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Review

Urgent needs of caregiving in ageing populations with Alzheimer's disease and other chronic conditions: Support our loved ones

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ABSTRACT

The ageing process begins at birth. It is a life-long process, and its exact origins are still unknown. Several hypotheses attempt to describe the normal ageing process, including hormonal imbalance, formation of reactive oxygen species, DNA methylation & DNA damage accumulation, loss of proteostasis, epigenetic alterations, mitochondrial dysfunction, senescence, inflammation, and stem cell depletion. With increased lifespan in elderly individuals, the prevalence of age-related diseases including, cancer, diabetes, obesity, hypertension, Alzheimer's, Alzheimer's disease and related dementias, Parkinson's, and other mental illnesses are increased. These increased age-related illnesses, put tremendous pressure & burden on caregivers, family members, and friends who are living with patients with age-related diseases. As medical needs evolve, the caregiver is expected to experience an increase in duties and challenges, which may result in stress on themselves, and impact their own family life. In the current article, we assess the biological mechanisms of ageing and its effect on body systems, exploring lifestyle and ageing, with a specific focus on age-related disorders. We also discussed the history of caregiving and specific challenges faced by caregivers in the presence of multiple comorbidities. We also assessed innovative approaches to funding caregiving, and efforts to improve the medical system to better organize chronic care efforts, while improving the skill and efficiency of both informal and formal caregivers. We also discussed the role of caregiving in end-of-life care. Our critical analysis strongly suggests that there is an urgent need for caregiving in aged populations and support from local, state, and federal agencies.

1. Introduction

The quality of life for millions of patients is impacted by caregiving (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). According to a study by the Centers for Disease Control and Prevention (CDC), over 22.3% of adults reported providing care or assistance to a friend or family member in the past 30 days (Prevention, 2018). In addition, one in three caregivers provided 20 or more hours per week of care, and over half have given care or assistance for 24 months or more (Prevention, 2018). Further analysis found that 10.4% of caregivers reported providing care or assistance to friends or family members with dementia or other cognitive impairment disorder (Prevention, 2018). In the United States (U.S.), long-term care facilities provide a major source of caregiving. However, most caregiving is through unpaid informal caregivers (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). middle-aged and older individuals provide a sizable percentage of this care, participating in the care of their spouses, parents, or children (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley

Abbreviations: AA, African Americans; AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; AMPK, AMP-activated protein kinase; CDC, Centers of Disease Control and Prevention; COVID-19, Coronavirus disease 2019; CVA, Cerebrovascular accident; DDR, DNA damage response; DHEA, Dehydroepiandrosterone; GI, Gastrointestinal; HaH, Hospital at Home; HELP, Hospital Elder Life Program; LV, left ventricular; PACE, Program for All-Inclusive Care for the Elderly; PD, Parkinson's disease; VA, Veterans Affairs.

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and Crews, 2007). Caregivers, such as family members, friends, and professional caretakers, support individuals with their social and medical needs (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007).

Caregiving may involve assistance with one or more activities of daily living, such as mobility, dressing, bathing, grooming, and feeding, or instrumental activities of daily living such as bill-paying, shopping, cooking, medication management, and providing transportation (Hoffman and Zucker, 2016; Prevo et al., 2018; Sehar et al., 2022; Talley and Crews, 2007). This can include emotional support and assistance in managing a chronic illness or disability. As medical needs evolve, the caregiver may experience an increase in duties and challenges, which may result in stress on themselves, and potentially their family, friends, and community (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). Caring for an older adult or individual with special needs is a significant risk factor for the emergence of chronic illnesses in the caregiver (Hoffman and Zucker, 2016). Several aspects of the caregiver's life, including their capacity to work, participate in social activities and relationships, as well as maintaining their own emotional and physical health are impacted by the unpaid and informal care that they provide. (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). Specifically, caregiver stress contributes to unhealthy behaviors, including sedentary lifestyles, inadequate diet, social isolation, and excessive use of potential drugs of abuse such as alcohol and prescription medications (Hoffman and Zucker, 2016).

Given the burden of caregiving, understanding the physical and mental health load on caregivers, the variety of duties caregivers may perform. In addition, the societal and economic implications of long-term chronic illnesses or disability are crucial as our population ages and impairment increases (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). In addition, a detailed description of caregiving for diverse ageing populations may better allow for improved public health strategies to help individuals and their communities, improving the health of caregivers and those requiring care through improved data on these subjects (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). The need for caregiving is rising as the number of older adults and those with disabilities increases (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). By taking a calculated approach, public health professionals can encourage the necessary systemic changes that enhance the wellbeing of both caregivers and care recipients, educate healthcare professionals about the value of family caregivers, and ensure that caregivers have the resources and support they require to reduce the strain of caregiving (Hoffman and Zucker, 2016; Prevo et al., 2018; Talley and Crews, 2007). There is a need to understand the current characteristics of caregivers, how caregivers provide care to a family member or friend with dementia or other cognitive impairment disorders, and what the health status is concerning caregivers in the US.

In this review, we examine the biological mechanisms of ageing and its effect on body systems, exploring lifestyle and aging, with a specific focus on age-related disorders. We will describe the history of caregiving, and review specific challenges faced by caregivers encountering an acute and chronic functional decline in the presence of multiple comorbidities. We review innovative approaches to funding caregiving, and efforts to improve the medical system to better organize chronic care efforts while improving the skill and efficiency of both informal and formal (professional) caregivers. Finally, we conclude by exploring the role of caregiving in end-of-life care.

1.1. Pathophysiology of ageing in the body

Ageing is a normal aspect of the course of a person's life cycle that results from a normal accumulation of a chronic loss of biosynthetic and cellular repair systems (Goldsmith, 2012; López-Otín et al., 2013; Pallin et al., 2014; Tchkonia and Kirkland, 2018). The ability to sustain homeostasis under stress decreases with age due to a steady drop in organ functional reserves. Age-related cell/organ degeneration and lack of regenerative potential are accelerated, and over time, the changes they induce ultimately result in death. Ageing affects all the organs and systems of human physiology as presented in Fig. 1. In humans, ageing is commonly regarded as a chronic disease that leads to a host of physiological changes throughout the entire body (Table 1). Frailty is a frequent syndrome in elderly patients that poses a higher risk of adverse health outcomes, including falls, incident impairment, hospitalization, and mortality due to diminished physiological reserves. Sarcopenia is a prominent risk factor for frailty (Boyle et al., 2009; Cleasby et al., 2016; Clegg et al., 2013; Fried et al., 2001; Moore et al., 2010; Searle and Rockwood, 2015). A measurable loss of reserve in the respiratory, cardiovascular, renal, hematopoietic, and clotting systems has been linked to frailty. A mediating factor is often nutritional status. Reduced basal metabolic rate brings about decreased hunger and nutritional deficits because of declining skeletal muscle mass. According to recent research, frailty may be related to variations in genes related to apoptosis and transcription regulation that are relevant to inflammation and muscle maintenance (Boyle et al., 2009; Cleasby et al., 2016; Clegg et al., 2013; Fried et al., 2001; Moore et al., 2010; Searle and Rockwood, 2015). Impaired grip strength, fatigue, sluggish gait speed, weight loss, and decreased activity have all been linked to sarcopenia and frailty. The kinetics of cellular metabolism, the creation of reactive oxygen species, and apoptotic pathways are all influenced by mitochondria. Due to altered sensitivity to the frailty syndrome in elderly patients, mitochondrial genetic variation may be linked to disease vulnerability. Dementia risk is also increased when fragility is present. Greater muscle strength was linked to a lower chance of acquiring Alzheimer's disease, according to clinical investigations of elderly individuals without dementia at baseline (Boyle et al., 2009; Cleasby et al., 2016; Clegg et al., 2013; Fried et al., 2001; Moore et al., 2010; Searle and Rockwood, 2015). The combination of decreased muscle strength, balance, and mobility is a common component of increasing loss of independent function, increasing the risk of falls. Ground-level falls can result in both injury and fear of future falls, leading to decreased mobility and further loss of skeletal muscle mass and functional strength. Decreasing mobility and inadequate nutrition can result in chronic skin breakdown and wounds, which are not only difficult to manage, but markedly increase stress in family caregivers. (Halter, 2022).

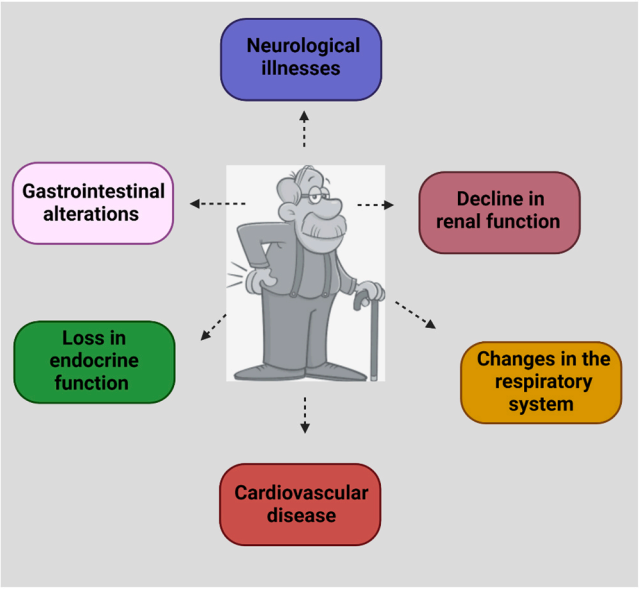

Fig. 1. Pathophysiology of ageing. The process of ageing affects numerous organs and systems in the human body including the heart, kidneys, brain, lungs, endocrine system, and digestive system. A portion of this decline is brought on by the loss of cells from these organs.

Table 1
Effects of ageing in different organ systems (Bhutto and Morley, 2008; Denic et al., 2016; Janssens et al., 1999; Strait and Lakatta, 2012; Wyss-Coray, 2016).

Organ System	Symptoms of Aging
Neurological	Cerebrovascular accident (CVA), Alzheimer's disease, other dementias, Parkinson's disease
Cardiovascular	Coronary artery disease and atherosclerosis, heart failure, hypertension, hematologic malignancy
Pulmonary	Chronic obstructive pulmonary disease (COPD), lung cancer, pneumonia
Musculoskeletal	Osteoporosis, osteoarthritis, fractures, skeletal malignancies
Endocrine	Diabetes mellitus
Urological/ Gynecologic	Urinary tract infections, urogenital cancer, cervical cancers, breast cancers, prostate cancer
Special Senses	Presbycusis, presbyopia, cataract, macular degeneration, glaucoma
Gastrointestinal	Malabsorption, GI malignancies, bowel obstruction, diverticular disease
Additional ageing concerns	Independence, falls, elder abuse and neglect, psychiatric concerns, skin breakdown, skin tears

1.2. Neurological

The prevalence of neurological illnesses in the general population, particularly in the elderly, makes them a significant worldwide health issue. Age also affects the impact of risk factors, clinical presentation, and the natural course of these diseases. The cellular environment of the brain changes with age, including the presence of mitochondrial dysfunction, intracellular accumulation of oxidatively damaged macromolecules, dysregulated energy metabolism, impaired cellular "waste disposal" mechanisms, impaired adaptive stress response signaling, compromised DNA repair, aberrant neuronal network activity, dysregulated neuronal Ca2 + handling, stem cell exhaustion, and inflammation (Lautrup et al., 2019). Age is by far the biggest risk factor for most neurological diseases (Dumurgier and Tzourio, 2020). Over the 1990–2016 period, the prevalence of dementia, stroke, or Parkinsonism has increased by a factor of two or three globally (Feigin et al., 2003). Parkinson's disease, diffuse brain shrinkage, neurodegeneration, and dementia are all conditions that are made more likely in older people by abnormal compensatory processes. The most common source of neurological impairment in older adults in Alzheimer's disease (AD) (Bhutto and Morley, 2008; Denic et al., 2016; Janssens et al., 1999; Strait and Lakatta, 2012; Wyss-Coray, 2016). Chronic progressive neurological disease with decreasing motor and cognitive function is a frequent cause of the increasing need for assistance from caregivers. Complex brain disorders like Alzheimer's and related dementias (ADRD) slowly erode people's memory and cognitive abilities. Daily activities and independence are gradually lost because of ADRDs. Being a significant burden on individuals, families, and society, ADRDs rank among the most expensive diseases to treat, with costs in the US expected to reach $305 billion in 2020 (Hurd et al., 2013). About 110,000 fatalities were attributed to ADRD in 2017, making it the seventh most common cause of death (Alzheimer's Association, 2016). Rapid cognitive deficits that affect many different areas of fluid cognition, including episodic memory, are symptoms of ADRD, an age-related disorder (Richards and Deary, 2005). According to some estimates, 50–80% of all cases of ADRD are never identified (Prince et al., 2011) since it is expensive and frightening, rendering it vulnerable to significant under-diagnosis at the population level (Connolly et al., 2011; Douzenis et al., 2010).

The greatest risk factor for dementia is chronological age, and the prevalence of dementia rises with age (Daviglus et al., 2010). The rate of aging varies significantly among people, and a growing body of research points to a link between perceptions of aging, cognitive changes, and dementia-related outcomes (Stephan et al., 2017). The risk of dementia is becoming progressively linked to a variety of age-related neuropathologies (Power et al., 2018). Dementia is extremely rare before the age of 60, and prevalence and incidence climb exponentially only after the age of 70, in contrast to the well-known age-related cognitive decline in nondemented patients that begins in young adulthood. This shows that the diseased brain processes must develop to a certain degree before they can induce cognitive impairment severe enough to develop into a clinically exhibited dementia condition. This degree of cognitive decline is considered a clinically significant threshold for dementia (Fratiglioni et al., 2010). Most neurodegenerative disorders have aging as their main risk factor. One in ten people 65 years of age and above have AD, and the prevalence of the condition rises with age (Hou et al., 2019). Cognitive impairment and dementia disorders exhibit significant heterogeneity in risk factors, symptoms, and underlying mechanisms. To develop effective prevention and treatment strategies, it is essential to consider and address this heterogeneity (Selbæk, 2021). For the ageing population with dementia, providing holistic post-diagnostic care, managing neuropsychiatric symptoms through appropriate interventions, and supporting family caregivers are crucial recommendations for individuals with dementia (Livingston et al., 2020).

1.3. Gastrointestinal

Although some Gastrointestinal (GI) illnesses are more common in the elderly, there are no GI diseases that are specific to this age group. Gastrointestinal alterations are typical in the old. While certain GI system changes with ageing are physiological, others are pathological and are more common in those over the age of 65 (Dumic et al., 2019) Esophageal, gastric, and colonic motility are particularly affected by changes in gut function with age. Postprandial hypotension, malnutrition, dysphagia, constipation, and fecal incontinence are all conditions that older people are more prone to. Nutrient absorption may be hindered by a decline in the number of myenteric plexus nerve cells that affect digestion absorption and the surface area of the small intestine because of villi degeneration. The age-related illnesses rise in the occurrence and severity of infections appears to be significantly influenced by the intestinal immune system's impairment, which includes the mucosal layer of the digestive tract (Soenen et al., 2016).

Age-related anorexia and the accompanying caloric and/or nutritional insufficiency can be caused by changes in taste and smell, changes in gut motility, and aberrant intestinal flora. Bowel blockages or constipation are caused by the weakening of the smooth muscle lining the intestinal tract, which can encourage diverticular disease, and requires significant daily monitoring and management. Additionally, changes in medication metabolism due to decreased hepatic metabolism increases the potential for adverse drug reactions and interaction (Halter, 2022).

1.4. Renal

As we age, the kidney's morphology, and function both significantly alter. Independent of obvious disease, the glomerular filtration rate gradually decreases. Glomerular, vascular, and concomitant parenchymal changes occur while other age-related diseases including diabetes and hypertension have a random detrimental impact on both form and function. Age-related declines in renal function have significant effects on a person's ability to maintain their homeostasis as well as their ability to employ medication therapy and receive and donate organs for transplantation (Martin and Sheaff, 2007; Ray and Reddy, 2023). A reduction in functioning glomeruli through sclerotic alterations occurs in the kidneys as a person ages. Furthermore, a decline in GFR is routinely observed as patients age, which puts elderly patients at a considerably higher risk for difficulties if they acquire chronic or acute renal illness due to a reduction in functional glomeruli (Bhutto and Morley, 2008; Denic et al., 2016; Janssens et al., 1999; Strait and Lakatta, 2012; Wyss-Coray, 2016). Progression to the need for dialysis is a significant point in advancing renal disease and failure, requiring a marked increase in medical treatments and skilled caregivers to provide both medical monitoring and transportation (Halter, 2022).

1.5. Cardiovascular

The greatest risk factor for cardiovascular disease is the unavoidable process of aging. Numerous questions remain regarding how the genetic pathways that regulate aging in model organisms influence cardiovascular aging, even though much research in the cardiovascular area has considered both young and old humans (North et al., 2012). In the USA, nine out of the top ten causes of death in 2021 were the same as they were in 2020. Heart disease, cancer, and COVID-19 were the three main causes of death in 2021 (Murphy et al., 2021). Overall the main cause of death in the United States is cardiovascular disease, which accounts for more than 40% of fatalities in those 65 years of age and older and includes conditions like atherosclerosis and hypertension, which induce heart failure and stroke. In the same age range, about 80% of all cardio-vascular deaths take place. Age is the main risk factor for cardiovascular disease, hence. Due to interactions between age-related cardiovascular changes in health and particular pathophysiologic mechanisms that underlie disease, the clinical presentations and prognosis of certain cardiovascular diseases are likely altered in older individuals with advanced age (Lakatta, 2002). The heart and arterial system are significantly impacted by aging, which increases the risk of cardiovascular diseases (e.g. atherosclerosis, hypertension, myocardial infarction, and stroke) (Lakatta and Levy, 2003a). Pathological changes such as hypertrophy, altered left ventricular (LV) diastolic performance, reduced LV systolic reverse capacity, increased arterial stiffness, and compromised endothelial function are examples of ageing cardiovascular tissues (Lakatta and Levy, 2003b). Age also has an impact on heart rate regulation by causing a decrease in both maximal heart rate and rate variability (Antelmi et al., 2004). In addition to the loss of cells in the sinoatrial node, which regulates heart rate, structural changes in the heart, such as fibrosis and hypertrophy, which decrease the transmission of electric impulses throughout the heart, also affect heart rate (North and Sinclair, 2012).

The risk of developing cardiovascular disease increases with age due to a loss of compensatory and cardioprotective systems, which would normally aid in delaying the onset of cardiovascular illness. Vascular stiffening increased left ventricular wall thickness, myocardial fibrosis, calcification of valves and structures connected to them, decreased aerobic tolerance, and an increase in problematic cardiomyocyte remodeling are all potential risk factors for cardiovascular events and chronic disease as people age (Bhutto and Morley, 2008; Denic et al., 2016; Janssens et al., 1999; Strait and Lakatta, 2012; Wyss-Coray, 2016).

1.6. Respiratory

As advancing age, the respiratory system experiences several anatomical, physiological, and immunological changes. Deformities of the thoracic spine and chest wall are examples of structural alterations that affect the compliance of the entire respiratory system, increasing the labor required to breathe. Age-related declines in respiratory muscle power might make it more difficult to cough effectively, which is crucial for clearing the airways. With aging, the airway receptors experience functional changes and are less likely to respond to medications used to treat the same problems in younger patients. Older persons are more susceptible to ventilatory failure during high-demand situations (such as heart failure, pneumonia, etc.) and potential negative consequences because they experience less dyspnea and have a weakened reaction to hypoxia and hypercapnia (Sharma and Goodwin, 2006). The main causes of age-related changes in the respiratory system include loss of elasticity and decreased compliance of the chest wall, which results in greater work of breathing, increased residual volume, and increased functional residual capacity. The strength and efficiency of the breathing muscles are also reduced as a person ages. This creates reduced tidal lung volume and is most apparent in the supine position, a common hazard of hospitalization. These changes lower elderly patient's threshold for recovering from an acute respiratory illness or diseases resulting in chronic respiratory failure (Bhutto and Morley, 2008; Denic et al., 2016; Janssens et al., 1999; Strait and Lakatta, 2012; Wyss-Coray, 2016). Additionally, normal ageing results in a slow decline in cardiac output due to decreased filling and heartrate with aging, contributing to a gradual decrease in the ability to deliver oxygen to working muscles This can result in reduced exercise tolerance necessary for activities previously accomplished with less effort. Fortunately, the rate of decline in maximal oxygen uptake (VO2 max) can be slowed by activity and exercise even at an advanced age (Halter, 2022).

1.7. Endocrine

In the context of metabolic and hormonal control, age-related loss in endocrine function can have a variety of implications in ageing populations (Bhutto and Morley, 2008; Denic et al., 2016; Janssens et al., 1999; Strait and Lakatta, 2012; Wyss-Coray, 2016). A reduction in the production of triiodothyronine and thyroxine leads to a general decline in metabolic activity. Furthermore, circadian rhythms are changed, and patients are more likely to experience less REM, rapid eye movement, and sleep. Age-related changes in insulin production and glucose metabolism contribute to the onset of diabetes mellitus in the elderly. An increased risk of cardiovascular disease, a loss of bone mass, and atrophy of estrogen-responsive tissue are all common side effects of menopause, which normally occurs in women in their sixth decade of life (Bhutto and Morley, 2008; Denic et al., 2016; Janssens et al., 1999; Strait and Lakatta, 2012; Wyss-Coray, 2016). Many of these endocrine changes can be tied together under sarcopenic changes in the elderly. Sarcopenia is a major contributing factor to the increased morbidity and mortality linked to chronic kidney disease (Fernandes and Valdes, 2015; Ho et al., 2011; Jang, 2016; Otomo-Corgel et al., 2012; Stefan et al., 2016; Wei et al., 2008). Around the age of 60, muscle mass decreases at a t rate of 1.5–3% each year, which increases after the age of 75. Sarcopenia is related to type II diabetes, cardiovascular disease, and progressive chronic kidney disease. Type II diabetes hastens the loss of muscle mass and strength due to insulin resistance, hyperglycemia, and diabetes comorbidities. Skeletal muscle mass accounts for more than 75% of all insulin-mediated glucose clearance, hence insulin resistance in this tissue is crucial (Fernandes and Valdes, 2015; Ho et al., 2011; Jang, 2016; Otomo-Corgel et al., 2012; Stefan et al., 2016; Wei et al., 2008). As such, elderly patients with comorbidities are more likely to develop sarcopenia, especially in the presence of diabetes.

1.8. Ageing populations – a global perspective

Future population ageing trends result from a combination of diminishing fertility and rising life expectancy in specific areas of the world (Lutz et al., 2008). In most developed nations, the average life expectancy of people has doubled during the past 200 years (Oeppen and Vaupel, 2002). The use of antibiotics improved medical treatment, and better water, food, cleanliness, housing, and lifestyle practices, as well as vaccination against infectious diseases and antibiotics, decreased mortality initially in the young then, after about 1950, in the 70-plus age group (Partridge et al., 2018). Overall, the world is aging rapidly. According to epidemiological statistics, 11% of the world's population is over 60, and that number is expected to rise by 22% in the year 2050 (Newgard et al., 2013). However, there are currently significant differences between continents and nations. Since 1950, the number of people has roughly doubled every 37 years, reaching 5 billion in 1987. After that, it will likely take more than 70 years for the world's population to double once more, reaching over 10 billion people by 2059 (2022a; 2022b). The period between 1962 and 1965 observed the fastest growth in the world population over the 100 years between 1950 and 2050, with an average annual growth rate of 2.1 For the first time since 1950, population growth slowed in 2020 (2022a; 2022b). Around 8.5 billion people could be on the planet in 2030, and another 1.18 billion could be

added over the next two decades, bringing the total to 9.7 billion by 2050. Nevertheless, the rate of growth in the world's population has slowed. While some nations and regions have seen their populations stabilize or even start to decline, others have seen continued population expansion. Between 2022 and 2050, eight nations are predicted to have the greatest contribution to the world population growth: the Democratic Republic of the Congo, Egypt, Ethiopia, India, Nigeria, Pakistan, the Philippines, and the United Republic of Tanzania (2022a; 2022b). Over the years 2022–2050, it is anticipated that the populations of the Democratic Republic of the Congo and the United Republic of Tanzania would increase significantly, at a rate of between 2% and 3% per year. Different rates of population increase among the world's top nations will affect their ranking; for instance, India is predicted to overtake China as the most populated nation in 2023 (2022a; 2022b). India, currently the second-most populated nation in the world, is expected to keep expanding and surpass China as the most populous nation in 2025–2030, with a population of 1.64 billion by 2050. According to projections, India would have reached 1.45 billion people by 2100 and will have seen the second-largest population loss in the period 2050–2100 behind China. Brazil and Bangladesh will come in third and fourth, respectively, in terms of population losses (Gu et al., 2021).

Globally, people are living longer, often into their 60 s and beyond (Beard et al., 2016). One in six individuals on the planet will be 60 or older by 2030. That number of people will double by 2050. Of even greater significance, between 2020 and 2050, the number of people 80 or older is projected to triple, reaching 426 million. Although population ageing was initially greatest in high-income nations, the greatest shift is currently being seen in low- and middle-income nations (2022a; 2022b). It is currently estimated that 12% of the world's population is over 60 and will rise to 22% by the year 2050. Eighty percent of senior citizens will reside in low- and middle-income nations by 2050 (2022a; 2022b). As such, nations will need to make significant changes to address their healthcare systems with their ageing populations (2022a; 2022b). Multimorbidity and non-communicable diseases present serious problems for global healthcare systems. The aging population is the main cause of the rising prevalence. Proper formal systems for providing long-term care and support to increasingly aging populations must be created and implemented because low- and middle-income countries are disproportionately affected (Mitchell and Walker, 2020).

The impact of ageing populations is further complicated by the diversity of elderly persons. The physical and mental abilities of some 80-year-olds are comparable to those of many 30-year-olds. Others notice considerable capacity losses much earlier in life. This wide spectrum of older people's experiences and demands must be taken into account in a comprehensive public health response (2022a; 2022b). Age-related diversity is not a coincidence. A significant portion results from how individual physical and social circumstances affect opportunities and health behaviors. Personal traits, such as the family of origin, gender, and race skew environmental relationships and cause health disparities. Across some societies, it is a common perception to think that older people are fragile, reliant on others, and a burden on society. These and other ageist attitudes can impact public policy and limit the possibilities for healthy ageing (2022a; 2022b). A drastic worldwide change in ageing populations will require changes in changing how people feel, approach, and act toward age and ageism. Communities must be developed in ways that foster the abilities of older people; delivering accessible person-centered integrated care and primary health services that are responsive to the specific needs of older people (Winterton et al., 2016). It is particularly to provide access to a variety of levels and systems delivering quality long-term care necessary to support the quality-of-life of individuals, their families, and their caregivers. (2022a; 2022b). According to Fang and colleagues, an inter-disciplinary collaborative approach is necessary to prepare and face the challenges as society continues to age. The authors targeted Chinese healthcare system and suggest that breaking knowledge gaps and eliminating boundaries among different sectors to further integrate and synergize different healthcare-related parties at societal, individual, and molecular levels will optimize the outputs of the healthcare system (Fang et al., 2015). Similar policy stratetiges can be implemented in US through the combined efforts and collaboration of various disciplines, including policies, geriatric care, drug development, personal awareness, the utilization of big data, machine learning, and personalized medicine, US healthcare system and the country itself has the potential to become a place that optimizes and celebrates the well-being and longevity of its elderly population in the forthcoming years.

While some variations in older people's health are inherited, the majority are related to their homes, neighborhoods, and communities, as well as by their sex, race, or financial status. Dementia has been elevated to the top of the global public health priority list because of the demographic shift toward an aging population around the world. 50 million people worldwide currently live with dementia, and 9.9 million new cases are reported annually (Prince et al., 2015). Evidence has recently come to light suggesting that dementia incidence may have decreased over the previous few decades in high-income nations (Ding et al., 2020). Physical and social settings can have a direct impact on health or act as obstacles or motivators that influence opportunities, choices, and healthy behavior. Family systems are particularly important. Maintaining healthy habits throughout life lowers the risk of non-communicable diseases, enhances physical and mental capabilities, and delays the need for acute and chronic care (2022a; 2022b). Individuals can still accomplish their goals despite capacity reductions when they live in supportive physical and social contexts. Supportive surroundings include places where it is easy to move about and have access to safe public spaces and transportation. Environmental and individual strategies must be considered when creating a public health response to ageing. Such strategies support recovery, adaptation, and psychosocial growth. Among these strategies, supporting both formal (professional) and informal (family or community) caregivers of vulnerable individuals remains critical for the long-term health of this population. The role of multiple comorbidities in the progression of disability and dependency in older adults has recently generated interest. Such comorbidities are becoming significantly more prevalent in low and middle-class nations as public health and medical advances markedly increase life expectancies. Education and support of systems to provide finance and structure to the role of both formal and informal caregivers is essential.

1.9. Biological mechanisms of ageing

There are numerous hypotheses on the biological origins of aging, which implies that numerous systems play a role in the aging process (Weinert and Timiras, 2003). According to Kirkwood's theory (Kirkwood, 2005), the underlying cause is primarily the result of a buildup of random, unrepaired molecular damage over time. Over time, this results in cellular abnormalities and tissue dysfunction, which raises the risk of frailty and age-related disorders. The main ageing-related mechanisms take place at the cellular level as cell growth gradually slows down until it stops altogether. In addition, ageing is influenced by changes in cellular metabolic activity, increased protein synthesis, apoptosis resistance, and an accumulation of cells. The total number of these senescent cells in our bodies remains manageably low as we age through young and middle adulthood and can be overcome by the body's higher number of cells that are still alive and operating following normal physiology (Goldsmith, 2012; López-Otín et al., 2013; Pallin et al., 2014; Tchkonia and Kirkland, 2018). The onset of age-related disorders occurs when we pass the capacity threshold in terms of the number of senescent cells in our bodies and their subsequent accumulation in our tissues. For instance, some argue that the onset of osteoarthritis is related to the buildup of senescent cells inside the areas of the affected joints, which then causes degeneration and eventually reduces the function of that joint and its utility in facilitating human mobility (Goldsmith, 2012; López-Otín et al., 2013; Pallin et al., 2014; Tchkonia and Kirkland,

2018). Another example is age related brain atrophy, even in those who are cognitively healthy, atrophy and consequent brain shrinkage are frequent with age. The weight of the brain is one of the first observations in an autopsy. An average brain weighs 1200–1400 g. The decline in brain mass begins around the age of 45–50 and reaches its lowest levels after 86 years (Dekaban and Sadowsky, 1978).

The human ageing process begins at birth. It is a life-long process with causes that are generally acknowledged, but whose exact origins are unknown. Several hypotheses attempt to describe the normal ageing process. Since living to a very old age holds little evolutionary benefit, some researchers believe that ageing is a biologically programmed mechanism. (Goldsmith, 2012; López-Otín et al., 2013; Pallin et al., 2014; Tchkonia and Kirkland, 2018). It has been suggested that the ageing process in humans results from hormonal mediation that is genetically pre-programmed through programmed senescence. Specifically, it is believed that the neuroendocrine system regulates the release of growth hormones and insulin, which play crucial roles is mediating the ageing process. The buildup of toxins at the cellular level throughout a patient's life is also believed to contribute to ageing through the formation of reactive oxygen species and the subsequent methylation alterations in our DNA (Goldsmith, 2012; López-Otín et al., 2013; Pallin et al., 2014; Tchkonia and Kirkland, 2018). More recently, additional mechanisms of ageing proposed, including DNA damage accumulation, loss of proteostasis, epigenetic alterations, mitochondrial dysfunction, senescence and inflammation, and stem cell depletion (Fig. 2).

1.9.1. *Genome instability*

Every organ and tissue experiences extensive functional deterioration as a result of the complicated, diverse process of aging. Phenotypically, the aging process is linked to a wide range of characteristics at the molecular, cellular, and physiological levels, including genomic and epigenomic changes, proteostasis loss, deteriorating cellular and subcellular function, and signaling system dysregulation. DNA damage impacts the majority, if not all, components of the aging phenotype, making it the most plausible common factor in the aging process. In order to create interventions that effectively combat age-related dysfunction and disease, it makes sense to focus on DNA damage and its mechanistic linkages with the aging phenotype (Schumacher et al., 2021). Similarly, telomere shortening is another hallmark of ageing as with age, telomere length decreases. The health and lifespan of an individual are impacted by the progressive shortening of telomeres, which causes senescence, apoptosis, or oncogenic transformation of somatic cells. Reduced survival and higher illness incidence have been linked to shorter telomeres (Shammas, 2011).

DNA Damage: Accumulation of DNA damage is a natural driver of ageing through repeated assaults from endogenous and exogenous genotoxins (da Silva et al., 2019; da Silva and Schumacher, 2021; Moskalev et al., 2013). The most conclusive evidence for increased DNA damage or mutations (e.g., spontaneous deamination and oxidative base modifications to strand breaks and crosslinks) has been the age-dependent increase in mutations (Vijg and Dollé, 2002; Zhang et al., 2019). Unrepaired lesions can have extremely harmful effects due to their interference with transcription and replication. Chromosomal aberrations and irreversible mutations accumulate and spread from inaccurate repair or mis-replication. As a result, cancer can result from mutations when tumor suppressor genes or oncogenes are impacted, which increases with age (Blokzijl et al., 2016; Hoeijmakers, 2009; Jaiswal et al., 2014; Osorio et al., 2018).

The DNA damage response (DDR), which detects specific DNA base changes, halts the cell cycle and repairs the lesion, is made up of highly specialized and conserved lesion-specific repair and signaling pathways. If lesions are successfully repaired, the DDR signaling is terminated and cells return to their original, prelesion state; if lesions are not successfully repaired, the DDR signaling persists, leading to cell senescence or death (d'Adda di Fagagna, 2008; Fitsiou et al., 2021). These initial steps can determine a cell's fate. These states can eventually speed up tissue ageing while simultaneously inhibiting carcinogenesis (Hoeijmakers, 2009).

Telomere Shortenting: Telomeres are protective segments at the ends of chromosomes. In vertebrates, they consist of TTAGGG repeats and

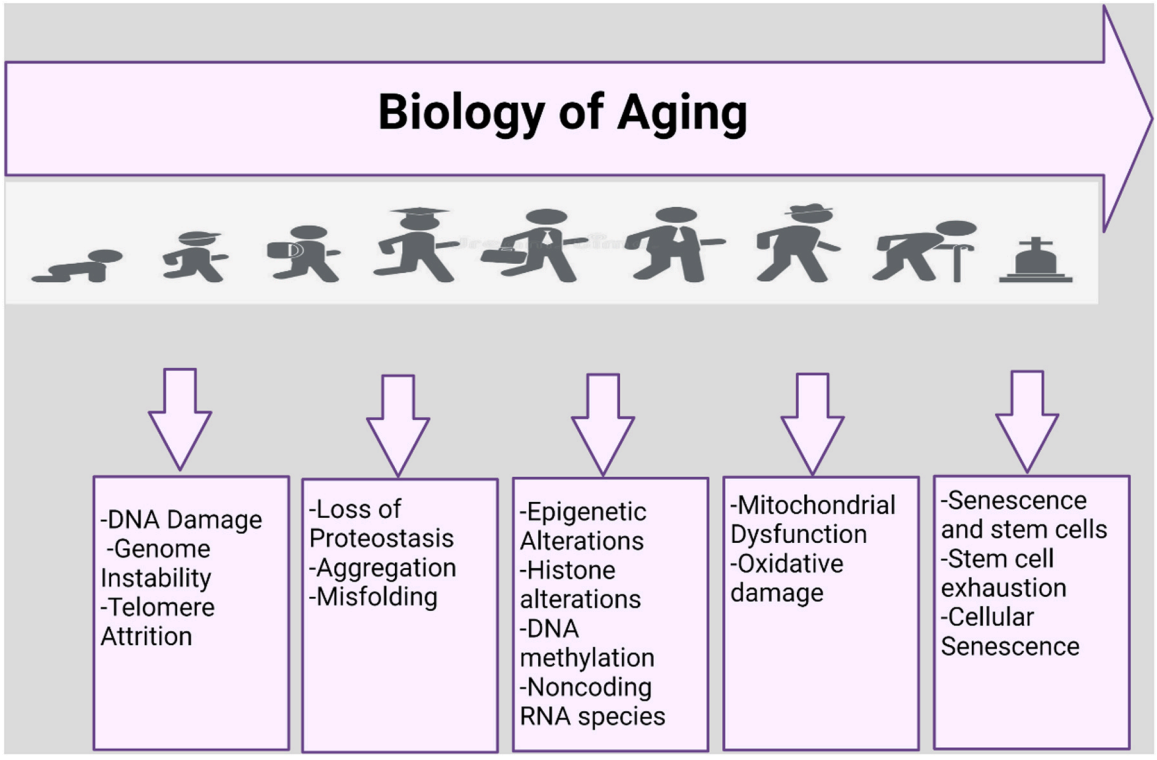

Fig. 2. Biological Mechanisms of Ageing. Major ageing hallmarks include DNA damage, loss of proteostasis, epigenetic alterations, mitochondrial dysregulation, and cellular senescence.

associated proteins. As telomeres shorten during DNA replication, they trigger a DNA damage response, leading to cell cycle arrest and cellular senescence (Tran and Reddy, 2021; Rossiello et al., 2022). When telomeres are severely shortened, a series of processes are initiated that activate the DDR which can cause cellular senescence and mitochondrial malfunction as well as accelerate stem cell ageing (Behrens et al., 2014; Zhu et al., 2019). Telomeres gradually shorten with age (Canela et al., 2007), and the rate of telomere shortening has been used to estimate the lifetime of species (Whittemore et al., 2019). Several human disorders have also been linked to telomere shortening, which is assumed to be a factor in age-related tissue dysfunction (Armanios et al., 2009; Decker et al., 2009; Kong et al., 2013; Rudolph et al., 1999). One of the most prevalent theories holds that the reduction of telomere length causes mammalian cells to age (Mikhelson and Gamaley, 2008). Point mutations inside the telomere cause faster telomere length attrition and result in premature ageing, which supports this fact (Fyhrquist and Saijonmaa, 2012). There is strong evidence to suggest that elevated oxidative stress and inflammation are key factors in the shortening of telomeres, possibly through reducing telomerase activity and/or TRF-2 levels (Prasad et al., 2017).

1.9.2. Proteostasis

Proteostasis networks ensure protein homeostasis, detecting and correcting abnormalities for normal functioning. Under typical circumstances, these systems quickly detect and correct proteome abnormalities to reestablish basal homeostasis. Numerous cells and organs gradually lose the capacity to maintain proteostasis with aging under both stress and resting conditions. Many human pathologies, particularly neurodegenerative illnesses like Alzheimer's disease or Parkinson's disease, are characterized by a loss of proteostasis as a pathogenesis (Kaushik and Cuervo, 2015).

To form exact three-dimensional structures, proteins must fold and assemble. It might be tough to attain and maintain a suitable folded state in a congested cellular environment (Bartlett and Radford, 2009). A closely controlled system made up of chaperones and protein-degradation machinery is required to take coordinated action at various phases to maintain protein homeostasis or proteostasis (Hipp et al., 2019; Klaips et al., 2018). When the proper folding state of the proteins cannot be maintained, the proteostasis mechanisms guarantee that the misfolded proteins are removed (Klaips et al., 2018). However, this process can be hampered when DNA mutations affect essential proteostasis proteins that effect proper protein folding (Ben-Zvi et al., 2009; David et al., 2010; Walther et al., 2015). The development of age-related disorders including AD, PD, and HD can then be attributed to altered proteostasis function (Klaips et al., 2018). There is strong evidence that proteostasis and healthy aging are closely related. The longest-living species have been found to have more stable proteomes (Treaster et al., 2014) (cellular proteins that are more resistant to damage), and, for example, in the case of the long-lived naked mole rat, proteome stability correlates with enhanced activity in the proteostasis systems (Pérez et al., 2009). Furthermore, mammalian and invertebrate lifespans and healthspans are increased by interventions that alter the activity of the proteostasis networks. Disruption of proteostasis causes the cell to adapt. Cells have created a variety of methods to lessen misfolding and eliminate misfolded proteins in order to deal with this condition. The emergence of chaperones, which attach to incomplete peptide chains, is one of these methods. This helps the peptides fold correctly and prevents them from folding too early. Additionally, chaperones prevent proteins from becoming denaturized, which is why these proteins are also known as heat shock proteins (Guo et al., 2022).

The proteostasis network's various components, from translation through degradation, must be tightly regulated and communicate with one another in order to maintain proteome integrity (Matai and Slack, 2023). However, as cells get older, the burden of misfolded proteins outweighs their ability to keep the proteome intact, which causes cellular function to be disrupted. The proteostasis network has a critical role in controlling both the development of age-related diseases and lifespan, according to accumulating data using the model organism *C. elegans*. Invaluable knowledge about the regulation of various proteostasis nodes at the organismal level has also been gained from these studies in *C. elegans*. This knowledge, which includes the regulation of these nodes by cell non-autonomous mechanisms, can be crucial for identifying new therapeutic targets to postpone age-related diseases in humans (Zhang et al., 2022). Current research is constantly driving toward the discovery of genetic and pharmaceutical therapies that can improve organismal proteostasis and lengthen life. An effective technique to influence the healthspan of an organism appears to be through the control of stress responses by cell non-autonomous processes (Thompson and De-Souza, 2023).

1.9.3. Epigenetic alterations

A cell's response to injury or extracellular signals can be modified by altering the epigenetic landscape, which regulates transcription regulatory networks that impact tissue function. Several transcription factors have been discovered as playing important roles in ageing (Alcedo and Kenyon, 2004; Ogg et al., 1997). As people age, chromatin state and structure change (Booth and Brunet, 2016; Feser and Tyler, 2011). Leading causes of genomic instability continue to include telomere attrition and accumulation of mutations brought on by a steady decline in DNA damage repair with ageing. Yet, it is now known that epigenetic mechanisms play a significant role in the changes in genomic structure and function that come with age. Histone alterations, DNA methylation, and noncoding RNA species are the three mainstays of epigenetic control (Gonzalo, 2010). Age-associated epigenetic marks for histones include: H3K4 trimethylation (H3K4me3), H3K9 trimethylation (H3K9me3), and reduced H3K27 trimethylation (H3K27me3) (Booth and Brunet, 2016). Different H3K27me3 demethylases regulate the insulin/insulin-like signaling (IIS) pathway, the heat shock response, and fat metabolism, which have opposing effects on longevity (Greer et al., 2010; Han et al., 2017; Jin et al., 2011; Labbadia and Morimoto, 2015; Maures et al., 2011; Ni et al., 2012). The loss of heterochromatin is a characteristic of an ageing epigenome (Ni et al., 2012; Shumaker et al., 2006; Wood et al., 2010). The DNA methylation landscape may be utilized as an epigenetic clock for chronological age since differentiating methylation marks gradually accumulate (Bollati et al., 2009; Fraga et al., 2005; Hernando-Herraez et al., 2019; Horvath and Raj, 2018). Dysregulation of DNA methylation patterns throughout ageing impacts gene expression since DNA methylation is a regulatory mark often linked with transcriptional repression (Hernando-Herraez et al., 2019). Age-related transcriptional drift is likely influenced by the modifications in DNA methylation patterns, chromatin state and structure, histone marks, and transcription factor binding and activity (Bryois et al., 2017; Hernando-Herraez et al., 2019; Lai et al., 2019; Maures et al., 2011; Rangaraju et al., 2015; Stegeman and Weake, 2017). For example, the longevity of *C. elegans* increased when transcriptional drift related to ageing was suppressed (Rangaraju et al., 2015). Gene expression characteristics of cellular ageing make it possible for chronological and biological ages to be classified using transcriptome clocks of aging.

Given the wide range of cellular functions that epigenetic mechanisms can influence, it has been suggested that epigenetic changes could play a significant role in the pathophysiology of ageing and ageing-related disorders, particularly cancer. The accumulation of epigenetic flaws with age may enhance cellular transformation and increase cancer susceptibility, as some epigenetic abnormalities are interestingly frequent in ageing and cancer (Gonzalo, 2010). Researchers have begun to understand how noncoding (nc)RNA species contribute to the integrity and operation of the genome. MiRNAs are the best-studied ncRNAs. MiRNAs have been implicated in a wide range of biological processes, including the control of cell cycle, differentiation, apoptosis, and tumor suppression (Grillari and Grillari-Voglauer, 2010). The buildup of genomic instability is thought to be a major contributor to ageing. It's interesting to note that several miRNAs are activated in response to

cellular stress, which results in lower quantities of proteins needed for DNA repair (Crosby et al., 2009). HIF-1 (hypoxia-inducible factor-1) specifically activates miRNAs (Pulkkinen et al., 2008). Significantly, overexpression of hypoxia-induced miRNAs has been observed in some human cancers (Liao et al., 2014), pointing to a potential role for these ncRNAs in the increased risk of cancer with ageing (Grammatikakis et al., 2014).

1.9.4. Mitochondrial dysfunction

Literature suggests that age-related diseases and aging are closely linked to an imbalance between energy supply and demand. This imbalance may be corrected through a variety of interventions, such as increased physical activity and calorie restriction as well as naturally occurring molecules that target conserved pathways for longevity. The importance of mitochondria in the development of age-related disorders such as neurological and cardiovascular diseases has come to light in addition to their role as energy producers (Amorim et al., 2022). It was discovered in the first half of the 20th century that calorie restriction lengthened mouse life span (Harman, 1956; Pérez et al., 2009a; Pérez et al., 2009b). This supported the growing theory that life span regulation may be aided by metabolism in general and potentially energy metabolism. The "Rate of Living Hypothesis," which developed throughout the early 20th century, was founded on the understanding that metabolism may affect aging. It said that animals with greater metabolic rates had shorter life spans than species with lower metabolic rates (Harman, 1956; Pérez et al., 2009a; Pérez et al., 2009b). For instance, whereas certain reptiles, like turtles, with apparently sluggish metabolic rates may live for many decades, rats with high metabolic rates would only survive for a few years. Naturally, this theory could not explain why certain creatures live a long time. The Free Radical Theory of Aging, which assumed that the production of oxygen radicals as a byproduct of biological processes should be enhanced in animals with higher metabolic rates, eventually replaced the Rate of Living Hypothesis (Harman, 1956; Pérez et al., 2009a; Pérez et al., 2009b). In turn, these free radicals would interact with cellular components and change the structure and operation of the cells. Furthermore, it was thought that the buildup of oxidative stress caused by the metabolism would result in an ageing phenotype.

The accumulation of molecular damage in the cells can lead to organelle dysfunction including mitochondria, which have been associated with multiple age-associated pathologies (Frazier et al., 2019; Koopman et al., 2012; López-Otín et al., 2013). Age-dependent mitochondrial dysfunction stems from many sources, including accumulation of mitochondria DNA mutations, dysfunction of mitochondrial proteins, structural alterations in mitochondrial membranes, an imbalance between fission and fusion events, and defective clearance of damaged mitochondria by mitophagy (Manczak et al., 2006; Pradeepkiran and Reddy, 2020; Tran and Reddy, 2021). Mitochondrial dysfunction was suggested to be a consequence of nuclear DNA repair deficiencies and might account for some of the degenerative pathologies such as neurodegeneration (Fang et al., 2016; Hussain et al., 2021). As the mitochondrial respiratory chain's efficiency declines, there is an increase in electron leakage, which leads to a corresponding decrease in ATP production and a rise in the production of reactive oxygen species (Reddy and Beal, 2005, 2008). Cell senescence and stem cell exhaustion are both known to be influenced by mitochondrial malfunction (Correia-Melo et al., 2016; Fujimaki and Kuwabara, 2017). On the other hand, enhancing mitochondrial activity via NAD+ repletion encourages stem cell activity and lengthens lifespan. Therefore, maintaining proper ATP function is critical for understanding the pathophysiology of ageing in humans.

1.9.5. Senescence and stem cells

Cells exhibiting resistance to apoptosis, morphological abnormalities, changes in gene expression, and a complex senescence-associated secretory phenotype (SASP) are all signs of cellular senescence, which is characterized by an irreversible cell-cycle arrest (Coppé et al., 2010; Coppé et al., 2008; d'Adda di Fagagna, 2008; Fitsiou et al., 2021). For instance, critically short telomeres, oncogene activation, or stressing agents, epigenomic changes, and mitochondrial dysfunction can all result in persistent DDR that causes cellular senescence (Muñoz-Espín and Serrano, 2014; Serrano et al., 1997; Shah et al., 2013; Toussaint et al., 2000; Wiley et al., 2016). Several of these characteristics have been observed in a variety of postmitotic cell types, such as neurons and glial cells (Bussian et al., 2018; Dimri et al., 1995; Jurk et al., 2012; Korolchuk et al., 2017; Nelson et al., 2012). Senescent cells accumulate in a variety of aged and diseased tissues (Bussian et al., 2018; Hernandez-Gonzalez et al., 2021; Jeyapalan et al., 2007; Ogrodnik et al., 2017; Ogrodnik et al., 2019; Wang et al., 2009; Wang et al., 2018); however, the accumulation rates appear to be tissue-dependent. The SASP is one way that senescent cells contribute to tissue dysfunction (Coppé et al., 2010). In stem cells, ageing has both quantitative and qualitative consequences. Overall, the qualitative alterations are more significant since they have an impact on a cell's ability to self-renew, mature, and interact with external signals, particularly those from the stroma. Even though hematopoiesis is often kept at healthy levels during normal aging, the reduced function becomes immediately apparent when aged stem cells are stressed. It is abundantly clear that the ability to self-renew has been compromised, that the range of developmental potential has been constrained, and that the number of old stem cell progeny subjected to hematopoietic demands has decreased (Van Zant and Liang, 2003). Along with the loss of regenerative capacity, a decline in stem cell number and function has also been linked to age-related tissue malfunction (Cerletti et al., 2012; Ermolaeva et al., 2018; Ermolaeva et al., 2013; Ertl et al., 2008; Mueller et al., 2014; Oh et al., 2014; Ren et al., 2017; Rossi et al., 2007). Accumulation of DNA damage, telomere shortening, loss of proteostasis, epigenetic modifications, and mitochondrial dysfunction are known factors driving stem cells.

1.9.6. Brain aging: a risk factor of dementia

Brain aging is a complicated process that starts early in life, progresses with age, and impacts everything from the subcellular to the organ level. Brain volume loss, white matter deterioration, cortical thinning, ventricular expansion, and loss of gyrification are the main morphological characteristics of brain aging. Neuron cell shrinkage, demyelination, dendritic degeneration, small vessel disease, metabolic slowdown, microglial activation, and the development of white matter lesions are pathophysiological aspects of brain aging (Blinkouskaya et al., 2021). Normal aging does not result in a significant loss of neurons, but the size, length, quantity, and branching of the dendrites, as well as the density of the dendritic spines, may diminish with age (Duan et al., 2003). The frontal and temporal cortex, putamen, thalamus, and nucleus accumbens all see sizeable shrinkage (Fjell and Walhovd, 2010). It should be emphasized that neurogenesis may partially compensate for neuronal death in the hippocampus, thus neurogenesis is impaired dramatically with aging (Isaev et al., 2019). The literature search implies that as we become older, our brain's anatomical and functional connection patterns also alter. The default mode network, a network of interconnected brain areas that are active when a person is not paying attention to their environment, appears to be notably affected by the identified differences/changes, which causes older persons to have lower within-network connections. Additionally, the reduction in cognitive function in older persons seems to be connected to their diminished functional connectivity (Damoiseaux, 2017).

The advent of neurodegenerative disorders, such as Alzheimer's disease, increases exponentially with age, suggesting that the brain is particularly susceptible to the aging process. After age 65, it is predicted that the prevalence of AD doubles every five years, and the majority of cases of AD—more than 95%—are caused by late-onset Alzheimer's disease (LOAD), which is most commonly associated with aging. Unknown mechanisms underlie the aging-associated sensitivity to LOAD. It is thought that cellular senescence, a permanent state of cell growth

arrest, plays a significant role in aging and aging-related illnesses, such as AD (Liu, 2022). Also, studies have shown that there is a link between a history of depression and an increased risk of dementia, and older adults with late-life depression, including those with early-onset depression and late-onset depression, exhibit significant cognitive impairment that may not fully recover after successful antidepressant treatment (Diniz et al., 2013). In the case of most advanced dementias, there is no cure, however, only two kinds of medications are currently approved to treat AD, cholinesterase enzyme inhibitors and N-methyl D-aspartate antagonists. These medications only work to treat the symptoms of AD; they do not treat the underlying cause of the disease (Breijyeh and Karaman, 2020). Although there are predictable trajectories that cognitive functions and the neurological underpinnings of those functions follow as they mature, these trajectories can be changed (Turrini et al., 2023). Numerous observational studies have demonstrated that late-life cognitive impairment, dementia, and AD are multifactorial and heterogeneous disorders driven by a constellation of genetic and environmental risk and protective factors, including vascular, lifestyle-related, and psychosocial factors, support the possibility of dementia prevention (Kivipelto et al., 2018).

1.10. Gender differences in ageing

Men and women age differently, with significant differences between them (Fig. 3). There is a paradox because, on average, women live longer than men, which is consistent with their younger biological ages as determined by molecular biomarkers. At the end of life, women are weaker and in worse health, whereas men continue to demonstrate superior physical function. Additionally, a lot of age-related illnesses exhibit sex-specific patterns (Hägg and Jylhävä, 2021). In general, men free of chronic medical disease remain more physically resilient than women as they age, even after lean body mass and total body weight are considered (Peiffer et al., 2010). Women's bone and muscular health are adversely affected by the cessation of sex hormones during menopause. As a result, women suffer from a large loss of bone mineral density than men. The interplay between load and bone strength is better maintained in older men, which may account for the lower number of fractures reported in males (Seeman, 2001). In contrast, men lose more skeletal muscle mass as they age than women do, even though different regions of the body may exhibit sex-dimorphic effects and that menopause quickens the loss in women (Doherty, 2003). Both sexes are affected by sarcopenia, but elderly women are more at risk. In general, healthy adult men have better visual perception than women (Li et al., 2011). Yet, men are more likely to experience hearing loss. In addition, women's lungs are smaller and structurally different than men, which makes heavy exercise and breathing more difficult as women age (LoMauro and Aliverti, 2018). Age-related cardiac remodeling affects both men and women, although men experience a larger loss of myocytes and systolic performance in both humans and animals (Keller and Howlett, 2016). With regards to kidney function, men experience a larger loss in glomerular filtration rate as they age, while women are protected from large declines in kidney function from higher levels of estrogen before menopause (Gordon and Hubbard, 2019). These physiological differences between men and women as they age are due to several molecular mechanisms.

Molecular biomarkers show that women have younger biological ages than men. However, as they near the end of their lives, women have less muscle strength and more organ system decline than men. Despite evidence that men typically outperform women in physical function tests as they near the end-of-life, overall, women tend to outlive men. (Austad and Fischer, 2016; Gordon and Hubbard, 2019). Given that men and women have different life expectancies, levels of frailty, and biological ageing, several hypotheses have been put out to explain why men and women age differently (Austad and Fischer, 2016; Maklakov and Lummaa, 2013; Sampathkumar et al., 2020). The sex chromosomes (X and Y chromosomes) and the hormonally driven distinctions in biology are the two most well-explained biological explanations for their sex difference. There are obvious phenotypic differences between men and women since they are born with different sets of chromosomes—women have double X versions whilst men have XY versions. As a result, men are more likely to develop X-linked recessive disorders, such as hemophilia.

In addition to chromosomal differences, many biological variations between men and women can be attributed in large part to sex-specific hormones. Through the pituitary gland, the hypothalamus controls the

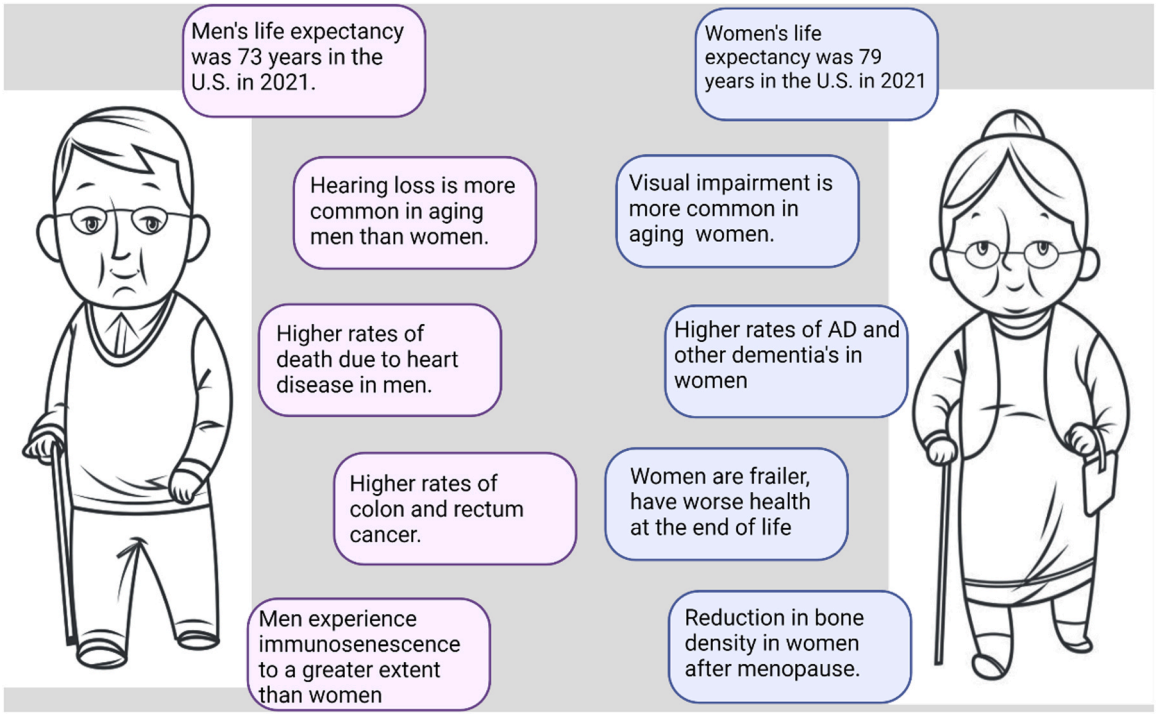

Fig. 3. The most notable sex disparities are in age-related illnesses, functionality, and frailty in men and women.

gonads' secretion of hormones, such as androgens (testosterone) in males as well as estrogen (estradiol, estrone, and estriol) and progestogens in women. Prenatal exposure to sex steroids has a lifelong impact and contributes to sex differences in neuroanatomy and neurochemistry. The most noticeable endocrine changes associated with ageing are caused by sex hormones. Menopause marks the beginning of the period of reproductive ageing that is characterized by decreased ovarian hormone output. Yet, the molecular factors that underlie menopause start sooner because of compensatory processes in the hypothalamus and pituitary. In contrast to women, men do not have a steep decline in testosterone levels as they reach advanced middle age. As a result, male andropause is more difficult to characterize because testosterone levels drop more gradually. Many men are asymptomatic despite having very low testosterone levels, and the threshold at which symptoms of declining testosterone levels begin to develop varies greatly between individuals.

In addition to estrogen and testosterone, the steady decline in dehydroepiandrosterone (DHEA) and DHEA sulfate production from the adrenal glands is a third important aging-related endocrine alteration that affects both men and women (Papierska, 2017). In peripheral tissues, DHEA is converted to testosterone and estradiol. In postmenopausal women, DHEA is the source of practically all estrogens, whereas up to 50% of sex hormones in old men come from the conversion of DHEA to testosterone (Papierska, 2017). Dehydroepiandrosterone is believed to have important antiaging effects, such as increasing cognitive function, anti-inflammatory activity, anti-atherosclerotic, and anti-osteoporotic, even if it's physiological significance and exact mechanism(s) of action are not fully understood.

1.11. Exercise and ageing – improving neurocognitive performance in the elderly

Among the treatments examined to improve longevity and reduce cognitive decline in the elderly, exercise remains one of the best ways to encourage brain plasticity, improve cognition, and lower the risk of cognitive decline in later life (Bernardo et al., 2016; Chen and Zhong, 2013; Hardie, 2004; Mattson, 2012; Radak et al., 2010; Schwartz et al., 2013; Smith et al., 2010; van Praag et al., 2014; Zhu et al., 2015). Specific types of exercise can increase muscle strength and mobility throughout the lifespan, providing decreased risk of sarcopenia and functional decline. There is proof that an evolutionary need for physical activity encourages advantageous adaptive responses that could reduce or even eliminate the negative impacts of a sedentary, overindulgent lifestyle. Increased physical activity has positive impacts at several levels of cellular organization, with mitochondria being the preferred target organelles. Improvements in redox modulation bioenergetics, a reduction in apoptotic signals, acceleration of mitochondrial biogenesis, and modification of autophagy are some of the mitochondrial adaptations to exercise. Through the stimulation of neurotrophic factors, IGF-1, vascular endothelial growth factor, and antioxidative enzymes, moderate and high-intensity exercise has been shown to have a neuroprotective effect (Bernardo et al., 2016; Chen and Zhong, 2013; Hardie, 2004; Mattson, 2012; Radak et al., 2010; Schwartz et al., 2013; Smith et al., 2010; van Praag et al., 2014; Zhu et al., 2015). It has been demonstrated that the expression of these cellular products improves cerebral blood flow, inhibits tau phosphorylation, and inhibits the development of synaptic connections in cognitive regions. Greater cardiorespiratory fitness is positively correlated with more brain volume and greater neuronal white matter integrity, according to diffusion-tensor magnetic resonance imaging research. Power and balance-based exercise enhance executive function, episodic memory, procedural memory, attentional capacity, and processing speed, among other cognitive functions (Bernardo et al., 2016; Chen and Zhong, 2013; Hardie, 2004; Mattson, 2012; Radak et al., 2010; Schwartz et al., 2013; Smith et al., 2010; van Praag et al., 2014; Zhu et al., 2015).

Through transcriptional mechanisms that control the contraction of muscle fibers and metabolic genes, the activation of skeletal muscles during exercise appears to contribute to the cognitive benefits of aerobic exercise (Bernardo et al., 2016; Chen and Zhong, 2013; Hardie, 2004; Mattson, 2012; Radak et al., 2010; Schwartz et al., 2013; Smith et al., 2010; van Praag et al., 2014; Zhu et al., 2015). Brain plasticity is preserved throughout life and can be increased by physical activity and other interventions that trigger the AMP-activated protein kinase (AMPK). Leptin, adiponectin, and ghrelin are metabolic hormones and cytokines that control glucose homeostasis, appetite, and exercise physiology. AMPK functions as a mediator for these hormones and cytokines. Regular exercise encourages an efficient, energy-demanding stress response that involves a variety of developed neuroendocrine reactions (Bernardo et al., 2016; Chen and Zhong, 2013; Hardie, 2004; Mattson, 2012; Radak et al., 2010; Schwartz et al., 2013; Smith et al., 2010; van Praag et al., 2014; Zhu et al., 2015). Although the routes and signaling mechanisms used by the brain to control peripheral glucose metabolism are still poorly understood, they play important roles in this process. Overall, physical activity causes a variety of alterations in the brain and peripheral areas that work together to support stress robustness. A society-wide effort will be needed to incorporate brain and body health programs in the educational and healthcare systems, communities, and workplaces, although even periodically stimulating the brain and body through exercise is helpful (Bernardo et al., 2016; Chen and Zhong, 2013; Hardie, 2004; Mattson, 2012; Radak et al., 2010; Schwartz et al., 2013; Smith et al., 2010; van Praag et al., 2014; Zhu et al., 2015).

1.12. Current status of caregiving in the United States

Many older persons want to grow old in their homes as opposed to a community living arrangement. The demographics of ageing in the US indicate a need to transform Health Care Systems to find innovative solutions to the problems of maintaining independence, dignity, and safety of vulnerable elderly in a cost-effective model. (Reed et al., 2020) An increasing number of individuals will also significantly increase the demand for caretakers. (Prevention, 2018). Models have shown that there will be only four prospective family caregivers for each senior in 2030. According to the CDC, over half (53.8%) of caregivers had provided care or assistance for 24 months or longer. One in three (31.3%) caregivers provided 20 or more hours of care every week, while 10.4% of caregivers said they helped friends or family members who had dementia or another form of cognitive impairment. The needs of the caregiver are frequently neglected (Prevention, 2018). Regular checkups and health insurance can improve a person's health state. Currently, 92.9% of caregivers who are 45 years of age and older said they have health insurance of some kind, and 79.3% received a routine checkup (Prevention, 2018). It is physically and emotionally taxing to provide care. 53% percent of caregivers said that a deterioration in their health makes it harder for them to provide adequate care. Regularly unwell days, whether psychologically or physically, interfere with a caregiver's sleep. A caregiver's health may be significantly impacted by getting little sleep (defined as less than 7 h in 24 h), which can also hinder their capacity to provide care. In the previous month, 14.5% of caregivers said they had 14 or more mentally unwell days (Prevention, 2018). In addition, 36.7% of caregivers said they don't get enough sleep.

Caregivers are more likely to have multiple chronic conditions when they disregard their own needs while providing care (Rawat et al., 2023). As caregivers may disregard their own needs while providing care for others, caregivers are more likely to have several chronic conditions. 35% of caregivers aged 45–64%, and 53% of those greater than 65 years-of-age have two or more chronic conditions present. Individuals with chronic conditions may encounter restrictions brought on by their illness, and for such individuals, providing care to someone else often becomes more difficult as their disease progresses, requiring increasingly extensive self-care. Disability status is described as any level of activity restrictions brought on by mental, emotional, or physical issues, as well as any health issues requiring the use of special

equipment such as a wheelchair, cane, special bed, or special phone (Prevention, 2018). 32% of caregivers aged 45–64%, and 36% of caregivers aged 65 and older reported a disability. Among caregivers surveyed, 17.2% of middle-aged and older people who are not now caregivers anticipate giving care or help to a friend or member of their family with a health issue or handicap during the next two years. 20.0% of adults aged 45–64 who do not now provide care for someone expect to do so in the future (Prevention, 2018). Given the challenges reported by caregivers, the CDC suggests several recommendations for improving caregiving for elderly patients (Table 2) (Prevention, 2018).

1.13. Alzheimer's association on racial disparities among Alzheimer's disease caregivers

Challenges faced by caregivers of individuals with Alzheimer's disease can be significantly different depending on a caregiver's racial status. A survey of 1392 U.S. citizens by the Alzheimer's Association was performed on those who now or recently provided unpaid care for an adult family or friend who was 50 years of age or older and was having symptoms associated with dementia (Association, 2021). The sample consisted of caregivers who identified as 313 White, 309 Hispanic, 305 African Americans, 301 Asian, and 154 Native American. 10 caregivers identified as belonging to another racial or ethnic group. More than 36% of African Americans, 18% of Hispanic, and 19% of Asian Americans believe prejudice is a barrier to accessing Alzheimer's and dementia care, according to the Alzheimer's Association poll of U.S. adults (Association, 2021). They specifically anticipate being treated differently according to their race, ethnicity, or color. Among the different factors examined, affordability is one of the other perceived hurdles to treatment mentioned by survey participants, followed by a lack of adequate local health care (particularly among Black Americans and Asian Americans), a lack of good health insurance coverage, and a lack of family and social support.

In addition, other studies have found that caregivers reported issues with healthcare providers including communication issues with care recipients, family members, and/or significant others, issues with socialization, recreation, and personal enhancement time as well as issues with physical health and health maintenance, managing care recipients' activities of daily living, and difficult behaviors exhibited by caregiver recipients (Wells et al., 2017). Fewer respondents believed that language was a barrier to getting dementia care, although almost 23% of Asian Americans and 17% of Hispanic caregivers reported similar observations. More than two-thirds of African Americans say it is more difficult for African Americans to receive high-quality treatment for dementia or Alzheimer's disease when questioned specifically about the influence of race or ethnicity on care quality. Likewise, two in five Native Americans and Hispanic Americans as well as one-third of Asian Americans reported that their race or ethnicity makes it more difficult to obtain care (Association, 2021).

The greatest hurdle, according to caregivers, is prejudice, which is cited as a barrier by 25% of African Americans, 19% of Native Americans, 17% of Asian Americans, and 8% of Hispanic caregivers (Association, 2021). More than half of caregivers who identify as Native American, African Americans, or Hispanic reported that they have encountered racial prejudice when navigating medical facilities for the care recipient. For 47% of Asian Americans, the same is true. In addition, 41% of caregivers who offer unpaid care to an African American person feel that their race makes it more difficult for them to access high-quality medical treatment (Association, 2021). Overall, the main issue reported by most minority groups was the lack of being heard by employees or providers because of their race, ethnicity, or color, which was reported by 42% of African American caregivers, 3% of Native Americans, 30% of Asian Americans, and 28% of Hispanics caregiver (Association, 2021). Only 17% of White caregivers reported having similar experiences with healthcare providers. Compared to 11% of White caregivers, more than 1 in 4 non-White caregivers reported experiences with healthcare professionals have treated them as if they are less intelligent. Additionally, at least 20% of caregivers who are not White claim to have received less respect and/or decency from their employers (Association, 2021). Most people who are caring for a non-White person agree that healthcare professionals must be aware of the racial or ethnic background and experiences of the person they are caring for (Association, 2021).

Additional information was revealed by the Alzheimer's Association study of caregivers showed that for many family members and friends who look after a loved one with dementia, the benefits of caring for them may help balance stress (Association, 2021). More than half of unpaid caregivers asked said they help someone with personal care activities including eating, dressing, and bathing. The proportion of caregivers who provide this type of care is highest among African Americans and Hispanic caregivers, followed by Asian Americans, and Native Americans. Compared to other groups, African Americans (78%) and Hispanic Americans (83%) are less concerned about burdening their family if they are diagnosed with Alzheimer's disease (Association, 2021). Nearly all caregivers agree that providing care is rewarding even though nearly two-thirds of caregivers say it is stressful. The results of the Alzheimer's Association surveys show that there is still much work to be done in addressing health and healthcare disparities in the care of people with Alzheimer's and dementia.

1.14. Caregiving - role in US health care

Any person (e.g., a family member, a friend, a respite caregiver, or a primary caregiver) who offers care to someone who requires additional assistance or care is referred to as the caregiver (Schulz et al., 2020). Specifically, caregivers are those who provide support to someone who has physical, mental, or cognitive impairments, usually without payment. Unlike professional caregiver staff, informal caregivers encompass a wide range of backgrounds, and the type, length, and degree of support given are highly variable. (Schulz et al., 2020). Informal caregiving is not a new responsibility. Individuals have always supported family members and others they consider close to them emotionally, physically, and financially. In recent years, there has been a growing number of people providing extended, complex informal caregiving in response to the increasing length of life of persons with multimorbidity, and an underfunded and disjointed health and social support system that struggles to handle chronic diseases and disabilities. The inability of the system to handle these complexities in elderly care has contributed to placing much of the responsibility for care on family members, often at tremendous s cost to themselves. (Schulz et al., 2020). Recent research on the role of informal and informal caregiving indicates that the beneficial effect of informal social support may be independent of whether caregivers have formal social support. Significantly lower

Table 2
CDC recommendations for improving caregiving for elderly patients (Prevention, 2018).

1.) Increase messaging that emphasizes both the important role of caregivers and the importance of maintaining caregivers' health and well-being.
2.) Educate the public about the importance of caregiving before they begin and the resources and supports available to them.
3.) Educate healthcare providers to be mindful of the health risks for caregivers, encourage caregivers' use of available information and tools, and make referrals to supportive programs and services.
4.) Evaluate caregiver training and support programs to determine program accessibility, effectiveness, and impact.
5.) Estimate the gap between workforce capacity and anticipated demand for services to support people with dementia and disability and their caregivers.
6.) Increased awareness of and access to evidence-based programs and services that can help caregivers and care recipients and increase access to these programs and services.
7.) Encourage caregivers to get regular check-ups, use preventive services and engage in self-care to maintain health
8.) Ensure that caregivers with a disability and/or chronic diseases have access to self-management programs to maintain their health.

caregiver burden was observed among caregivers with informal social support from family members and relatives, while among sources of formal social support, only support from family physicians was significantly associated with lower caregiver burden. (Shiba et al., 2016) Over the past several decades, the structure of the U.S. family has become less consistent and geographically isolated, challenging the ability of family members to offer consistent support to the primary caregiver.

Although caregiving roles differ significantly depending on the type and precipitating cause of disability, (i.e., dementia, stroke, cancer), the trajectory begins with emerging awareness on the part of the caregiver that there is a problem, necessitating sporadic assistance including transportation of the care recipient to medical appointments, communicating with health care providers, and monitoring care recipient functioning (Schulz et al., 2020). Over time this evolves into increasing care needs, which require assistance with household tasks (e.g., monitoring symptoms and medications, hiring care providers, coordinating care, providing emotional support) and then self-care tasks (e.g., helping with dressing, ambulating in the home, dealing with insurance, managing symptoms). Evidence has long suggested that when patients and caregivers are treated as a dyad, outcomes for both are improved. The care of informal caregivers is improved by offering home-based medical care using innovations in self-management, decision support, information systems, and delivery redesign. (Collins and Swartz, 2011) Nearly half of the informal caregivers use some form of technology to improve the quality of the care that they provide. The development of devices such as automatic medication dispensers, telemedicine visits, alarm, and video devices, and lifting systems has relieved the caregiver burden and improved the safety of the care recipient at home. (Collins and Swartz, 2011).

Older frail individuals with impairments and significant illnesses require markedly increased assistance from caregivers, particularly as they approach the end-of-life (Angus et al., 2004; Gibbons et al., 2014; Givens et al., 2012; Kelley et al., 2013; Penrod et al., 2012; Pottie et al., 2014; Rabow et al., 2004; Stajduhar et al., 2010). Caregivers, often spouses and family members with lived experience and deep emotional relationships with the patient are likely to take on additional responsibilities, such as managing symptoms, making difficult decisions about moving into hospice or long-term care, acting as a proxy in medical decisions, and recruiting paid caregivers. Moreover, vulnerable frail individuals undergo difficult transitions between healthcare facilities at the end of life, often requiring consecutive hospital stays, including life-threatening critical care admissions, sometimes necessitating life-supporting treatments. The usage of services may result in significant out-of-pocket costs for families and fragmented care, which results in tremendous strain on those already suffering the stresses of multiple comorbid illnesses, and their caregivers (Angus et al., 2004; Gibbons et al., 2014; Givens et al., 2012; Kelley et al., 2013; Penrod et al., 2012; Pottie et al., 2014; Rabow et al., 2004; Stajduhar et al., 2010). The healthcare delivery and financing systems need to be redesigned to help older adults with multiple clinical, functional, and social issues best maintain the best possible quality of life, thereby reducing stress on caregivers. Culturally appropriate and effective care is best achieved with a community base rather than the typical institutional focus (Hansen, 2008).

Despite the effective, often high-level care provided by informal caregiving, caregivers and their loved ones continue to have unmet needs, basic caring needs of ageing individuals are represented in Fig. 4. Before 1940, 40% of medical practice in the US was conducted in the home. Since that time, the increasing sophistication of the healthcare system, including primary and specialty medical care, and the ascendency of hospitals as centers for all things medical have relegated home-based services to a minor role (Sloane et al., 2022). Assisted living and similar domiciliary care settings, which have served as a "bridge" to nursing home care for many years have seen nearly 75% growth (Sloane et al., 2022). These facilities provide professional caregiving for individuals who require assistance with self-care, often focused on oversight of physical safety, diet, and medications, all in a social setting. The US regulatory definition of home services blurs the line between home and institutional care. Informal caregiver support is typically provided by agencies or domiciliary facilities in the form of group education and therapy sessions, often free of charge. Participating in an informal caregiver support group is a valuable opportunity for many, however, to

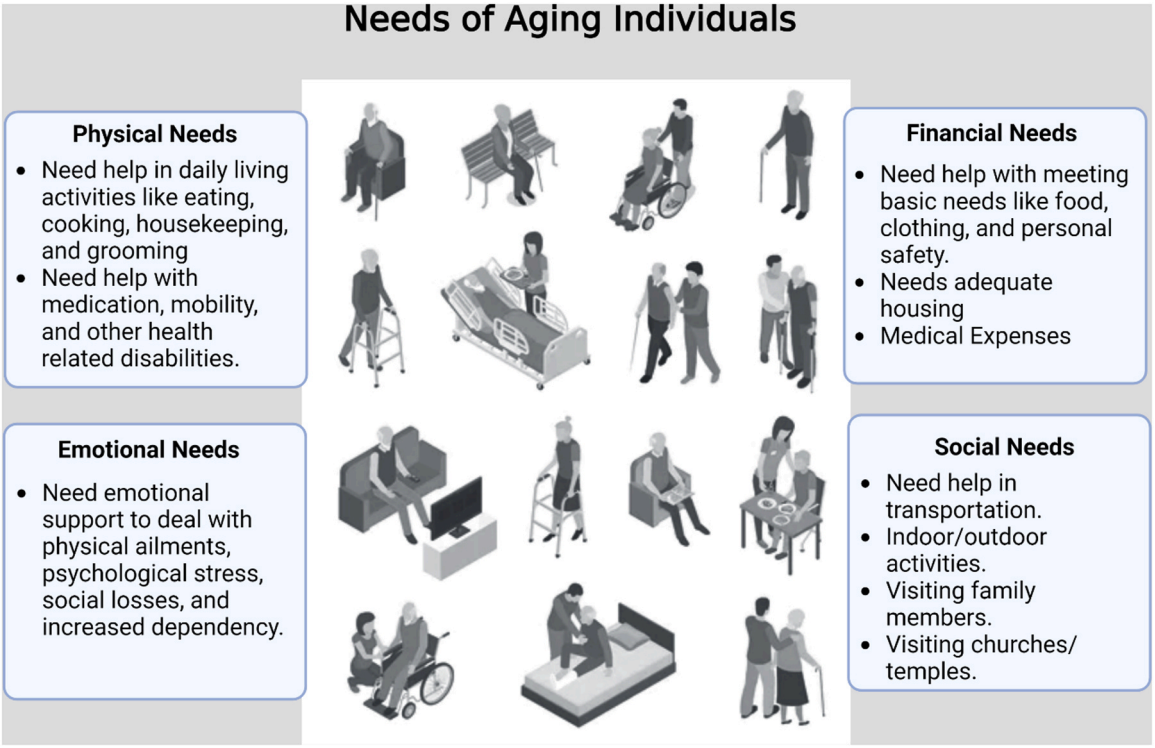

Fig. 4. Basic care needs of the elderly include physical needs, emotional needs, financial needs, and social needs.

provide efficient support services for many family caregivers, it is necessary to conduct a comprehensive assessment by dementia-specific qualified nurses. A recent study revealed that a high number of at-home family caregivers who rejected caregiver supporting groups did so due to personal, service, and relationship factors. Innovative, easily accessible, and personal support can be developed for individuals with high rejection rates, typically those who care for individuals with higher functional status (Zwingmann et al., 2020).

It is important to articulate an economic case for the value and cost-effectiveness of providing a combination of patient care and caregiver support. Perhaps the most important consideration is the acute care hospital. Even with high-quality care, the hospital can be a dangerous place for older adults. Iatrogenesis, including delirium, infection, and loss of function is widespread and can have long-lasting effects that extend far beyond the initial hospitalization. The greater initial diagnostic precision and prognosis of acute illness in the Emergency Department that has developed over the past decade coupled with the rapid acceleration of technology have created a substantial opportunity to provide more care outside of the hospital through Hospital at Home (HaH) programs (Brody et al., 2023). This person-centered care approach provides a community-based option to involve and support caregivers, reducing a feeling of powerlessness, and allowing them to maintain a home relationship and environment, empowering them to participate in a critical event in the life of a vulnerable person. Such participation also permits a better acceptance of the reality of the condition of their loved one and education into the true needs as disease progression creates changes in the caregiving role. While the PCC model is safe and effective and offered internationally and in the U.S. Department of Veterans Affairs (VA) for years, it has not achieved acceptance in the U.S. without regulatory or reimbursement frameworks. Care models successfully implemented in the VA single-payer system hold promise to address persistent dilemmas in long-term care, such as the management of multimorbidity and social drivers of health, integration, and support of family caregivers, and mental health integration. These models also demonstrate the value of incorporating care approaches that have been developed outside of the U.S. and argue for greater integration across different health systems (McConnell et al., 2022).

The Hospital Elder Life Program (HELP) is a model of care that has expanded greatly in the U.S. acute hospital setting over the past 20 years. HELP is intended to be incorporated within the framework of existing hospital units, and has the unique advantage of delivering practical, evidence-based interventions to support older, at-risk, adults for the duration of their hospitalization. Interventions include the support of a trained interdisciplinary team and volunteers, who may work as a team with available family caregivers, including the provision of respite time away from the hospital for caregivers. The HELP program improves safety and decreases the length of stay and subsequent morbidity by reducing the risk of delirium (Inouye et al., 2000). The program also provides support and education to family caregivers, whose hospital experience is often frustrating and exhausting. Caregiver support, while often not recognized, may allow them to better manage the critical post-hospital experience in the home.

The U.S. Balanced Budget Act of 1997 included the inclusion of the Program for All-Inclusive Care for the Elderly (PACE) as a provider within the Centers for Medicare and Medicaid Services (CMS) structure. This was a monumental step in the drive to rebalance long-term care for older adults toward a community-based approach. PACE serves older adults who are certified by the state to need a nursing home level of care. The qualification also requires that individuals live safely in the community with the support of PACE and their informal caregivers at the time of enrollment (McNabney et al., 2022). The PACE Center is the hub of care coordination and provision of many services. This includes the Adult Day Health Center where participants come to socialize and receive care tailored to their needs. The typical frequency of center attendance is 2–3 days per week. Participants access primary care, social workers, and rehabilitation staff while at the center, and transportation is provided by PACE. The PACE team must participate in all aspects of medical and psychological care and are financially responsible for all episodes ("full risk"), including specialty consultation and hospitalization costs. Complimentary to the goal of allowing individuals to remain living in the community are efforts to minimize the need for hospitalization and to control costs by intensive management through interdisciplinary teams. PACE participants typically remain in the program from enrollment until death, providing the opportunity for longitudinal continuity of care with a familiar care team and true patient and family-centered care (McNabney et al., 2022).

1.15. Caregiving at the end-of-life

Although dementia is a terminal disease, patients often experience a protracted course of cognitive and functional decline. This decline is sometimes accompanied by the worsening of one or more concurrent chronic medical conditions, leading to individuals living with severe disabilities for years before their death. Recurrent episodes of illness and hospitalizations compound caregiver responsibilities and financial stress (Tay et al., 2022). Additionally, as patients lose their mental capacity, family caregivers assume surrogate decision-making responsibilities, and many feel uncomfortable making decisions on the patient's behalf due to inadequate knowledge concerning end-of-life issues in dementia (Tay et al., 2022). Recent research indicates that long-term informal family caregiver burden may be driven by worsening functional abilities and behavioral symptoms, rather than a cognitive decline in persons with Alzheimer's Disease (Reed et al., 2020). For end-of-life care in the home for advanced dementia to be tenable, relevant national agencies and stakeholders are recommended to work collectively to support family caregivers holistically (Tay et al., 2022).

Evidence suggests that end-of-life caregiving needs markedly increase caregiver stressors and responsibilities, particularly in caring for individuals who require medical decision-making, often resulting in significant caregiver burden (Angus et al., 2004; Gibbons et al., 2014; Givens et al., 2012; Kelley et al., 2013; Penrod et al., 2012; Pottie et al., 2014; Rabow et al., 2004; Stajduhar et al., 2010). End-of-life care may entail admission to a hospice program or placement in a long-term care facility. Another important consideration is that a caregiver's task progression and caregiver burden is cumulative (Schulz et al., 2020). Over time, the caregiver's job becomes more difficult, time-consuming, and stressful as the care recipient's impairment and requirement for care increases. While changes may appear rapidly for cancer caregivers as the patient switches from one treatment modality to another, often with periods of acute illness and severe pain, Alzheimer's Disease has a characteristically very slow progression with daily variations and loss of individual personal characteristics, making it very emotionally taxing on family caregivers, particularly a spouse. Recent research indicates that individuals with multimorbidity and coexisting dementia have functional needs comparable to hospice enrollees with no dementia. The authors suggest changes to hospice care models and policy to ensure appropriate dementia care (Harrison et al., 2023).

During an end-of-life period, every aspect of a caregiver's life, from their health and quality of life to their relationships and financial security, is affected. (Schulz et al., 2020). Despite providing effective, and often high-level care, informal caregivers and their loved ones still have many unmet needs, and utilization of supportive services is often restricted. At times, this can be a caregiver's choice, often due to the need for control and fierce loyalty. More often, however, a lack of assistance is based upon a lack of knowledge of available resources, the complexity or geographic unavailability of the delivery system, or the lack of necessary financial resources. Therefore, changes in care delivery and payment are needed to help support caregivers with family members with chronic illnesses during the critical end-of-life period. (Angus et al., 2004; Gibbons et al., 2014; Givens et al., 2012; Kelley et al., 2013; Penrod et al., 2012; Pottie et al., 2014; Rabow et al., 2004; Stajduhar et al., 2010). In the U.S., the Family Medical Leave Act (FMLA), and

Medicaid have been created to help the growing need for supporting caregivers (Raj and Singer, 2021). These laws specify who qualifies as a caregiver, the extent of their duties, and the appropriate methods of support. The FMLA allows eligible workers of covered employers to take unpaid time off for personal and family matters without running into the danger of losing their jobs (Raj and Singer, 2021). This permits multiple family members to participate as caregivers, at times rotating for a limited period during periods of significant stress, or when disease progression or primary caregiver health issues make them unable to provide necessary support and safety. Unfortunately, low-wage workers are more likely to work for employers not required to provide FMLA, and caregivers with lower levels of education are less likely to use paid leave options (Chen, 2016).

Most individuals prefer to die in their homes with their family present. Originally, hospice emerged as an informal program that provided individuals at the end of life to die at home with attention to the control of their symptoms. Over the past century, Hospice care has evolved to become an essential part of the health care system. Hospice and Palliative Care is an interdisciplinary medical specialty that focuses on symptom management and caregiver support. Palliative consultation often begins the process of education and support well before patients and families decide to enroll in a Hospice care plan. In the U.S., Hospice Care is currently a CMS benefit, requiring certification by a physician that an individual is likely to die within six months. The individual must always reside in a home with a caregiver present, or transfer to a long-term care facility. Caregivers actively participate and receive education and support regarding the patient's illness, current condition, and prognosis. All medical expenses of the hospice experience, including medications and medical equipment are covered by Medicare. Caregiver support during the final phase of chronic illness and bereavement support after death are essential aspects of this program.

Despite the significant success, challenges to the growth of hospice programs include a marginal understanding of admission requirements and goals throughout the medical community, challenges of prognostication, and often a strong desire to provide treatment to prolong life. Unfortunately, many hospice admissions occur during the final days of life.

Many caregivers find it difficult to continue their role through the time of death. The end of a long journey increases isolation and caregivers become focused on control. Care requirements often become very challenging, and both depression and fatigue contribute to poor quality of life (Eisenmann et al., 2020). Often, particularly after an acute change in status leading to hospitalization, it becomes necessary for a patient with multiple morbidities to be transferred to a nursing home for necessary care. The financial burden is significant, although Medicaid will fund institutional care once the patient and their spouse "spend down" to the near-poverty level. The Hospice Medicare benefit does not fund institutional care, leading to a severe financial challenge for many caregivers and their families. Among 16 randomized trials results showed improvement in depression resulting from early admission of cancer patients to hospice and palliative care. Emerging studies such as this have proposed the CARES framework to guide care for caregivers in oncology settings: Considering caregivers as part of the unit of care, Assessment of caregiver situation and needs, Referral to appropriate services and resources, Education about practical aspects of caregiving, and Supporting caregivers through bereavement (Alam et al., 2020).

Several U.S. states have initiated their solutions to support caregivers. California's In-Home Supportive Services Program, a part of Medi-Cal, the state's Medicaid program, is a consumer-directed care model in which the individual receives cash to employ the caregivers of his or her choosing, including family caregivers. This model is one of several that allows financial compensation to ease the economic burden on caregivers. Medi-Cal outperformed professional management models for the delivery of supportive services to older persons on several measures, including client satisfaction and quality of life. Perhaps most significant was the fact that a paid family caregiver was associated with more positive outcomes (Hansen, 2008). Medi-Cal and previously described models of care such as PACE and the Department of Veterans Affairs will increase CMS's focus on the establishment of supportive, culturally appropriate caregiving in the home. Such models are necessary to ensure affordable dignity and quality of life for individuals with multiple comorbidities, their caregivers, families, and communities. Financial and ethical responsibility will improve efficient, appropriate use of medical services, allow early integration of Palliative Care, recognize signs of approaching death, symptom assessment and management, advanced care planning, person-centered care, continuity of care, and collaboration of health care providers to engage family members and others to provide culturally appropriate care (Eisenmann et al., 2020). Such outcomes may significantly reduce public spending on the non-essential medical care of vulnerable older adults at the end of life.

2. Conclusion and future directions

The COVID-19 pandemic was particularly significant in its effect on older vulnerable adults, long-term care institutional care, caregivers, families, and communities. The devastating effects remain particularly challenging for individuals requiring professional and family caregivers. The combination of significant population increases and an increase in life expectancy, particularly in developing countries, indicates that other chronic morbidities, including Alzheimer's disease, are likely to emerge as drivers of change in all healthcare systems. A leading cause of mortality and impairment in old age is Alzheimer's disease and associated dementias (ADRD). Age is the single most important determinant in the development of ADRD, as it is with many chronic illnesses. The understanding of biological mechanisms of aging provides valuable insights into the development and progression of neurodegenerative diseases. By understanding the shared and/or individual pathways between healthy ageing and neurodegeneration, researchers can develop novel treatments and interventions that aim to slow down, prevent, and/or reverse the ageing process and mitigate the impact of neurodegenerative diseases on aged individuals.

When an individual has a neurodegenerative condition, they frequently lose their independence over time. To manage the activities of daily living, the person need the assistance of a caregiver. Caregiver support provided by a variety of models improves patient, caregiver, family, and community outcomes in a variety of important ways. If the business case can be made for models like PACE or California's In-Home Supportive Services Program, the result may be a redesigned, cost-effective system that emphasizes care coordination and works seamlessly through transitions of care for the benefit of both older adults and family caregivers (Hansen, 2008) Developing healthcare systems need a path forward, and established healthcare systems need to reevaluate their resources. Family caregiving is culturally natural in many societies, cultures, and communities. A shift toward integrating a powerful segment of the population into an advanced healthcare and public health system that is focused on technology and defeating disease is an important step forward for mankind.

Caregiving is complicated, and there is still much that needs to be done to reinforce and redefine caring policy (Raj and Singer, 2021). To accommodate various caregiving scenarios, caregiving policy at the state and federal levels must be significantly modified to provide caregivers of adult relatives with the resources and assistance they require. Finally, caregivers have additional challenges while attempting to support their loved ones and themselves due to the difficulty of negotiating siloed health, social services, and other programs within states. With multi-agency solutions, policymakers should concentrate on coordinating financial incentives that integrate caregiving across several programs (Raj and Singer, 2021). To improve our healthcare system and the lives of caregivers, the range of caregiving must be clarified and strengthened.

Despite these challenges, caregiving is rewarding for many

caregivers. When caregivers assist care receivers, they frequently gain confidence, learn how to oversee challenging circumstances, develop a stronger bond with the care recipient, and gain reassurance that the care recipient is receiving high-quality care. The actual effects on caregivers, however, vary depending on the caregiver's personal and environmental factors (Schulz et al., 2020).

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Conceptualization by PHR. All authors prepared original draft and edited and finalized manuscript. All authors have read and agreed to the final version of manuscript for publication.

Declaration of Competing Interest

The authors declare that they have no known competing interests.

Data Availability

No data was used for the research described in the article.

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