., memory deficit, language, visuospatial ability) [13, 60–62] • Impairment of consciousness [62] • Possible disturbances of perception and transient illusions, delusions, or hallucinations [60–62]	• Problems with memory [66, 67, 71] • Cognitive impairment (e.g., difficulty in orientation and visuospatial ability) [67, 69–71] • Difficulty in coping with problems [66, 71]
Affective domain	
• Possible disturbance of emotion, including anxiety symptoms, depressed mood, irritability, fear, anger, euphoria, or apathy [60–62]	• Feeling down [66, 67]/sad or depressed [67, 69]/lack of joy or fulfillment in daily life [71] • Feeling nervous or anxious [66, 67]
Other domains (sleep–wake cycle, functional independence, nutrition, sensory deficits, social support)	
• Possible disturbance of the sleep-wake cycle (e.g., reduced arousal of acute onset or total sleep loss followed by reversal of the sleep–wake cycle) [60–62]	• Requiring help in basic or complex activities of daily living [65, 67, 69–72] • Unexplained weight loss [22, 63, 64, 67, 69–72]/poor nutrition or eating [67, 70, 71]/experiencing dry mouth [71] • Poor hearing/poor vision [66, 67] • Poor social interactions (feeling alone, feeling helpless) [65–67, 69, 71]

[a]The contents of this column are based on the internationally accepted diagnostic criteria of delirium (DSM-5TR, ICD10, and ICD11) [13, 60–62].

[b]The contents of this column are based on the most widely employed tools for assessing frailty in the absence of a gold standard [42]: frailty phenotype [63], FRAIL scale [7], Study of Osteoporotic Fractures frailty criteria [64], PRISMA-7 [65], Tilburg Frailty Indicator [66], Geriatric 8 frailty questionnaire for oncology [67], Groningen Frailty Index [67], Short Physical Performance Battery [68], Edmonton Frailty Scale [69], Multidimensional Prognostic Index [70], Kihon Checklist [71], Frailty Risk Score [72]. The column does not take into consideration the frailty index per se, which, by definition, can include any age-related health deficit, encompassing diseases, signs, symptoms, and functional limitations across several organs and systems. Moreover, the determinants of frailty included within each tool, which do not clearly reflect signs or symptoms of the condition (such as age, gender, marital status, illnesses, and the use of multiple medications), have not been listed in the column.

care units [100]. Patients with frailty had a higher incidence of delirium, with nearly twice the risk compared to those without frailty. This increased risk only marginally explained the higher mortality risk and prolonged length of stay in patients with delirium. A similar magnitude of risk was also reported by Sanchez et al. [105], who found that frail patients had a 71% increased risk of experiencing an episode of delirium compared to non-frail ones. At the same time, they demonstrated how the combination of baseline frailty and incident delirium was associated with a 35.9% rate of in-hospital mortality compared to the 6.6% rate reported among non-frail individuals who had not experienced the acute neuropsychiatric condition. Frailty was found to be a risk factor for delirium in older patients hospitalized for COVID-19 infection, with the risk being nearly three times higher even after accounting for several possible confounders [106]. Nevertheless, null results have also been reported [107, 108]. For example, a recent study conducted in older persons admitted to the hospital because of the COVID-19 infection failed to demonstrate an association between higher clinical frailty scale scores and incident delirium [107]. It is possible that differences in study populations, settings of care, and the assessment tools could explain such conflicting results. Dementia is a very strong risk factor for delirium [109], and frailty tools with a stronger emphasis on cognition will more likely demonstrate associations between frailty and delirium risk [110–113].

From delirium to frailty

Little is known about how delirium could be a risk factor for the development of frailty or how it might rather worsen a preexisting frailty status. Only one study has investigated the causal relationship between delirium and postoperative frailty in a cohort of patients undergoing cardiac surgery [114]. The authors found that postoperative delirium was associated with a threefold increase in the odds of having postoperative frailty in a short-term follow-up. However, no information was provided regarding the changes in the severity of frailty before and after the delirium episode and whether the coexistence of dementia could impact this relationship.

Frailty is a dynamic entity, and older adults can transition from being robust to exhibiting varying degrees of frailty, with some patients reaching a point of irreversible frailty [99]. Delirium comes with significant motor abnormalities, which could then contribute to the physical aspects of incipient frailty [13]. Furthermore, delirium can indirectly contribute to decreased motor and physical functioning by increasing the likelihood of cognitive decline [115, 116]. The hypothesis that delirium and frailty can feed each other in this spiral is supported by the evidence that delirium is a risk factor for functional decline [117, 118], which can be considered a clinical outcome of frailty [7]. Likewise, functional decline following delirium makes dementia likely if incomplete recovery occurs [97, 119–121].

Novel findings from the CASCADE study—a prospective study with a 2-year follow-up of 210 older individuals receiving home care in Norway, 76% of whom had moderate-to-severe frailty at baseline—showed incident delirium was independently associated with lower cognitive test scores after 6 months [122]. Notably, greater neuronal injury during any episode of delirium—measured by neurofilament light chain—was associated with greater cognitive decline at follow-up. In other words, axonal-level changes may represent a mechanism through which delirium gives rise to cognitive impairment in individuals with frailty.

This result aligns with those from two other longitudinal studies of delirium and dementia. Dementia has long been recognized as a risk factor for delirium. Even though delirium is a well-established risk factor for incident dementia [123], the long prodrome might result in delirium uncovering latent disease processes. More recent evidence suggests that delirium itself constitutes a risk factor for dementia and exacerbates cognitive decline. Prospective studies assessing cognition before, during, and after acute illness found incident delirium to be associated with decline over 2 and 6 years, and thereby with incident dementia [122, 124, 125]. In contrast, a higher baseline cognitive function was associated with a favorable cognitive outcome. Even so, individuals with higher baseline cognition who experienced severe and prolonged delirium experienced the highest degree of cognitive decline, at levels similar to those with a high amyloid burden in other cohorts [122, 124, 125]. This suggests a relationship between baseline cognition and delirium severity, that is, that patients with good cognitive function may experience more severe effects when delirium occurs due to a more toxic insult. Part of the dilemma in teasing out the relationship among baseline cognition,

the degree of frailty, and the severity of acute illness is the paucity of frailty-specific measures of the severity of acute illness.

Common pathophysiological pathways

Quinlan et al. categorized underlying pathways of both frailty and delirium, including inflammation, stress, genetics, atherosclerosis, and nutrition [126]. These factors collectively contribute to—and might indeed further boost—mechanisms of aging via several processes commonly referred to as the hallmarks or pillars of aging (e.g., cellular senescence, mitochondrial dysfunction, and genomic instability) [24, 25]. These commonalities in overarching pathways may help explain why frailty is a significant risk factor for delirium and why delirium can further contribute to frailty exacerbation [121]. Here, we examine some factors involved in the pathophysiology of both frailty and delirium, recognizing that these mechanisms likely operate synergistically rather than independently.

Inflammation

Frailty is closely linked to a pro-inflammatory state. Elevated levels of pro-inflammatory cytokines—such as interleukin-6 (IL-6), tumor necrosis factor-alpha, and C-reactive protein (CRP)—have been linked to frailty, although mostly from cross-sectional studies [127, 128]. Various factors—including age-related changes, chronic diseases such as cardiovascular disease and diabetes, obesity, physical inactivity, poor nutrition, and psychosocial stressors—can trigger systemic inflammation. Inflammation contributes to frailty through multiple mechanisms—including sarcopenia, insulin resistance, endothelial dysfunction, oxidative stress, dysregulation of the hypothalamic–pituitary–adrenal axis, and dysregulation of immune function [129]. Delirium often arises from acute systemic inflammation triggered by factors, such as infection, surgery, trauma, or medications, which releases pro-inflammatory cytokines and activates immune cells that impact the central nervous system. Higher levels of CRP and IL-6 have been linked to delirium incidence, duration, and severity [130–133]. Delirium is also characterized by neuroinflammation involving microglial activation and the release of pro-inflammatory cytokines within the brain, contributing to neuronal dysfunction and cognitive impairment. Additionally, it can be hypothesized that inflammation-induced disruption of the blood–brain barrier permits peripheral immune cells and inflammatory mediators to enter the brain, exacerbating neuroinflammation and neuronal dysfunction in delirium [45, 134]. There is further evidence that genetic factors might also influence vulnerability to delirium from inflammation. For instance, individuals with the COMT Val/Val genotype appear to have protection against delirium after surgery compared to other genotypes (i.e., Met/Met and Val/Met) [135]. Regarding ApoE $\varepsilon 4$ and $\varepsilon 2$ carrier status, neither has shown an association with delirium incidence or severity in elective surgery patients [136]. However, among ApoE $\varepsilon 4$ carriers, elevated CRP levels have been linked to the incidence of postoperative delirium [137].

Neurodegeneration

Neurodegenerative processes are often at play in frailty. White matter hyperintensity volume has been associated with frailty [138], and concurrent decline in cognitive and physical function has been linked to worse trajectories of several markers of brain aging, including reduced gray matter and hippocampal volumes and increased accumulation of white matter hyperintensities [139]. Accumulation of markers of Alzheimer's pathology—such as beta-amyloid and tau—has been linked to gait speed, a prominent feature of frailty [140]. Frailty can also result from brain damage caused by stroke, traumatic brain injury, or other insults—impairing mobility, coordination, and cognitive abilities. Conversely, individuals with cognitive impairment, dementia, or underlying neurodegenerative processes without clinical manifestations are at an increased risk of developing delirium. Cortical thinning—a marker of neurodegeneration—has been associated with delirium severity in surgical patients without dementia [141]. Acute brain insults can directly cause delirium by disrupting brain function, leading to structural damage or functional disturbances in neurotransmitter systems that impair cognitive processes. Additionally, delirium can result in neuronal injury or exacerbate preexisting brain damage, creating a vicious cycle of cognitive decline [74, 122, 124]. These findings reinforce the notion that neurodegeneration is a key determinant of vulnerability to acute cognitive dysfunction in response to physiological and environmental stressors. Thus, delirium—as an indicator of stress in a system already struggling to cope with stressors—might drive further frailty [142]. In short, it is not delirium per se, but the damage that

it causes, aging changes, and potentially its precipitants, which contribute to this cycle.

Cerebral and muscle metabolism

Cerebral metabolic insufficiency occurs when brain energy demands surpass its supply, resulting in a deficit of essential energy substrates, such as glucose and oxygen [45]. Conditions, such as hypoglycemia, hyperglycemia, or insulin resistance, can affect glucose delivery to the brain, leading to decreased energy production and neuronal dysfunction [143]. In addition, mitochondrial dysfunction can exacerbate cerebral metabolic insufficiency by decreasing ATP production and increasing oxidative stress, potentially leading to delirium through compromised brain energy metabolism and subsequent neuronal injury [144]. Cerebral metabolic insufficiency can also impair motor coordination, muscle function, and balance, increasing the risk of falls, fractures, and physical frailty. Overall, cerebral metabolic insufficiency may accelerate cognitive decline, exacerbate frailty over time, and predispose individuals to delirium. Poor muscle health—characterized by weakness and decreased physical function—is a defining clinical feature of frailty [63, 145]. Reduced mobility is a risk factor for delirium, as immobility can contribute to disorientation, social isolation, and sensory deprivation, all of which are associated with cognitive impairment and delirium [146, 147]. Furthermore, reduced mobility is also considered an early marker of cognitive decline and dementia, which are in turn associated with delirium [148, 149]. Dysfunction in muscle metabolism—such as insulin resistance, impaired glucose utilization, or mitochondrial dysfunctions—can affect energy metabolism throughout the body, including the brain, influencing frailty [144]. Disrupted energy metabolism is associated with delirium, as it may lead to cerebral metabolic insufficiency and neuronal dysfunction [150]. Muscle health is also influenced by nutritional status, as inadequate protein intake can lead to muscle wasting and weakness, resulting in frailty and increased susceptibility to delirium [63, 151].

Vascular burden

Overall, vascular factors contribute to the pathophysiology of frailty and delirium through their effects on cerebral perfusion, inflammation, oxidative stress, and blood–brain barrier function. Hypertension, atherosclerosis, and diabetes can lead to cerebral hypoperfusion, depriving neurons of oxygen and nutrients. Acute vascular events—such as transient ischemic attacks, microbleeds, or strokes in strategic brain areas—can lead to acute cognitive fluctuations (i.e., delirium) and increase the overall vulnerability of older adults (i.e., frailty). Chronic vascular conditions such as small vessel disease can damage the brain's microvasculature, contributing to cognitive and physical decline and exacerbating vulnerability to acute stressors [152]. Vascular risk factors—such as smoking and history of myocardial infarction—have been associated with postoperative delirium, even after adjustment for preoperative cognition [153]. Vascular factors can compromise the integrity of the blood–brain barrier, on one side triggering neuroinflammation in the brain and on the other contributing to frailty and increasing susceptibility to delirium.

Vascular factors also play a critical role in frailty by influencing muscle function, mobility, and the body's response to stressors [154]. Poor vascular health can lead to muscle wasting, decreased mobility, impaired balance, and an increased risk of fractures, all of which are hallmark features of physical frailty. For instance, peripheral artery disease contributes to poor muscle vascularization, leading to limitations in physical function and making individuals more vulnerable to functional decline and adverse outcomes. Similarly, the geriatric syndrome of orthostatic hypotension—a condition characterized by a sudden drop in blood pressure that occurs when a person transitions from lying down or sitting to standing up—has also been defined as an example of cardiovascular frailty given its similar conceptualization and multifactorial nature [155].

A unifying framework

Taken together, epidemiological evidence suggests frailty is a substrate for developing delirium, with some support for the idea that delirium may accelerate worsening frailty. At the same time, the existence of common pathophysiological pathways implies that frailty and delirium could be two different—sometimes coexisting—manifestations of an underlying accelerated biological aging. Here we attempt to establish a unifying framework that may help untangle the complex—not necessarily unidirectional—relationship between frailty and delirium, fram-

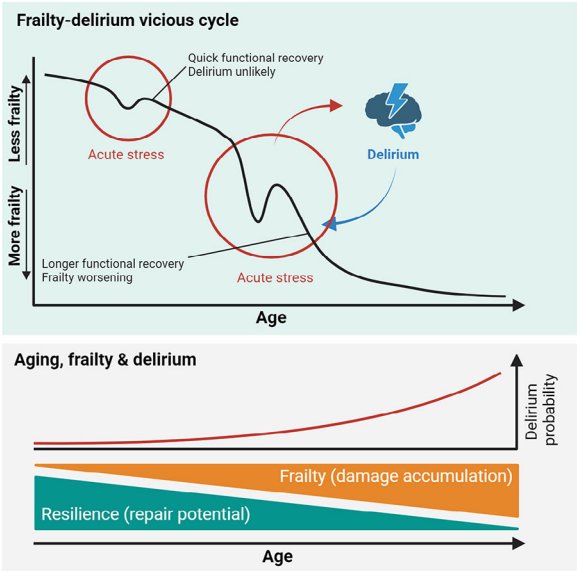

Fig. 2 *Unifying framework of the interplay between frailty and delirium.*

ing their clinical significance and guiding future research (Fig. 2).

It may be that delirium belies an underlying condition of frailty, much like delirium serves as an indicator of the presence of dementia. Frailty may represent the critical component determining why persons with the same disease may or may not develop delirium under similar circumstances, that is, when experiencing pneumonia or a hip fracture. Emerging evidence suggests that the pathophysiological hallmarks of delirium and dementia are somewhat distinct. Delirium may be independently associated with pathologic processes driving cognitive decline, differing from those typically observed with dementia [156]. These findings lead to alternative explanations regarding the pathologic correlates of cognitive impairment, positioning delirium and/or its precipitants as critically interrelated mechanisms [156]. If we adopt the latter perspective, the presence of frailty would explain why some individuals can tolerate a given pathological burden and other individuals cannot, being more prone to develop delirium.

It should be noted that some studies reporting the association between frailty and delirium may be subject to how frailty is operationalized. Studies have shown that delirium is predicted by frailty, up to six times more, depending on the frailty measurement tool used [113]. The frailty paradigm—whether based on deficit accumulation or phenotypic frailty—stems from different conceptual foundations capturing different domains. For instance, using physical frailty, we primarily measure physical performance because slow gait, grip strength, low activity, involuntary weight loss, and exhaustion are the five component criteria of the physical frailty phenotype. In contrast, a higher score on the frailty index proxies the cumulative impairment across several organs and systems associated with the progressive exhaustion of biological repairing and coping mechanisms. Deiner et al. found that a 42-item frailty index—but not physical frailty—was associated with delirium incidence and that neither the frailty index nor physical frailty were associated with delirium severity [84]. Notably, elements related to cognition were excluded from the frailty index to allow comparability of the assessment tools [84]. Cognition is not part of the original frailty phenotype, though the phenotype is associated with low cognitive performance and incidence of dementia [157, 158], which is in turn a strong predictor of delirium [45]. Accordingly, frailty assessment models that incorporate cognition into the frailty phenotype have been proposed to better capture delirium risk. In a multicenter study of 6030 community-dwelling persons with follow-up at 4 years, Avila-Funes et al. showed that adding cognitive impairment evaluation to the physical frailty classic assessment led to an improvement in the predictive validity for adverse health outcomes and resulted in a better identification of older persons with intrinsic vulnerability than when only the domains of physical function were considered [159]. Overall, these findings suggest that some frailty contributors/domains are not always accounted for that are precisely related to delirium development. A deeper knowledge of such aspects of the aging process—possibly by maintaining an explorative approach to omics analyses—would improve our understanding of the relationship between frailty and delirium [160–162].

As a second hypothesis—plausible though with less evidence at present—delirium could trigger a vicious cycle, leading to higher cognitive and physical impairments, with further depletion of coping mechanisms and acceleration in the development and worsening of frailty. Methodological challenges abound, relating to delirium clinical heterogeneity, baseline cognition, and acute stressors, coupled with difficulties including older adults

experiencing delirium in prospective studies with frailty outcomes. Nonetheless, the studies identified here point toward a temporal association between delirium and incident or worsening frailty. Indeed, the effect of delirium on cognitive decline rate—independent of the neuropathological markers of dementia—suggests delirium possibly contributes to frailty [156]. This notion is further reinforced by the interaction among brain, sensorimotor, and muscle health, linking frailty with sarcopenic traits and cognition [163, 164].

A unifying hypothesis posits that frailty and delirium represent two sides of the same coin—expressions of an underlying biological vulnerability stemming from the progressive exhaustion of compensatory and reparatory mechanisms observed with age. To a certain extent, frailty may be considered the best proxy of this progressive damage accumulation. Frailty is conceptually identified as a state of reduced biological resilience in individuals when confronted with internal or external stressors, often of minor intensity [165]. Similarly, delirium may also indicate an individual's diminished resilience in response to stressors. When the brain's functional reserve is insufficient to cope with relevant stressors, signs of acute brain failure may manifest, characterized by motor and non-motor clinical features, acute onset, and a fluctuating course. In support of this hypothesis also comes the evidence of a phenotype shared by frailty and delirium, encompassing motor and cognitive symptoms, among others. Furthermore, it is noteworthy that the degree of frailty impacts how features, such as neuropathology [166], biomarkers [167], and polygenic risk [168], affect the development of late-life dementia. According to this perspective, delirium would represent the plastic and acute manifestation (or an alternative sign) of frailty. The conceptual framework that links frailty and delirium, if broadened, may serve as a model applicable to various other geriatric syndromes, including falls, sarcopenia, sensory impairment, and depression. Just as frailty and delirium share underlying vulnerabilities and reciprocal relationships, these syndromes often intertwine and influence each other in complex ways. Inouye et al. proposed a feedback loop model that interconnects geriatric syndromes, including delirium, falls, pressure ulcers, incontinence, and functional decline [4]. Older age, baseline cognitive impairment, physical status, and impaired mobility serve as common risk factors predisposing individuals to these syndromes, eventually leading to physical frailty [5]. Frailty—acting through both cognitive and physical domains—perpetuates a multifactorial feedback loop, exacerbating the geriatric syndromes, increasing frailty, and ultimately culminating in adverse health outcomes such as institutionalization and death. Although clinically distinct, these syndromes share underlying impairments in a discrete set of age-related pathologies [6]. In addition to the epidemiological and clinical research, exploring the interplay of geriatric syndromes from a geroscience perspective has the potential to expand our current understanding of these conditions, which may ultimately translate into targeted interventions for better care of older people's health. Studying the interplay of syndromes also recognizes that many are fellow travelers. One lesson from tackling metabolic causes and consequences of frailty has been an emphasis on multimodal interventions [169]. Recognizing frailty as a complex system should make us wary of studying single interventions to treat it—as with metabolic dysregulation in frailty, multimodal interventions are more likely to be effective.

Current evidence does not allow for definitive conclusions regarding the theoretical models on the relationship between frailty and delirium. Of the three hypotheses—that frailty predisposes to delirium, that delirium triggers or accelerates frailty, or that both conditions are manifestations of accelerated biological aging—the first is perhaps the most substantiated by studies. However, all hypotheses warrant further investigation, as they carry significant scientific and clinical implications.

Clinical implications

If it is confirmed that frailty increases the risk of delirium, this highlights the need for preventive strategies that target the determinants of frailty. Clinically, this would involve the early identification and comprehensive management of frailty to potentially reduce the incidence of delirium. Scientifically, it calls for research to uncover the specific elements of frailty that are most predictive of delirium, which could inform intervention strategies that could prevent its onset in at-risk populations. Prospective studies could evaluate the effectiveness of targeted interventions, such as physical rehabilitation, nutritional optimization, and cognitive therapies, in reducing the risk of delirium.

If delirium occurrence contributes to the development or worsening of frailty, the focus shifts toward acute management strategies to mitigate the impact of delirium. Clinically, this would underline the importance of immediate and effective delirium management protocols in hospital settings, such as environmental interventions, minimizing use of potentially harmful medications, and enhancing sensory input to prevent long-term frailty. From a research perspective, investigations would need to address the causal pathways through which delirium impacts physical and cognitive decline, with longitudinal follow-up to trace the progression of frailty post-delirium.

Lastly, recognizing that both frailty and delirium may represent facets of accelerated aging requires that we take a holistic view of health in old age. This model supports an integrative care approach that considers the broad spectrum of geriatric health issues rather than isolated syndromes. Clinically, this would promote comprehensive geriatric assessments that evaluate a patient's overall vulnerability to a range of age-related conditions. Scientific inquiry under this framework would likely be interdisciplinary, exploring common molecular, cellular, and physiological pathways that underpin aging-related decline. Such research could encompass the development of novel biomarkers and the integration of genetic, epigenetic, and environmental factors to better understand and intervene in the aging process.

Regardless of the prevailing model, it is crucial to promote research within this framework to explore these hypotheses further. This requires adopting standardized and rigorous tools for the accurate definition and measurement of both frailty and delirium. Addressing current limitations in the scientific literature involves conducting longitudinal studies to (1) clarify the causal relationship between delirium and the development of frailty, (2) evaluate the impact of delirium and delirium severity on the worsened degree of frailty severity, and (3) to explore the complex interplay between delirium superimposed on dementia and frailty.

The importance of comprehensively understanding frailty and delirium in tandem goes beyond academic interest and directly impacts the quality of healthcare for older individuals. Prevention emerges as a critical theme because recognizing early signs of frailty or delirium allows for timely interventions that could prevent the onset or exacerbation of the other. This proactive approach could significantly reduce the healthcare burden by decreasing the frequency of acute crises and by alleviating the long-term impacts of these geriatric syndromes. Thus, understanding how these conditions intersect provides a dual benefit: enhancing our ability to safeguard against one while simultaneously fortifying defenses against the other. Ultimately, this approach aims at maintaining autonomy and quality of life in the aging population.

Conclusions

Frailty and delirium appear to be linked by concurrently acting or subsequently causally determined mechanisms that would explain their co-occurrence in clinically complex individuals, beyond mere chance. Although research on frailty as a condition predisposing to delirium attracted interest in the past, the literature on delirium as a possible trigger of frailty is still limited, despite this being a plausible mechanism. According to an overarching hypothesis, frailty and delirium can be alternative, sometimes concurrent, manifestations of an underlying accelerated aging process. A direct implication of such a model is that it would identify the geroscience approach as a possible avenue to prevent and delay frailty and delirium, as well as other burdensome geriatric syndromes. However, the heterogeneity of the available studies and several methodological pitfalls make further research necessary. In particular, it is important to develop more longitudinal investigations examining the bidirectional association between frailty and delirium and expand the knowledge across different settings of care. Ultimately, uncovering the interconnections between frailty and delirium would pave the way for preventive measures that can significantly enhance the health and autonomy of older adults. Implementation of integrated care strategies that prioritize early detection and intervention is essential to reduce the severe consequences of these syndromes on the aging population.

Author contributions

Giuseppe Bellelli: Conceptualization; writing—original draft; methodology; writing—review and editing; project administration; supervision; visualization. **Federico Triolo**: Writing—original draft; conceptualization; methodology; writing—review and editing; project administration; visualization. **Maria Cristina Ferrara**: Writing—original draft; conceptualization; methodology; visualization; writing—review and editing; project

administration. **Stacie G. Deiner**: Writing—original draft; visualization; writing—review and editing. **Alessandro Morandi**: Writing—original draft; visualization; writing—review and editing. **Matteo Cesari**: Writing—original draft; writing—review and editing; visualization. **Daniel Davis**: Writing—original draft; visualization; writing—review and editing. **Alessandra Marengoni**: Visualization; writing—review and editing; writing—original draft. **Marco Inzitari**: Writing—original draft; writing—review and editing; visualization. **Leiv Otto Watne**: Writing—original draft; writing—review and editing; visualization. **Kenneth Rockwood**: Writing—original draft; visualization; writing—review and editing. **Davide Liborio Vetrano**: Writing—original draft; writing—review and editing; visualization.

Conflict of interest statement

The authors declare no conflicts of interest.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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