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Review Article

Late Life Depression: A Narrative Review

Tiffany Field*

University of Miami/Miller School of Medicine and Fielding Graduate University, USA

***Corresponding author:** Field T, University of Miami/Miller School of Medicine and Fielding Graduate University, USA

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Abstract

The recent literature (last five years) on late life depression is predominantly focused on risk factors/predictors of late life depression along with studies on effects, buffers, and interventions. Late life depression has typically been self-reported or diagnosed starting at age 60. The prevalence rates for late life depression were highly variable in this literature, ranging from a low of 7% in Italy to a high of 37% in Chile, a variability that may relate to the year or type of data collection and/or cross-cultural variation. Negative effects have included loneliness, suicidal ideation, cognitive decline, frailty, functional limitations, low heart rate variability, biological aging (short telomere length and white matter lesions) and earlier mortality. Risk factors have included loneliness, aging anxiety, life stressors (marital discord and job strain), physical problems (activities of daily living), physical health (elevated blood pressure), physical weakness (handgrip, frailty, falls and disability) and unhealthy intake (poor diet, excessive alcohol and vitamin D deficiency). Buffers/protective factors have included positive views on aging, resilience, practicing religion, a Mediterranean diet, and remaining active. Interventions have included cognitive training, mindfulness, physical activity and ketamines. Multiple underlying mechanisms have been suggested including dysfunctional connectivity between different networks in the brain. Although the data highlight the severity of late life depression, the recent literature has been based on different measures appearing on self-report surveys that have yielded mixed results across samples.

Prevalence of Late Life Depression

First, some myths about late life depression in a paper entitled "Depression among older adults: A 2-year update on common myths and misconceptions" are worth summarizing [1]. These authors concluded: 1) depression is not more common in older adults; 2) late life depression is not more often caused by psychological factors; 3) those who experience late life depression respond to psychological interventions as well as younger adults, but not to antidepressants; 4) late life depression follows a more chronic course (i.e. a greater rate of relapse); and 5) late life depression is frequently moderated by comorbidity.

Late life depression has typically been measured by self-report scales on surveys in very large sample studies on aging (ageing in the case of European studies). Most frequently, late life depression has been measured by the Geriatric Depression Scale, although occasionally it has been measured by the Center for Epidemiological Studies-Depression Scale or the Hamilton Depression Scale. Diagnostic interviews have rarely been conducted. Late life has been most frequently referred to those over 60 years of age, although some "late life" samples have been as young as 50. In contrast, a sample in a study on centenarians averaged 102 years-old.

The prevalence of late life depression has varied from a low of 7% in Italy (Fanelli et al, 2020) to a high of 37% in Chile [2] (Table 1).

Prevalence	First Authors
7% Italy	Fanelli
8% Ghana	Boima
9% China	Zhang
12% Ireland	Briggs
13% Germany	Qiao
27% France	Qiao
28% Greece	Tsaras
37% Chile	Moreno

Table 1: Prevalence of Late Life Depression.

The prevalence between those lower and upper rates has ranged between lows of 8% for Ghana [3], 9% for China [4], 12% for Ireland (Briggs et al, 2018), and 13% for Germany [5], but significantly higher rates at 27% for France and 28% for Greece [6].

Although prevalence across countries has not been compared in the same study except for the European sample that included Germany and France [5], the variability in prevalence may relate

to the different years in which the data were collected and/or cross-cultural variation. Other potential sources of variability have included age, for example in Ghana, where older adults had twice the rate of depression as younger adults (8% versus 5%) [3].

Gender distribution in the samples may also differ across studies. For example, in the Chilean sample of 3,786 older adults, variability was noted across gender with 21% of males (6% major depressive disorder) and, not surprisingly, almost twice as many females (37%), experiencing depression (twice the major depressive disorder diagnosis as the males at 12% versus 6%). In that sample, only 19% of the males and 34% of the females with positive screens had received a clinical diagnosis, suggesting a high proportion of individuals who were undiagnosed. In the case of the female sample, depression occurred in older adults with a lesser probability of a diagnosis.

Although anxiety is often comorbid with depression, anxiety measures were less frequently included in these surveys. In a sample of community-dwelling adults older than 60 in China (N=4103), for example, 9% were noted to have comorbid depression and anxiety [7]. And, treatment resistant depression has been reported in as many as 30% of older patients with depression in another sample from China [8].

Late Life Depression Effects

Studies on late life depression effects have surprisingly appeared less often in this recent literature than risks/predictor variables (Table 2).

Effects		First Authors
	Psychological	
Loneliness		Power, Hsueh
Suicidal ideation		Bickford
	Cognitive	
Decline		Manning, Samir
Dementia		Lee
	Physical	
Frailty		Chang, Borges, Voshaar
Functional limitations		Wassink-Vossen
	Physiological	
Low heart rate variability		Brown
	Quality of Life	
Pro=health status		Han
Insomnia		Tsaras
	Neurological	
DNA methylation patterns		Han
Telomere shortening		Mendes-Silva, Schroder
White and gray matter lesions		Manning, Greene
Inflammation		Van den Berg

Table 2: Effects of Late Life Depression.

Researchers might have been studying the negative effects earlier and have more recently focused on risk/predictor variables. Because most of the studies are cross-sectional, effects and risk/predictor variables have often been reciprocal. They have been treated as risks or effects depending on the interests of the researchers and their selected data analyses. For example, loneliness has been treated as both an effect of depression and as a risk/predictor variable for depression by different research groups. The research on late life depression effects can be categorized as psychological, cognitive, physical, physiological and neurological effects.

Psychological Effects

Psychological effects of late life depression have ranged from loneliness to suicidal ideation. Loneliness as a negative effect of late life depression has been the focus of at least two recent studies. In one study entitled "Depression symptoms predict increased social and emotional loneliness in older adults" (N=373 adults greater than 50-years-old), a cross-lagged approach within a structural equation modelling framework suggested that depression symptoms at baseline predicted emotional and social loneliness, but loneliness at baseline did not predict depression [9]. This finding may have resulted from the direction of the variables entered, as loneliness has been a predictor as well as a mediator variable in other studies. Interestingly, both depression and loneliness were reciprocally related across two years and they both decreased between the two waves of assessments which may have related to their being research effects (i.e. participants receiving support from engaging in research).

In the second study suggesting that loneliness resulted from depression, the paper was called "A longitudinal cross-lagged panel analysis of loneliness and depression" [10]. The data came from the Taiwan Longitudinal Study on Aging (N=3920, Mage=68) noting that depression and loneliness were bidirectional, but the direction was stronger for depression as the initial symptom. This type of data analysis seemed the most appropriate for determining the strongest initial symptom in a bidirectional relationship.

Suicidal ideation and suicide are the most extreme psychological effects that have been cited for late life depression in this recent literature. In a study on suicidal ideation and late life depression (N=88, M= 72-year-old adults with major depressive disorder), the Geriatric Suicide Ideation Scale and the Hamilton Depression Rating Scale were given [11].Surprisingly, suicidal ideation was independent of depression severity. However, suicidal ideation was correlated with the poorest frailty measures including gait speed and muscle weakness and with functional

disability including impaired financial capacity, social interaction and communication skills. The prevalence of suicide has been noted to be 15 in 100,000 in 65–84-year-old adults and 18 per 100,000 in 85-year-old and older adults [12].

Cognitive Decline

Cognitive decline has been noted as a negative effect of late life depression in a few studies. In a study entitled "Cognitive variability, brain aging and cognitive decline in late life depression", dispersion or within person performance variability was noted across cognitive tests [13]. In this study (N=121 adults with late life depression and 39 healthy controls), greater baseline dispersion predicted cognitive decline one year later even when controlling for baseline cognitive function, demographics and clinical confounders. Dispersion was also correlated with white matter brain lesions in those with late life depression as well as with anxiety for both groups. Notably, as in many of these studies, the late life depression and healthy control groups were unequal sample sizes which would affect the reliability of the results.

In another study demonstrating cognitive effects, aging adults with major depressive disorder experienced a decline in cognitive function (Samir et al, 2018). The decline in cognitive function was related to peripheral IL-6 levels that contributed to inflammation that, in turn, negatively affected cognitive function. Late life depression was a correlate of dementia but not necessarily a cause of dementia in a sample of 16,607 adults greater than 65-years-old [14]. While dementia was noted as an effect of late life depression, it could also have been a risk factor for late life depression.

Physical Effects

Physical effects have included frailty, falls, functional limitations and disability. Frailty has been defined as the accumulation of deficits in six dimensions including disease status, sensory dysfunction, balance, functional limitations, health risk behaviors and decreased life satisfaction [15]. In a study entitled "Depression as a determinant of frailty in late life", clinical interviews as well as two screens were given for depression, and frailty was determined by two screens (N=315 geriatric outpatients, mean age=72) [16]. Frailty occurred in 15% of those who had no depression, 47% of those who had subthreshold depression and 65% of those who had major depressive disorder. Thus, there appeared to be a dose–dependent relationship between late life depression and frailty. In an 8-week randomized placebo-controlled trial on 121 greater than 60-year-old adults with major depressive disorder [17]. 63% were considered low frailty while 37% were labeled high frailty risk. In a six-year prospective clinical cohort study on the bidirectional association between frailty and major depressive disorder, greater frailty was related to baseline depression and to less remission from depression [18]. Depression was also associated with biological aging.

Depression has also been a risk factor for incident falls in a study entitled "Risk factors for incident falls in older men and women" from the English Longitudinal Study on Ageing (N=3,298 greater than 60-year-old adults), depression was a risk factor for falling [19]. Additional risk factors were noted for men including greater comorbidity and pain and balance problems

Functional limitations have been noted in the Netherlands Study on Depression in Older Persons (N= 378 adults greater than 60-years-old) [20]. In this study, the depressed adults had greater functional limitations based on growth mixture modeling suggesting two trajectories. 81% had high disability over time and 19% had functional recovery which was predicted by a decrease in depression. Females experienced fewer functional limitations which were related to their greater education, greater gait speed and less depression. One in five depressed older patients experienced functional recovery. Non-remission was related to greater chronic somatic disease, less sense of mastery and greater anxiety.

Depressive symptoms have also been predictive of disability. In a study on 65-88 year-old adults with major depressive disorder (N=78), the Hamilton Depression Rating Scale and the Late Life Function and Disability Instrument were administered (Morin et al, 2020). In a linear regression analysis model, depression accounted for 27% of the variance in disability.

Physiological Effects

Low heart rate variability has been noted as a physiological effect of late life depression. In a meta-analysis on five clinical and six observation studies of adults greater than 60-years-old (N= 550 adults with clinical depression), only low frequency heart rate variability was low in depressed patients [21]. Low heart rate variability as an index of sympathetic activity is notably indicative of depression but not related to anti-depressant use in these samples that were considered heterogeneous.

Quality of Life

Given significant frailty and functional limitations in those with late life depression, it is not surprising that health-related quality of life was also a correlate of depression. In a study on centenarians from China (N=1002, median age =102 years), many covariates were entered into the data analysis on depression and quality of life [22]. 82% of the sample were females, 38% experienced minor depression and 10% major depressive disorder. Poor health status was noted in 45% of the sample. For every one point increase on the Geriatric Depression Scale, there was a 20% increase in poor health state. Surprisingly, there was a negative relationship between depression and the number of comorbidities.

In another quality of life study, depression and insomnia symptoms contributed to quality of life based on the World Health Quality of Life and the Geriatric Depression Scales [6]. In this sample from Greece (N=200 adults who were greater than 60-years-old), 28% experienced depression, 41% had insomnia and 19% had comorbid depression and insomnia. Surprisingly, sleep problems have rarely been mentioned in this literature on late life depression, although a separate literature on sleep problems in the aging involves depression as a variable.

Neurological Involvement

The neurological research in this recent literature on late life depression has included studies on biological aging, length of telomeres and white matter lesions. In a study entitled epigenetic aging and major depressive disorder, a sample of 811 depressed adults and 319 control adults were included from the Netherlands Study on Depression and Anxiety [23]. Based on pathway enrollment analysis, greater epigenetic aging occurred in the depressed group including DNA methylation patterns in the blood and brain tissue, suggesting that the depressed group was biologically older than their chronological age. These results are tenuous, however, because of the extremely different sample sizes of the two groups.

Telomere shortening has occurred in late life depression. Telomeres (structures of the extremity of chromosomes that prevent genetic instability) seem to shorten as a hallmark of cellular aging [24]. In this study, telomere length was shorter in a group of adults experiencing late life depression (N=45) versus a no depressed group (N=33) of adults 60-90- years-old. Telomere length was negatively correlated with depression based on the Hamilton Depression Rating Scale as well as medical burden but was not correlated with cognitive performance based on the Mattis Dementia Rating Scale.

In a review on the relationship between telomeres and depression, telomeres were noted to shorten with age and changes in telomerase activity were noted in peripheral blood cells and brain tissues in those with major depressive disorder [25]. Other relevant biological mechanisms were noted in this review including HPA axis activity leading to oxidative stress, inflammation, genetic and epigenetic changes.

As already noted in the study on cognitive decline in adults experiencing late life depression, variability across cognitive tests was correlated with white matter lesions [13]. In a review on neurological changes and depression, structural MRIs were said to reveal both white and gray matter lesions as well as cerebrovascular disease associated with late life depression [12]. Comorbid cognitive effects were also cited including impaired memory recall, executive function and processing speed.

The risk of mortality for late life depression was 2.5 times that of non-depression in the Netherlands Study of Depression in Older Persons (Jeuring et al, 2018). In this sample of 378 depressed and 132 non-depressed adults, the Inventory of Depressed Symptomatology and a diagnostic interview at two and six years suggested the risk of early mortality. Depression was also associated with earlier age onset, greater severity, pain, neuroticism, loneliness and chronic disease.

In a later publication by the same group on the same sample of depressed aging adults, the risk of early mortality was based on a regression adjusting for several potential confounding variables including age, sex, education, smoking, alcohol use, physical activity, medications and somatic comorbidity [26]. The authors suggested that the mortality risk associated with depression could also relate to inflammation-based sickness, frailty and mild cognitive impairment.

Risk Factors/Predictor Variables

Risk factors/predictor variables for late life depression comprise the majority of the studies in this narrative review (33 of 87 studies). They include 9 studies on psychological risk factors, 6 on lifestyle variables and 18 on physical predictor variables (Table 3)

Risk Factors		First Authors
	Psychological	
Ageism		Bodner, Gum, Segel-Karpas, Protsenko, Li
Loneliness		Domenech-Abella, Yoon, Srivastavan
	Lifestyle Stressors	
Sexual		Willie-Tyndale, Rotter
Marital discord		Whisman
Job strain		Qiao
Retirement		Li
Excessive alcohol		Keyes
Low quality diet		Gomes
	Physical	
Physical health		Tan
Hand grip strength		Muhammed
Activities of daily living		Muhammed
Frailty		Jia

Table 3: Risk Factors/Predictor Variables for Late Life Depression.

Psychological Variables

The psychological risk factors in this recent literature have include ageism (negative perceptions about aging) which has been called subjective aging and "grim" age and loneliness related to spousal loss, social isolation or simply being lonely.

Ageism

Negative perceptions about aging have led to greater depression among Chinese older adults [27]. This relationship resulted from structural equation modeling on a sample of 8,404 older adults. In another study entitled "Day-to-day variability in subjective age and ageism attitudes and their association with depressive symptoms" (N= 134, mean age =70), daily subjective age and ageism attitudes led to depressive symptoms among "old-old" respondents [28]. A time-lagged analysis suggested that ageist

attitudes during previous days contributed to feeling older and more depressed but not the reverse. Depression did not precede ageism in this relatively small sample.

In a study on self-perceptions of aging mediating the longitudinal relationship between hopelessness and depressive symptoms, hopelessness in 2008 was an independent predictor of self-perceptions of aging four years later and, in turn, a predictor of depression six years later [29]. Given the age of this study, it's not clear that these results would generalize to self-perceptions of aging today.

In another study on daily fluctuations in subjective age and depressive symptoms (N= 334), daily variation in subjective age was correlated with depressive symptoms [30]. More depressive symptoms occurred on the days when the participants were feeling older. The attitudes towards aging (greater perceptions of loss and low psychological growth) moderated this effect. The moderating effect of loss was greater with age.

"Grim age" has been considered an epigenetic predictor of mortality in major depressive disorder [31]. Based on DNA methylation levels, the authors suggested that a DNA metric was trained on time to death data and outperformed its predecessors in predicting both morbidity and mortality.

Loneliness

Loneliness has been distinguished from social isolation in several studies. An example is a study that reported loneliness and major depressive disorder as being bi-directional two years later [32]. In contrast, the relationship between social isolation and major depressive disorder was unidirectional. This is not surprising as depression has typically led to loneliness but isolating oneself socially would not be an adaptive response to feeling depressed.

In a couple studies, loneliness has been related to spousal loss. For example, in a longitudinal study from Korea (N=685), increased depression was noted following reduced social involvement and increased loneliness in men from 1 to 4 years following the loss [33]. No change in depression or social involvement/loneliness was noted for women, raising the question of the underlying mechanism for this phenomenon. Spousal loss has typically been more difficult for men and has more often led to early mortality for men possibly because of their reduced social involvement and increased loneliness.

In a study from India on the association between widowhood and living alone with depression among older adults, the sample was drawn from the Longitudinal Aging Study in India (N=30,639, 260) [34]. In this sample, 9% were depressed, 10% widowed (8% of those currently married),14% living alone and 8% were co-residing with someone widowed. The widowed were 34% more likely to be depressed, the living alone were 16% more likely to be depressed and the widowed and living alone were 56% more likely to be depressed, suggesting that living alone significantly increases the odds of widowhood leading to depression, as in a moderating variable.

Lifestyle Stressors

Several lifestyle stressors appeared in the recent literature as risk factors for late life depression. These include sexual performance problems, marital discord, job strain, retirement and excessive alcohol.

Sexual performance problems

In a study entitled "Sexual activity and depression problems in late life", aging and sexual activity were discussed in focus groups of adults greater than 50-years-old (N= 557) [35]. The men reportedly engaged in sexual activity more than the women (51 versus 41%) during the last four weeks even though 40% of the men reported erectile dysfunction. The males who engaged in sexual activity had five point lower depression scores, while the females with sexual complaints had two point higher depression scores.

Erectile dysfunction may have related to the testosterone deficiency syndrome which has also been noted in aging men [36]. In this study on 314 men greater than 60-years-old, 49% had testosterone deficiency syndrome and 29% had depressive symptoms. In the testosterone deficiency syndrome group, a significant positive correlation was noted between the syndrome and the metals manganese and chromium. Manganese toxicity is also associated with depression which may be a mediator of the relationship between manganese and testosterone deficiency. Similarly, chromium is associated with mood changes as well as sleep disturbances.

Marital discord

Marital discord is another stressor that has been noted as a risk factor for late life depression [37]. In this Irish Longitudinal Study on Ageing (N =1,445 couples), an actor–partner dependence model was explored. Actor effects of marital discord on depression were greater for men versus women, likely because men were more often the perpetrators and may have felt guilty. This effect was significant after adjusting for family and friends' discord. It was not clear if adjusting for marital discord, in turn, led to significant effects of discord with family and friends on depression. It was also surprising that the emphasis was on the effects that existed for the actor but not for the partner who is usually the victim of marital discord.

Job strain is still another risk factor for depression. In a sample from the Survey of Health, Aging and Retirement (N=7,879), greater depression was experienced by those aging adults with high physical and psychosocial strain [5]. Job strain at baseline was predictive of depression, although depression at baseline was not associated with subsequent high job strain. This was, surprisingly, not a reciprocal relationship.

Retirement has also been a risk factor for late life depression. In a meta-analysis of 25 longitudinal studies published between 1980 and 2020, retirement was associated with greater depression symptoms [38]. However, retirement as a risk factor for depressive symptoms was specifically for involuntary versus voluntary

retirement. And, the association between retirement and depressive symptoms was greater for eastern versus western countries.

Other late life stressors have been mentioned in an extensive review [39-41]. Some that have received less attention include caregiving, financial stress, loss of independence, bereavement, retirement from a low stress job, the loss of role identities (marital, parental, employment) and living in an institution. Having coping resources (meaning and a goal in life) was a moderator for the relationship between interpersonal stressful events on depression in at least one study [14]. In this six-year study on 588 aging adults, coping resources effectively reduced depressive symptoms.

Alcohol consumption has also predicted depressive episodes in late life depression [42]. In this longitudinal sample of older adults in 19 countries (N= 57,276), heavy drinkers had higher depression scores than moderate drinkers. But, surprisingly, long term alcohol abstainers and occasional drinkers also had higher depression scores than moderate drinkers.

Low quality diet has also been a predictor of depressive symptoms in aging adults. In a study from Brazil (N= 1,378), 15% were noted to be depressed [43]. The odds ratio for this reciprocal relationship was 3.8 for males and 2.1 for females. The higher odds ratio for males suggests a greater relationship between poor diet and late life depression for males.

The COVID-19 pandemic has notably affected depression in adults 50 years and older (MacNeil et al, 2022). in a study from Canada (N = 22,622), for example, a logistic regression was used to estimate the odds of depression during COVID. Folks with a history of depression had four times the risk of experiencing depression during COVID. Other factors were being female, having lower savings, health stressors and family conflict.

Physical Risk Factors

A number of physical health risk factors for late life depression have been reported in this literature. These include physical health in general, vitamin D deficiency, hypertension, hand grip strength, activities of daily living, frailty, falling and disabilities.

Physical health. In a meta-analysis on prediction models for depression among older adults, 14 studies were included on 20 different models [44]. In this meta- analysis, physical health was the most common predictor for late life depression. Age and cognitive function were also significant predictors.

Hypertension. Hypertension has also been a risk factor for depression [3]. In this study from Ghana, those aging adults with blood pressure greater than 140/90 had an increased risk of depression. In addition, older adults had twice the depression (8.4 versus 4.5%) as younger folks.

Vitamin D deficiency. This deficiency has also been associated with depressive symptoms in later life (Oliveire et al, 2018). In this study from England (N= 5,607), 9% were depressed. Those women who had less than 30 and less than 50 on their vitamin D levels had depressive symptoms and for males those with levels less than 30 were depressed. Vitamin D deficiency may have related to frailty-bone loss which has also been a risk factor for depression.

Hand grip strength. In a study from the Longitudinal Ageing Study in India (N= 27,707 adults greater than 60-years-old), less hand grip strength was related to greater depression [45]. Older adults with less hand grip strength, in turn, had greater cognitive impairment.

Activities of daily living. In another study by the same author from the Longitudinal Ageing Study in India, older adults who had difficulty in basic activities of daily living were more depressed [46]. In this study, a greater prevalence of depression occurred in the 9% who were depressed, 15% who had difficulty in basic activities of daily living (like bathing and dressing), 12% who had difficulty in instrumental activities of daily living (like preparing meals and doing laundry), 10% who were unmarried, 10% who were living separately and 10% who were socially inactive.

Physical frailty. Physical frailty has also been a risk factor for major depressive disorder in the aging. In a study from the Irish Longitudinal Study on Ageing (N= 3,671), physical frailty according to five criteria led to greater depression [47]. The physical frailty phenotype (five criteria) was used which defines frailty as fatigue, resistance (difficulty walking up to 10 steps on stairs), ambulation (difficulty walking several hundred yards), illness (five or more of 11 illnesses) and weight loss of greater than 5% total weight within one year. After correcting for several variables including living arrangements, health behavior, common chronic diseases including hypertension, diabetes, cancer, lung disease, heart problems and stroke, a greater incidence of shrinking and exhaustion led to the onset of major depressive disorder over a four-year period.

Frailty based on the Fried Prototype Criteria has been related to depressive symptoms among Chinese adults [4]. In this sample (N =1168), 9% had depressive symptoms, 35% had pre–frailty symptoms and 6 % had frailty symptoms. The percentage of depressive symptoms increased from robust adults (5%) to pre-frail (11%) to frail adults (32%). The odds of having depression for pre-frailty was 1.75 and prevalent frailty had a risk index of 5.64. Depressive symptoms were associated with a 2.79 fold increased risk of three-year incident frailty. Clearly this was a reciprocal relationship where frailty could be considered a risk factor for depression and previous depression could be considered a risk factor for frailty.

In another sample on the comorbidity of depression and frailty among older adults, the West China Health and Aging Trend Study was tapped for participants (N=4,103 community dwelling adults greater than 60-years-old) [7]. In this study, the prevalence of pre-frailty was 47% and frailty was 7% and the prevalence of comorbid depression was 9%.

In at least one study, mortality was associated with frailty and depressive symptoms in older adults [15]. In this longitudinal research from Taiwan, comorbid frailty and depressive symptoms

were associated with greater mortality. Depression led to frailty but that was a weaker direction than frailty leading to depression. Unfortunately, these data were collected from 1987 to 2007 which suggests they may not generalize to today's population.

Fear of falling and falling. Frailty may predispose to worrying about falling and experiencing falling. Worrying about falling has been associated with depressive symptoms in aging adults [48]. In this sample (N=3,333 greater than 70-years-old), those with fall worry had more moderate/severe depressive symptoms in 2019 and an increase in fall worrying by 2020. Experiencing falling has also been a risk factor for depression [49]. In this sample (N= 9,355), those who experienced falling had a 1.36 greater risk of becoming depressed.

Chronic illnesses. Chronic illnesses have been a risk factor for depression in the aging. In a study on chronic illness and functional limitations, effects of chronic illness on depression were mediated by functional limitations [23]. Chronic illnesses led to negative self-perceptions that moderated (exacerbated) the effects of illness on depression.

Disability. Disability onset has also been associated with comorbid depression and anxiety [50]. Disability was defined by these authors as receiving help from another person for self-care or mobility activities. They noted a dose-response relationship between disability and onset of depression/anxiety symptoms. Twenty per cent of the sample reported mild or moderate symptoms at baseline while the prevalence of depression rose to 30 to 38% with disability onset.

Buffers against Late Life Depression

Several buffers have been noted for late life depression in the recent literature. These include having a younger subjective age, resilience, religiosity, physical activity, a Mediterranean diet and retirement (Table 4).

Buffers	First Authors
Younger subjective age	Xiao
Resilience	Laird, Reynolds
Religiosity	Foong
Attitudes toward treatment	Nair
Physical activity	Marques, DeSousa
Mediterranean diet	Pagliai
Retirement	Odone

Table 4: Buffers/Protective Factors for Late Life Depression.

Subjective age. Having a younger subjective age has been associated with fewer depressive symptoms among Chinese older adults (N=609) (Xiao et al, 2019). The relationship between subjective age and depressive symptoms may have been partially mediated by perceived control.

Resilience. Resilience has been defined as grit, active coping, accommodative coping, self-efficacy and spirituality [41]. In a study entitled "Promoting resilience and reducing depression in older adults", resilience was defined as the ability to adapt and thrive in the face of adversity [51]. In that study, successful aging was defined as engagement in life, maintenance of high cognitive and physical function and avoidance of disease [51]. In a study on the clinical correlates of resiliency and geriatric depression, the Conners – Davidson Resiliency Scale was given to 337 adults older than 60 years [42]. The definition starting with "grit" was used. In this sample, resilience was negatively associated with depression and white matter integrity. In addition, it was negatively associated with apathy and anxiety and positively associated with quality of life, variables that potentially confounded the relationship between resilience and depression.

A related resilience factor has been called "intrinsic capacity" [52]. In this sample (N=24,136 adults greater than 60), high intrinsic capacity was related to greater activity and yoga and less depression based on a logistic regression analysis.

Several other resilience factors have been discussed in an elaborate review on resilience in late life depression [43]. These include temperament (behavioral inhibition), personality factors such as low extraversion and high neuroticism, and low self-esteem. In addition, the practice of religion and a belief in eternal life were buffers, although greater prayer has been notably associated with greater depression.

Religiosity. Religiosity has decreased the effects of depression in older adults in at least three studies. In the first study entitled "Moderating effects of intrinsic religiosity on the relationship between depression and cognitive function among community-dwelling older adults (N= 2,322 in Malaysia) a moderator hierarchical regression analysis was conducted [53]. Religiosity decreased the negative effects of depression on cognitive function after controlling for demographic variables. In a second study that had one of the lowest rates of depression (Ghana at 8%), participants who had no religion had seven times the rate of depression [3].

In a systematic review of older adults' attitudes toward treatments for depression, 11 studies were included [54]. The participants in the research basically preferred self- management strategies that were aligned with their experience and social image including most prominently prayer and socializing. Thus, praying has had mixed effects across studies.

Physical activity. Physical activity has also been a buffer against late life depression in a study from 14 European countries over a four year follow up from the years 2011 to 2015 [55]. In this Survey of Health, Age and Retirement in Europe (N=32,392), the EURO-D 12-item Scale of Depression (number of symptoms) was used and the intensity and frequency of activity were reported. Moderate and vigorous physical activity at least once per week were negatively correlated with depression after controlling for demographic variables, self-related health and chronic diseases. Although this old database may not generalize to today's adults

with late life depression, these results were virtually the same on approximately twice the sample size (N=64,688) by the same authors [55]. In this larger sample, the researchers were looking at the effects of different levels of physical activity on depressive symptoms. Not surprisingly, a dose-response relationship was noted between physical activity and depressive symptoms. The significantly greater number of females in this sample is a limitation of this study, not unlike many other surveys in this literature.

In a systematic review on molecular mechanisms for the positive effects of physical exercise on depression in the elderly, 11 studies met inclusion criteria [56]. Aerobic and resistance training were the most common and on average were moderate intensity exercises of 60 minutes duration, three times a week for 24 weeks. Exercise increased IGF–1 and the expression of BDNF and its receptors in the hippocampus and prefrontal cortex, inhibiting depressive–like behavior.

Mediterranean diet. A Mediterranean diet has also reduced the risk of late life depression in a sample from Florence, Italy on 90 to 99 year-old adults (N=388) [57]. The Mini–Mental State Exam and the Geriatric Depression Scale were included along with the Mediterranean Diet Score. Consumption of more olive oil and fruit was associated with less depression. The sample, however, was limited to depressed participants who were older female widows, limiting the generalizability of the data.

Retirement. In a study entitled "Does retirement trigger depressive symptoms?", a meta-analysis was conducted on 41 studies [58]. As the authors suggested, retirement is a major life transition and existing studies had presented contradictory results. The meta-analysis on 557,811 participants from 60 databases suggested a protective effect of retirement on the risk of depression. Further, studies with the highest quality of longitudinal and validated measures suggested a stronger effect of retirement on depression. Retirement reduced the risk of depression by 20%. Surprisingly, no statistical differences were noted between genders. The results of this meta-analysis were also at odds with the meta-analysis reviewed under risk factors [38]. That meta-analysis, however, included fewer studies (25 versus 41) and the negative effects of retirement appeared to be related to involuntary retirement which would be expected to have negative effects.

Interventions

In the recent late life depression literature, interventions have included education to decrease ageism against older adults. Interventions for those who are depressed have included physical activity, strength training, serious games, mindfulness, and nontraditional interventions like yoga and ketamines (Table 5).

Interventions	First authors
Education to reduce ageism	Burnes
Cognitive training and physical activity	Gunning
Strength and aerobic training	Moraes
Serious games	Kim
Mindfulness meditation	Reangsing
Non-traditional therapies	Laird
Antidepressants	Briggs
Ketamines	Sukhram, Greene
Sleep deprivation	Shanafi

Table 5: Interventions for Late Life Depression.

Decreasing ageism. In a meta-analysis on interventions to decrease ageism against older adults, 63 studies were included (N=6,124) [59]. The meta-analysis revealed that education and intergenerational contact were the most effective interventions for reducing ageism against older adults. Stronger effects were noted for females and younger groups.

Cognitive training and physical activities. Interventions that have been reportedly effective with depressed aging adults include cognitive training and physical activities [60]. Cognitive training has been effective via video games for reducing late life depression. Physical activity is reported ly effective via a number of mechanisms including that it "promotes neurogenesis, upregulates neurotrophic factors and suppresses pro-inflammatory signaling and oxidative damage as well as improves vascular health and increased cerebral blood flow" [60].

Strength training and aerobic training. These two types of training have been compared for their effects on depression in older adults [61]. In this study, 27 aging adults were randomly assigned to strength training or aerobic training. Depression was reduced in 50% of the participants. However, the two exercise groups cannot be compared because different rating scales were used for depression in the two different groups. In addition, the sample size was too small for that comparison.

Serious games. Serious games have been notably effective based on a systematic review and meta-analysis of 17 studies in the recent literature on late life depression (1,280 older adults) [62]. In this meta-analysis games for physical activity and games for both physical activity and cognitive function were noted to decrease late life depression but not cognitive function games alone. No effects were noted for the duration or the number of serious games.

Mindfulness meditation. Meta-analysis has also been performed on mindfulness meditation research [63]. In this analysis on 1,076 72-year-old adults, a significant decrease in depression was noted for protocols of less than five weeks of mindfulness meditation. The decrease in depression was greater for the Asians than the Europeans who in turn had a greater decrease in depression than the North Americans. Guided meditation was more effective than non-guided meditation. Some have suggested that nontraditional therapies like meditation, physical activity, or art therapy may be more effective because they are more accepted. Greater acceptance may relate to their being used by non–depressed adults [12].

In a review of the literature on non-traditional therapies, several have been notably effective [39]. These include not only mindfulness meditation but mindfulness-based stress reduction, journaling, yoga, tai chi, kirtans, chanting, a balanced diet and sufficient sleep. Other more medical interventions include cognitive behavior therapy (CBT), ECT biofeedback, heart rate variability feedback and antidepressants [40]. An example of an effective intervention is the peer-led combination of CBT, physical exercise and sleep activities on zoom (14 weeks) leading to decreased depression and stress and increased physical activity, brain health behavior and sleep quality [64]. But this study needs replicating as it is based on a very small sample (N=24 with only 20 completing the intervention).

Participants in at least one study had mixed views on psychotherapy and antidepressants [54]. Antidepressants were frequently used for late life depression until recently. Antidepressants have reportedly only been effective for 30% of those with late life depression likely because of their treatment resistant depression [13]. And, the prevalence of untreated depression has also been increasingly high. For example, in a study on 7,000 adults greater than 50 years old, although 12% were depressed, only 29% of those were on antidepressants in the Irish Longitudinal Study on Ageing.

Ketamines have recently been used more frequently as they are thought to be more immediately effective than antidepressants. In a review entitled "Antidepressant effects of ketamines on inflammation–mediated serotonin dysregulation", ketamine infusions in 5 to 7 studies have notably decreased depression by 50% in 56% of those treated [65]. The effects reputedly involve a reduction in pro-inflammatory cytokines including IL-6 and TNF-1. Rapid treatments have not only included ketamines but also sleep deprivation and acute exercise which have been effective in a few hours to a week [66]. These are reputedly effective due to activation of the endocannabinoid system.

Potential Biomarkers and Underlying Biological Mechanisms

Biomarkers and potential underlying mechanisms have been explored in the recent literature on late life depression. These include cortisol, IL–beta as a marker of inflammation, homocysteine, amyloid, DNA methylation, and disconnected brain networks (Table 6).

Biomarkers and Mechanisms	First authors
>Cortisol, nesfatin-1 and IL-Beta	Wu
>Inflammation	Rozing
>C-reactive protein	Frank
>IL-6 and TNF-alpha leading to <serotonin and BDNF	Kuo
<Functional connectivity in the brain	Laird
>Hippocampal and prefrontal atrophy	Laird
Low low-frequency heart rate variability	Laird

Table 6: Biomarkers and Potential Underlying Mechanisms for Late Life Depression.

Inflammation and its Biomarkers

Serum cortisol, nesfatin-1 and IL-beta have been diagnostic biomarkers in elderly patients with treatment -resistant depression [8]. The stimulation of the HPA axis and over secretion of cortisol contributes to neurodegeneration which is a significant risk for late life depression and cognitive decline [41].

Total plasma homocysteine was also related to depression in a sample of older Hispanic adults after adjusting for age, sex, education, smoking, diabetes, hypertension, alcohol intake, stroke and dementia [67]. After controlling for these many variables in this sample (N=1,418 adults greater than 55 years old), homocysteine explained a significant amount of the variance in the number of depressive symptoms. The authors expressed the concern that excessive homocysteine can damage the interior wall of arteries and increase the chance of forming clots. Amyloid deposition has also been associated with plaques and depression symptoms in the Mayo Clinic Study of Aging (N=1028) [68].

And, late life depression has been associated with greater levels of growth-differentiating factor -15 (GDF-15), a pro-aging mitokine. In this sample (N=393 greater than 70 years old), GDF-15 was associated with increasing chronological age, decreasing telomerase activity and increased early mortality risk. It was also related to a greater incidence of comorbid physical illness and declining executive cognitive function.

Inflammation has been noted as the increase of inflammatory cytokines that interact with neural transmitters, most especially serotonin and dopamine that contribute to mood and cognitive symptoms of depression [38]. Inflammation and its biomarkers have been the focus of a few studies on potential mechanisms underlying late life depression. In a study entitled "Inflammation in older subjects with early and late – onset depression", the Netherlands Study of Depression in Older Persons" was tapped for this database [69]. In this study on 350 persons greater than 60-years-old, 119 had late onset and 231 had early onset depression. C-reactive protein (CRP) levels were more strongly associated with late-onset depression than early onset. The IL-6 levels were

significantly lower and declined in depression. Unfortunately, the comparison of these two groups was confounded by the differences in sample size.

CRP levels have distinguished two types of depression in a sample from the English Longitudinal Study on Ageing (N=3,510 adults greater than 50-years-old) (Frank et al, 2021). In this study, CRP levels mediated the relationship between polygenic scores and depressive symptomatology. This finding was specific to somatic symptoms but not cognitive-affective symptoms. These researchers also confirmed the two-factor structure of the CES-D depression scale as being somatic symptoms and cognitive-affective symptoms based on a factor analysis.

Others have also suggested that inflammation and its markers have been the molecular basis for late life depression [70]. They have indicated that the cytokines representing inflammation increase with age and they decrease serotonin. In late life depression, IL-6 and TNF–alpha lead to decreased serotonin and a BDNF (brain-derived neurotrophic factor) decrease which may contribute to the memory impairment and dementia that are seen in late life depression that are reciprocally related to BDNF. The authors suggested that these factors are responsible for the limited treatment response to antidepressants (48%) and a remission rate of only 34%.

Decreased Functional Connectivity

An interesting mechanism has been proposed in a paper entitled "Brain–based mechanisms of late life depression [60]. According to these authors, in late life depression negative cognitive biases and processing happen for both internal and external stimuli which contribute to negative self-referential thoughts, guilt, rumination, self-criticism, feelings of worthlessness and sadness and resistance to traditional antidepressant treatment. This is compounded by apathy which is experienced by one third to one half of those suffering from late life depression. This is related to "decreased extrinsic functional connectivity between the salience network (which is critical for prioritizing stimuli), the executive control network (which is involved in maintaining goal-directed behavior in the face of changing internal and external demands) and the default motor network (which plays a key role in individuals' understanding of their place in the world).". They also mention white matter abnormalities as a hallmark of small vessel disease. They locate the areas of the brain that are involved such as the medial prefrontal cortex, the poster cingulate cortex and the precuneus in the default mode network.

Other Biomarkers

Other biomarkers have been suggested including neuroimaging markers [40]. Neuroimaging markers have included the atrophy that has been shown in the hippocampus and the prefrontal cortex, with fMRI studies suggesting increased activation of the prefrontal cortex and the amygdala during emotion regulation tasks.

Cardiovascular markers have shown an association between depression and cardiovascular disease with two times the risk of developing cardiovascular disease for those who are depressed [41]. This has already been mentioned as being confounded by unhealthy behaviors such as bad diet and physical inactivity. The low low frequency heart rate variability already mentioned reflects both sympathetic and parasympathetic activation. Endocrine changes have included the decreased reproductive hormones. The reproductive hormones that have been emphasized include estrogen which the authors suggest have been "important for brain regions vulnerable to age – related changes including the prefrontal cortex and the hippocampus".

Methodological Limitations

Several methodological limitations can be noted about these recent studies on late life depression. Significant variability has been reported on the sampling methods, on the sample sizes, and the prevalence and results of the studies. Self-report surveys have been the most frequently used method for data collection. Logistic regression analyses have typically been used. They have controlled for confounding variables, for example, gender, socioeconomic status and education that might instead be risk factors or mediating/moderating variables if they had been analyzed by mediation/moderation or structural equations analysis. These confounding variables that might be important for intervention purposes may have been obscured by these analyses.

Several of the effects that have been noted could also be risk factors and risk factors could be effects, as in bidirectional, reciprocal variables, although they have rarely been considered reciprocal. In some studies bidirectional effects have been reported. However, as some have noted, the research has been "methodologically heterogeneous in terms of design, inclusion criteria, measures of multimorbidity and depression and length of follow-up'. Several of the measures are short or dichotomous which limits the reliability of these measures. For example, in a review of the 21 functional assessments that have been used, only two had formal validation data. The direction of effects cannot be determined as most of the studies are correlational and several of the longitudinal studies have focused on cross-sectional data instead of their longitudinal datapoints.

Many of the results are relationships between late life depression and other effects, risk variables or buffers/protective factors selected by the researchers. Rarely has late depression been compared to early onset depression or the depression experienced by younger adults. Surprisingly, sex differences have been rare, although several studies were exclusively male or female, limiting generalizability. The prevalence of late life depression, its measures and its effects are so variable that systematic reviews and meta-analyses have been inconclusive.

Biomarkers and potential underlying mechanisms for late life depression have been suggested in reviews on the topic, although mechanism studies have rarely appeared in the recent literature. And, several of the recent intervention studies have not randomly assigned participants to comparison groups. Despite these methodological limitations, the recent literature highlights the effects and risk variables for late life depression, although it

doesn't conclude that aging is associated with more depression necessarily than other stages of life.

Despite all the negative effects reported for aging and depression and the methodological limitations mentioned for this recent literature, at least one research group has suggested that the prevalence of depression has decreased with age [71]. The authors argue that this has related to a bias toward positive information, increased emotion regulation, less regret and greater socioeconomic status. And, they also reported less prediction errors, i.e. that differences between predicted and actual events decreased with age which led to less negative affect and less susceptibility to affective disorders like depression [72].

Conclusions

The recent literature (last five years) on late life depression is predominantly focused on risk factors/predictors of late life depression along with studies on effects, buffers, and interventions. Late life depression has typically been self-reported or diagnosed starting at age 60. The prevalence rates for late life depression were highly variable in this literature, ranging from a low of 7% in Italy to a high of 37% in Chile, a variability that may relate to the year or type of data collection and/or cross-cultural variation. Negative effects have included loneliness, suicidal ideation, cognitive decline, frailty, functional limitations, low heart rate variability, biological aging (short telomere length and white matter lesions) and earlier mortality. Risk factors have included loneliness, aging anxiety, life stressors (marital discord and job strain), physical problems (activities of daily living), physical health (elevated blood pressure), physical weakness (handgrip, frailty, falls and disability) and unhealthy intake (poor diet, excessive alcohol and vitamin D deficiency).

Buffers/protective factors have included positive views on aging, resilience, practicing religion, a Mediterranean diet, and remaining active. Interventions have included cognitive training, mindfulness, physical activity and ketamines. Multiple underlying mechanisms have been suggested including dysfunctional connectivity between different networks in the brain. Although the data highlight the severity of late life depression, the recent literature has been based on different measures appearing on self-report surveys that have yielded mixed results across samples.

References

1. Haigh EAP, Bogucki OE, Sigmon ST, Blazer DG. (2018) Depression Among Older Adults: A 20-Year Update on Five Common Myths and Misconceptions. Am J Geriatr Psychiatry.26:107-122.
2. Moreno X, Gajardo J, Monsalves MJ.(2022) Gender differences in positive screen for depression and diagnosis among older adults in Chile. BMC Geriatr.22:54.
3. Boima V, Tetteh J, Yorke E, Archampong T, Mensah G, et al.(2020) Older adults with hypertension have increased risk of depression compared to their younger counterparts: Evidence from the World Health Organization study of Global Ageing and Adult Health Wave 2 in Ghana. J Affect Disord.277:329-336.
4. Zhang N, Shi GP, Wang Y, Chu XF, Wang ZD, et al. (2020) Depressive symptoms are associated with incident frailty in a Chinese population: the Rugao Longevity and Aging Study. Aging Clin Exp Res 32: 2297-2302.
5. Qiao YM, Lu YK, Yan Z, Yao W, Pei JJ, et al. (2019) Reciprocal associations between job strain and depression: A 2-year follow-up study from the Survey of Health, Ageing and Retirement in Europe. Brain Behav 9: e01381.
6. Tsaras K, Tsiantoula M, Papagiannis D, Papathanasiou IV, Chatzi M, et al. (2022) The Effect of Depressive and Insomnia Symptoms in Quality of Life among Community-Dwelling Older Adults. Int J Environ Res Public Health 19: 13704.
7. Zhao W, Zhang Y, Liu X, Yue J, Hou L,et al. (2020) Comorbid depressive and anxiety symptoms and frailty among older adults: Findings from the West China health and aging trend study. J Affect Disord 277: 970-976.
8. Wu X, Dai B, Yan F, Chen Y, Xu Y, et al. (2022) Serum Cortisol, Nesfatin-1, and IL-1β: Potential Diagnostic Biomarkers in Elderly Patients with Treatment-Resistant Depression. Clin Interv Aging 17: 567-576.
9. McHugh Power J, Hannigan C, Hyland P, Brennan S, Kee F, et al.(2020) Depressive symptoms predict increased social and emotional loneliness in older adults. Aging Ment Health.24:110-118.
10. Hsueh YC, Chen CY, Hsiao YC, Lin CC.(2019) A longitudinal, cross-lagged panel analysis of loneliness and depression among community-based older adults. J Elder Abuse Negl.31:281-293.
11. Bickford D, Morin RT, Woodworth C, Verduzco E, Khan M, et al. (2021) The relationship of frailty and disability with suicidal ideation in late life depression. Aging Ment Health.25:439-444.
12. Greene RD, Cook A, Nowaskie D, Wang S.(2020) Neurological Changes and Depression: 2020 Update. Clin Geriatr Med.36:297-313.
13. Manning KJ, Preciado-Pina J, Wang L, Fitzgibbon K, Chan G, et al.(2021) Cognitive variability, brain aging, and cognitive decline in late-life major depression. Int J Geriatr Psychiatry.36:665-676.
14. Lee ATC, Fung AWT, Richards M, Chan WC, Chiu HFK, et al.(2021) Risk of incident dementia varies with different onset and courses of depression. J Affect Disord.282:915-920.
15. Chang HY, Fang HL, Ting TT, Liang J, Chuang SY, et al.(2019) The Co-Occurrence Of Frailty (Accumulation Of Functional Deficits) And Depressive Symptoms, And Its Effect On Mortality In Older Adults: A Longitudinal Study. Clin Interv Aging.14:1671-1680.
16. Borges MK, Aprahamian I, Romanini CV, Oliveira FM, Mingardi SVB, et al.(2021) Depression as a determinant of frailty in late life. Aging Ment Health.25:2279-2285.
17. Brown PJ, Ciarleglio A, Roose SP, Montes Garcia C, Chung S, et al.(2022) Frailty and Depression in Late Life: A High-Risk Comorbidity With Distinctive Clinical Presentation and Poor Antidepressant Response. J Gerontol A Biol Sci Med Sci.77:1055-1062.
18. Oude Voshaar RC, Dimitriadis M, vandenBrink RHS, Aprahamian I, Borges MK, et al.(2021) A 6-year prospective clinical cohort study on the bidirectional association between frailty and depressive disorder. Int J Geriatr Psychiatry.36:1699-1707.
19. Gale CR, Westbury LD, Cooper C, Dennison EM.(2018) Risk factors for incident falls in older men and women: the English longitudinal study of ageing. BMC Geriatr.18:117.

20. Wassink-Vossen S, Collard RM, Wardenaar KJ, Verhaak PFM, Rhebergen D, et al. (2019) Trajectories and determinants of functional limitations in late-life depression: A 2-year prospective cohort study. Eur Psychiatry 62: 90-96.

21. Brown L, Karmakar C, Gray R, Jindal R, Lim T, et al.(2018) Heart rate variability alterations in late life depression: A meta-analysis. J Affect Disord.235:456-466.

22. Han K, Yang S, Jia W, Wang S, Song Y, et al.(2020) Health-Related Quality of Life and Its Correlation With Depression Among Chinese Centenarians. Front Public Health.8:580757.

23. Han LKM, Aghajani M, Clark SL, Chan RF, Hattab MW, et al.(2018) Epigenetic Aging in Major Depressive Disorder. Am J Psychiatry.175:774-782.

24. Mendes-Silva AP, Vieira ELM, Xavier G, Barroso LSS, Bertola L, et al. (2021)Telomere shortening in late-life depression: A potential marker of depression severity. Brain Behav.11:e2255.

25. Schroder JD, de Araújo JB, de Oliveira T, de Moura AB, Fries GR, et al. (2021) Telomeres: the role of shortening and senescence in major depressive disorder and its therapeutic implications. Rev Neurosci 33: 227-255.

26. van den Berg KS, Wiersema C, Hegeman JM, van den Brink RHS, Rhebergen D, et al. (2021) Clinical characteristics of late-life depression predicting mortality. Aging Ment Health 25: 476-483.

27. Li Y, Chan WCH, Chen H, Ran M.(2022)Widowhood and depression among Chinese older adults: examining coping styles and perceptions of aging as mediators and moderators. Aging Ment Health.26:1161-1169.

28. Bodner E, Shrira A, Hoffman Y, Bergman YS.(2021) Day-to-Day Variability in Subjective Age and Ageist Attitudes and Their Association With Depressive Symptoms. J Gerontol B Psychol Sci Soc Sci.76:836-844.

29. Gum AM, Ayalon L.(2018) Self-perceptions of aging mediate the longitudinal relationship of hopelessness and depressive symptoms. Int J Geriatr Psychiatry.33:591-597.

30. Segel-Karpas D, Shrira A, Cohn-Schwartz E, Bodner E (2022) Daily fluctuations in subjective age and depressive symptoms: the roles of attitudes to ageing and chronological age. Eur J Ageing 19: 741-751.

31. Protsenko E, Yang R, Nier B, Reus V, Hammamieh R, et al. (2021) "GrimAge," an epigenetic predictor of mortality, is accelerated in major depressive disorder. Transl Psychiatry 11: 193.

32. Domènech-Abella J, Mundó J, Haro JM, Rubio-Valera M.(2018) Anxiety, depression, loneliness and social network in the elderly: Longitudinal associations from The Irish Longitudinal Study on Ageing (TILDA). J Affect Disord.246:82-88.

33. Yoon H, Park GR, Kim J (2022) Psychosocial trajectories before and after spousal loss: Does gender matter? Soc Sci Med 294: 114701.

34. Srivastava S, Debnath P, Shri N, Muhammad T (2021) The association of widowhood and living alone with depression among older adults in India. Sci Rep 11: 21641.

35. Willie-Tyndale D, Donaldson-Davis K, Ashby-Mitchell K, McKoy Davis J, Aiken WD,et al. (2021) Sexual Activity and Depressive Symptoms in Later Life: Insights from Jamaica. Clin Gerontol 44: 316-330.

36. Rotter I, Wiatrak A, Rył A, Kotfis K, Ciosek Ż, et al. (2020) The Relationship between Selected Bioelements and Depressiveness Associated with Testosterone Deficiency Syndrome in Aging Men. Medicina (Kaunas) 56: 125.

37. Whisman MA, Robustelli BL, Labrecque LT (2018) Specificity of the Association between Marital Discord and Longitudinal Changes in Symptoms of Depression and Generalized Anxiety Disorder in the Irish Longitudinal Study on Ageing. Fam Process 57: 649-661.

38. Li W, Ye X, Zhu D, He P.(2021) The Longitudinal Association Between Retirement and Depression: A Systematic Review and Meta-Analysis. Am J Epidemiol.190:2220-2230.

39. Laird KT, Krause B, Funes C, Lavretsky H.(2019) Psychobiological factors of resilience and depression in late life. Transl Psychiatry.9:88.

40. Laird KT, Lavretsky H, Paholpak P, Vlasova RM, Roman M, et al.(2019) Clinical correlates of resilience factors in geriatric depression. Int Psychogeriatr.31:193-202.

41. Laird KT, Lavretsky H, Wu P, Krause B, Siddarth P.(2019) Neurocognitive Correlates of Resilience in Late-Life Depression. Am J Geriatr Psychiatry.27:12-17.

42. Keyes KM, Allel K, Staudinger UM, Ornstein KA, Calvo E.(2019) Alcohol consumption predicts incidence of depressive episodes across 10 years among older adults in 19 countries. Int Rev Neurobiol.148:1-38.

43. Gomes AP, Oliveira Bierhals I, Gonçalves Soares AL, Hellwig N, Tomasi E, et al.(2018) Interrelatioship between Diet Quality and Depressive Symptoms in Elderly. J Nutr Health Aging.22:387-392.

44. Tan J, Ma C, Zhu C, Wang Y, Zou X, et al. (2023) Prediction models for depression risk among older adults: systematic review and critical appraisal. Ageing Res Rev 83: 101803.

45. Muhammad T, Maurya P.(2022) Social support moderates the association of functional difficulty with major depression among community-dwelling older adults: evidence from LASI, 2017-18. BMC Psychiatry.22:317.

46. Muhammad T, Hossain B, Das A, Rashid M.(2022) Relationship between handgrip strength and self-reported functional difficulties among older Indian adults: The role of self-rated health. Exp Gerontol.165:111833.

47. Jia F, Shi X, Li X, Wang B, Liu F, et al.(2020) Physical frailty and the risk of major depressive disorder: The Irish Longitudinal Study on Ageing. J Psychiatr Res.125:91-95.

48. Choi NG, Zhou Y, Marti CN, Kunik ME.(2022) Associations Between Changes in Depression/Anxiety Symptoms and Fall Worry Among Community-Dwelling Older Adults. J Appl Gerontol. 41:2520-2531.

49. Kim JH.(2021) Experiences of falling and depression: Results from the Korean Longitudinal Study of Ageing. J Affect Disord.281:174-182.

50. Dong L, Freedman VA, Mendes de Leon CF.(2020) The Association of Comorbid Depression and Anxiety Symptoms With Disability Onset in Older Adults. Psychosom Med.82:158-164.

51. Reynolds CF (2019) Promoting resilience, reducing depression in older adults. Int Psychogeriatr 31: 169-171.

52. Muneera K, Muhammad T, Althaf S.(2022) Socio-demographic and lifestyle factors associated with intrinsic capacity among older adults: evidence from India. BMC Geriatr.22:851.

53. Foong HF, Hamid TA, Ibrahim R, Haron SA.(2018) Moderating effect of intrinsic religiosity on the relationship between depression and cog-

nitive function among community-dwelling older adults. Aging Ment Health.22:483-488.

54. Nair P, Bhanu C, Frost R, Buszewicz M, Walters KR.(2020) A Systematic Review of Older Adults' Attitudes Towards Depression and Its Treatment. Gerontologist.60:e93-e104.

55. Marques A, Bordado J, Peralta M, Gouveia ER, Tesler R, et al.(2020) Cross-sectional and prospective relationship between physical activity and depression symptoms. Sci Rep.10:16114.

56. De Sousa RAL, Rocha-Dias I, de Oliveira LRS, Improta-Caria AC, Monteiro-Junior RS, et al.(2021) Molecular mechanisms of physical exercise on depression in the elderly: a systematic review. Mol Biol Rep.48:3853-3862.

57. Pagliai G, Sofi F, Vannetti F, Caiani S, Pasquini G, et al.(2018) Mediterranean Diet, Food Consumption and Risk of Late-Life Depression: The Mugello Study. J Nutr Health Aging.22:569-574.

58. Odone A, Gianfredi V, Vigezzi GP, Amerio A, Ardito C, et al. (2021); Italian Working Group on Retirement and Health. Does retirement trigger depressive symptoms? A systematic review and meta-analysis. Epidemiol Psychiatr Sci.30:e77.

59. Burnes D, Sheppard C, Henderson CR Jr, Wassel M, Cope R, et al.(2019) Interventions to Reduce Ageism Against Older Adults: A Systematic Review and Meta-Analysis. Am J Public Health.109:e1-e9.

60. Gunning FM, Oberlin LE, Schier M, Victoria LW.(2021) Brain-based mechanisms of late-life depression: Implications for novel interventions. Semin Cell Dev Biol.116:169-179.

61. Moraes HS, Silveira HS, Oliveira NA, Matta Mello Portugal E, Araújo NB, et al.(2020) Is Strength Training as Effective as Aerobic Training for Depression in Older Adults? A Randomized Controlled Trial. Neuropsychobiology.79:141-149.

62. Kim Y, Hong S, Choi M.(2022) Effects of Serious Games on Depression in Older Adults: Systematic Review and Meta-analysis of Randomized Controlled Trials. J Med Internet Res.24:e37753.

63. Reangsing C, Lauderman C, Schneider JK (2022) Effects of Mindfulness Meditation Intervention on Depressive Symptoms in Emerging Adults: A Systematic Review and Meta-Analysis. J Integr Complement Med 28: 6-24.

64. Roberts JS, Ferber RA, Funk CN, Harrington AW, Maixner SM, et al. (2022) Mood Lifters for Seniors: Development and Evaluation of an Online, Peer-Led Mental Health Program for Older Adults. Gerontol Geriatr Med 8: 23337214221117431.

65. Sukhram SD, Yilmaz G, Gu J (2022) Antidepressant Effect of Ketamine on Inflammation-Mediated Cytokine Dysregulation in Adults with Treatment-Resistant Depression: Rapid Systematic Review. Oxid Med Cell Longev 2022: 1061274.

66. Sharafi A, Pakkhesal S, Fakhari A, Khajehnasiri N, Ahmadalipour A (2022) Rapid treatments for depression: Endocannabinoid system as a therapeutic target. Neurosci Biobehav Rev 137: 104635.

67. Castro F, Melgarejo J, Chavez CA, de Erausquin GA, Terwilliger JD, et al.(2021) Total Plasma Homocysteine and Depressive Symptoms in Older Hispanics J Alzheimers Dis.82:S263-S269.

68. Krell-Roesch J, Lowe VJ, Neureiter J, Pink A, Roberts RO, et al.(2018) Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: the Mayo Clinic Study of Aging. Int Psychogeriatr.30:245-251.

69. Rozing MP, Veerhuis R, Westendorp RGJ, Eikelenboom P, Stek M, et al. (2019) Inflammation in older subjects with early- and late-onset depression in the NESDO study: a cross-sectional and longitudinal case-only design. Psychoneuroendocrinology 99: 20-27.

70. Kuo CY, Lin CH, Lane HY.(2021) Molecular Basis of Late-Life Depression. Int J Mol Sci.22:7421.

71. Trapp S, Guitart-Masip M, Schröger E (2022) A link between age, affect, and predictions? Eur J Ageing 19: 945-952.

72. Ali NS, Hashem AHH, Hassan AM, Saleh AA, El-Baz HN.(2018) Serum interleukin-6 is related to lower cognitive functioning in elderly patients with major depression .Aging Ment Health.22:655-661.