# **Original Research**

# Association between Frailty and Depression among Elderly in Nursing Home

# Muhammad Zuhal Darwis<sup>1</sup>, Imran Safei<sup>2</sup>

<sup>1</sup>Faculty of Medicine, Universitas Muslim Indonesia, Makassar, South Sulawesi, Indonesia <sup>2</sup>Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Muslim Indonesia, Ibnu Sina Hospital, Makassar, South Sulawesi, Indonesia

\*Corresponding Author:

Muhammad Zuhal Darwis, Faculty of Medicine, Universitas Muslim Indonesia, Jalan Urip Sumoharjo, Makassar, South Sulawesi, Indonesia.

Email: mzuhaldarwis@gmail.com

Article info:

Received: May 13<sup>rd</sup>, 2022; Received in revised: June 14<sup>th</sup>, 2022; Accepted: June 16<sup>th</sup>, 2022; Published August 22<sup>nd</sup>, 2022.

This is an open access article under the CC-BY license (https://creativecommo ns.org/licenses/by/4.0/)



Cite this as: Darwis Z, Safei I. Association between Frailty and Depression among Elderly in Nursing Home. *SPMRJ*. 2022;4(2):55-62.

#### ABSTRACT

**Background:** Frailty is described by the collective decline of multiple physiological systems and increased vulnerability to multiple stressors. It is also linked to emotional distress and mental illness, especially depression. Both frailty and depression are correlated with many harmful consequences in the elderly, including decreased quality of life, escalated utilization of health services, and elevated morbidity and mortality. Given the prominence of frailty and depression in the elderly, and the deleterious consequences when they coexist, understanding the association between these factors is essential.

**Aim:** This study aims to analyze the association between frailty and depression among the elderly in the nursing home.

**Material and Methods:** This research was cross-sectional, and conducted at 3 nursing homes in South Sulawesi. Frailty and depression were measured. Frailty was assessed by Edmonton Frail Scale (EFS), while depression was evaluated by Geriatric Depression Scale (GDS). The data were analyzed with the Pearson test in SPSS 25.

**Results:** There were 27 participants, consisting of females 19 (70.3%), and males 8 (29.6%) with a mean age was  $73.15\pm8$ , included in this study. The mean EFS was  $5.89\pm3.15$ . The mean GDS result was  $3.74\pm3.14$ . Frailty has positive strong association with depression (r=0.6, p=0.001).

**Conclusion:** There was a strong and substantial association between frailty and depression among the elderly in the nursing home.

**Keywords**: Depression, Edmonton Frail Scale, Elderly, Frailty, Geriatric Depression scale, Nursing Home.

## Introduction

Frailty is frequently determined as a manifestation of the senescence process, defined by the collective decline of various physiological systems and increased vulnerability to multiple stressors.<sup>1</sup> The line between senescence and frailty appears to be obscured to the point where it has been suggested that everyone grows frail as they age.<sup>2</sup>

The frailty process can be divided into three stages: pre-frailty, frailty, and frailty complications. The pre-frail stage is often invisible, and the body's physiological sufficient to reserves are respond appropriately to acute illnesses, stress, injury, or any other trauma with the chance of full recuperation. A frailty state is defined by a sluggish, insufficient convalescence after every new acute illness, or injury, indicating that stress. the obtainable functional reserves are inadequate to support a full recuperation. complications Frailty are linked to physiologic susceptibility as a result of poor homeostatic reserves and a decreased ability of the individual to endure stress. Falls become more likely, and functional deterioration follows, resulting in disability, an elevated chance of hospitalization, institutionalization, cross-infection, and mortality.<sup>2</sup>

Rolfson et al. assessed a short and convenient screening tool in both outpatient and inpatient settings to measure frailty in the elderly. When compared to the assessment by geriatric specialists, the "Edmonton Frail Scale" (EFS) proved to be a reliable measure of frailty. The EFS had satisfactory construct validity, internal consistency, and reliability.<sup>2</sup>

The concept of frailty has become increasingly essential due to the necessity to acknowledge the health trajectories of the elderly and to avoid or at least postpone the onset of disability in the elderly population.<sup>3</sup> Frailty is also linked to mental disorders and emotional distress, especially depression.<sup>1</sup>

Depression is one of the most prevalent mental health illnesses in elderly. Depression affects up to 25 percent of individuals over the age of 60, the fastestgrowing population in the United States of America. Depression in elderly is overlooked because health sometimes practitioners consider depressive symptoms to be natural signs of aging. The occurrence of these symptoms in elderly may be linked to a dependency and the worsening of preexisting medical diseases. Depression in elderly is linked to an escalated possibility of morbidity and mortality, resulting in greater utilization of health services, selfcare neglect, and treatment non-adherence. Because of its rising frequency and negative consequences among the elderly worldwide. early identification of depression is critical geriatric in treatment.4,5

Cognitive impairment, functional decline and diminished quality of life are among the problems that older persons with depressed depression or symptoms confront. Previous research has shown that depressive symptoms are more frequent in the elderly than in younger people. The psychological symptoms of depression in the elderly are intimately linked to the decrease in function correlated with aging. Furthermore, when compared to the general population, social support status is a more relevant determinant of depression among elderly from other cultures. As a result, the symptoms and causes of depression in older persons might be more varied than in younger ones.<sup>4</sup>

It has been claimed that using selfreports can help identify depression symptoms in the elderly. Although, the potential hesitancy of somatic symptoms of depression (loss of weight, insomnia, decrease of energy, and reduced activity) with several adjustments and losses correlated with normal and pathological senescence need to be evaluated.<sup>5</sup>

To answer this problem, the Geriatric Depression Scale (GDS) was designed, first with 30 items and afterwards with 15 items to save respondents time and fatigue during administration. Both versions are one-dimensional and do not comprise items related to depression's somatic symptoms. They are simple to administer because dichotomous response format (Yes/No). An accumulative score equal to or more than 5 indicates mild depression and an accumulative score equivalent or more than 10 indicates moderate to severe depression, and thus follow up through clinical assessment is suggested to establish the diagnosis.<sup>5</sup>

Elderly with late life depression do not respond well to available treatments and therefore have enormous social, personal and economic costs. Treatment in the elderly may fail because pathophysiological models and diagnostic criteria of depression rely primarily on research in young adults, although pathophysiology and symptoms of late life depression tend to change with age.<sup>6</sup> The prevalence of depression in frail the elderly was 46.5%. Both frailty and depression are correlated with many harmful consequences in the elderly, including: decreased quality of life, escalated utilization of health services, and elevated morbidity and mortality. Moreover, the coexistence of frailty and depression was correlated with particularly poor outcomes, including precipitated cognitive impairment and disability.<sup>7,8</sup>

There are some reasons for the high comorbidity between frailty and depression. One is the commonalities of diagnostic criteria in some areas. such as unintentional weight loss. slowness. less physical activity, and fatigue, which makes it difficult to differentiate them from one another, especially in the elderly.<sup>3,8</sup> factor is that depression and frailty share a typical cause. which makes disengagement burdensome. Given the prominence of depression and frailty in the elderly, and consequences deleterious when they coexist, understanding the association between these factors is essential.<sup>8</sup> line with this explanation and finding, the following hypothesis was developed: frailty and depression have positive association in the elderly at the nursing home.

# Material and Methods

This study was a cross-sectional, conducted in 3 nursing homes which are *Pusat Pelayanan Sosial Lanjut Usia Mappakasunggu, Balai Rehabilitasi Sosial Lanjut Usia (BRSLU) Gau Mabaji*, and *Panti Werdha Theodora* Makassar, South Sulawesi, Indonesia in April 2022. Both variables were evaluated by standardized instruments, frailty was evaluated by Edmonton Frail Scale (EFS) and depression was assessed with Geriatric Depression Scale (GDS). Evaluation was done by a general practitioner who was supervised by a physiatrist specializing in geriatric rehabilitation.

The Edmonton Frail Scale (EFS) is a performance-based multifactorial frailty evaluation instrument invented to help the screening and assessment of the elderly patient with frailty in primary health care and at the bedside. EFS comprises 11 questions over nine distinct domains such as health status, cognitive, functional dependence, medication utilization, social encouragement, continence, nutrition. performance. functional and mood. Interpretation of EFS scores is from No frailty if the score is equal or under 5, Apparently vulnerable if the score is equal to 6 and 11, or between them and Severe frailty if the score is equal to 12 and 17, or between them.<sup>2,9</sup> EFS has good reliability, good construct validity and acceptable internal consistency. One research also found that EFS has sensitivity of 50% and specificity of 84% in predicting frailty.<sup>10</sup> A systematic review by Faller et al stated that EFS is one of the frailty detecting instrument with the highest number of clinimetric properties evaluated.<sup>11</sup>

Geriatric Depression Scale (GDS) had 15 questions, 10 implied the existence of depression when responded positively, while the remain of the questions, numbers 1, 5, 7, 11, 13. If responded negatively will indicate depression. Scores of 0 until 4 indicate normal; 5 until 8 show mild depression; 9 until 11 show moderate depression; and 12 until 15 show severe depression. It takes about 5 to 7 minutes to finished.<sup>12</sup> Α meta-analysis by Krishnamoorthy et al showed that GDS had sensitivity and specificity of 86% and 79%, with high diagnostic accuracy (Area Under Curve: 0.9).<sup>13</sup>

The sampling technique used in this research is purposive sampling. Purposive sampling is a form of non-probability sampling in which researchers rely on their judgment when choosing members of the population to participate in their research. The subject must meet the inclusion criteria to be included in this research. The inclusion criteria for subjects were: sixty years old or older, able to communicate and understand instruction, and willing to involve in this research. The exclusion criteria were uncorrected hearing problem difficulties and speech resulting in communication problems. Data were managed using SPSS 25 program. Since data were normally distributed, the pearson test was used to analyze the correlation between frailty and depression.

Before conducting the research, this research has passed the ethical clearance process by the Ethical Commission of the Faculty of the Medicine Muslim University of Indonesia and Ibnu Sina Hospital with register number UMI012203179.

## Result

were approximately There 64 population subjects in three nursing homes, but only 27 participants that meet the inclusion criteria were included in this study. The subject's features are listed in table 1. The mean  $\pm$  SD age was 73.15  $\pm$  8, the youngest is 61 years old and the oldest is 98 years old. There was 19 female (70.3%) and 8 male (29.6%) participants. The mean ± SD weight measured was 47.67±9.7. The lowest and the highest weight measured was 28 and 65 kg. The mean  $\pm$  SD height measured was

150.96±7.74. The lowest and the highest height measured was 139.45 and 171.3 cm. The mean ± SD Body Mass Index was  $20.95 \pm 4.19$ . The lowest and the highest body mass index were 13.3 and 29.2 kg/m<sup>2</sup>. The mean ± SD Edmonton Frail Scale was  $5.89 \pm 3.15$ , the lowest accumulative point was 2 and the highest accumulative point was 12. The mean ± SD Geriatric Depression Scale result was  $3.74 \pm 3.14$ , the lowest accumulative point is 0 and the highest accumulative point is 11.

As shown in Table 2, In the crosstabulation analysis we found there were 15 subjects (55.6%) that did not have frailty, consisting of 11 subjects (73.3%) who did not have depression and 4 subjects (26.7%) classified as mild depression. There were 11 (40.7%) subjects classified as apparently vulnerable, consisting of 5 subjects (45.5%) who did not have depression, 4 subjects (36.4%) have mild depression, and 2 subjects (18.2%) have moderate depression. Only one subjects (3.7%) have severe frailty and moderate depression.

We also found there were 16 subjects (59.3%) that did not have depression, 8 subjects (29.6%) had mild depression, and 3 subjects (11.1%) had moderate depression. Pearson's correlation test showed that frailty and depression have significant and strong positive relation (r =0.6, p = 0.001), which means the elderly with high frailty scores associated with high depression scores.

	n	Min	Max	Mean	SD
Age	27	61	98	73.15	8
Gender					
• Male	8	-	-	-	-
• Female	19	-	-	-	-
Weight	27	28	65	47.67	9.7
Height	27	139.45	171.3	150.96	7.74
Body Mass Index	27	13.3	29.2	20.95	4.19
Edmonton Frail Scale	27	2	12	5.89	3.15
Geriatric Depression	27	0	11	3.74	3.14
Scale					

Table 1. Subject Characteristics
----------------------------------

		Depression						
Variables		Normal	Mild	Moderate	Severe	Row		
			Depression	Depression	Depression	Total		
	No Frailty	11	4	0	0	15		
	Row	73.3%	26.7%	0%	0%	55.6%		
	Percent							
	Apparently	5	4	2	0	11		
	Vulnerable							
	Row	45.5%	36.4%	18.2%	0%	40.7%		
	Percent							
Frailty -	Severe	0	0	1	0	1		
	Frailty							
	Row	0%	0%	100%	0%	3.7%		
	Percent							
	Column	16	8	3	0	27		
	Totals							
	Column	59.3%	29.6%	11.1%	0%	100%		
	Percent							

#### Discussion

In this study, we found that frailty have strong and positive association with depression (r = 0.6, p = 0.001). This result support by other studies, Ribeiro et al reported that frail elderly had a greater risk of depression than pre-frail elderly with odds ratio = 3.92 and 95% confidence interval 1.48-10.4, meaning that chances of having depression in frail elderly were 3.92 times higher than pre-frail elderly, and because the odds ratio is higher than 1.0, frailty may be a possible factor for depression in the elderly and they are 95% confident that the odds ratio between depression and frailty in the population of Portuguese centenarian is between 1.48 and 10.4.<sup>14</sup> Soysal, et al in their meta-analysis study found that elderly with frailty had a greater odds of having depression with odds ratio = 4.42 and 95% confidence interval 2.66-7.35, meaning that chances of having depression in elderly with frailty were 4.42 times higher than elderly without frailty, and because the odds ratio is higher than 1.0, frailty may be a likelihood for depression in elderly and they are 95% confident that the odds ratio between depression and frailty is between 2.66 and 7.35. Elderly with depression was a high chance of having frailty with an odds ratio=4.07 and 95% confidence interval of 1.93-8.55, meaning that the probability of having frailty in elderly with depression was 4.07 times higher than elderly without depression, and because the odds ratio is higher than 1.0, depression may be a risk

factor for frailty in the elderly and they are 95% confident that the odds ratio between frailty and depression is between 1.93 and  $8.55.^{8}$ 

Depression and frailty are comorbid geriatric syndromes in a subclass of the elderly, according to a systematic review of 28 researches, and frailty is also a likelihood for the onset and perseverance of depression.<sup>3</sup> Frailty, its components, and functional impairment are possible factors depression. according to another for analysis that included both 23 cohort and 16 cross-sectional researches.<sup>15</sup> In certain studies, depressed symptoms have been linked to incident of frailty. A three-year cohort research in the United States of America (USA) found a link between depressive symptoms and frailty occurrence. Cohort research with 40.659 older women participating in 40 clinical facilities over three years found positive correlation between both of them. Another study proved that the occurrence of frailty was precisely proportional to the degree of depression. As stated in a prospective cohort research held in the USA, women who have a positive attitude toward life had half the risk of developing frailty as women who have a negative attitude toward life. Positive affect was also linked to a lower chance of developing frailty in African American women, according to research.<sup>16</sup>

Researcher's definitions and methodological techniques may have influenced the results we discovered in the literature. When frailty was defined in a

included cognitive, wider that sense nutritional sensory, physical, and characteristics, result from an American prospective cohort demonstrated that depression escalated the likelihood of frailty. Depressive symptoms have also been studied as possible factors for illnesses associated to or thought to be equivalent to frailty, including functional diminished. For example, a great degree of depressive symptoms was identified as a possible factor for moderate and severe functional deterioration in an American cohort research.16

Frailty is a multidimensional geriatric syndrome that can be altered by pain, mobility issue. instability. vulnerability, poor endurance, and more. All of these risk factors can cause functional dependence or disability, which initiate depression. Weight loss, can malnutrition. falls risk, and increased sedentary lifestyle in frailty also can trigger the persistence of mood symptoms typical depression, such as anhedonia, dismal, and worthlessness. However, depression can also prognosticate signs of frailty due to decreased social connection, walking speed activity.8,17 physical Several and pathophysiologic pathways connect late-life depression and frailty are described by mechanisms. overlapping such as cerebrovascular disease. chronic dysregulation inflammation. of the hypothalamic-pituitary-adrenal axis (HPA), and mitochondrial disruption.<sup>17,18</sup>

First overlapping mechanism is cerebrovascular disease. Katz theorized that cerebrovascular disease can cause late life depression and frailty manifestation in the elderly, such as weakness, slowness and gait disturbances. The cerebrovascular disease causes prefrontal white matter hyperintensity in the elderly patients with depression has long been known as a crucial factor to pre-frailty.8 The vascular depression hypothesis suggests that subclinical cerebrovascular ischemia alters frontostriatal brain pathways, resulting in impaired mood regulation and cognitive impairment in the senescence process.<sup>19</sup>

Second overlapping mechanism is chronic inflammation. Recent study upholds a positive correlation among frailty

and inflammatory cytokines for example interleukin 6 (IL 6), which is also discovered to be escalated in adults with depression.<sup>19,20</sup> Chronic inflammation may also have a role in the development of depression and frailty in older people. Frailty has been linked to elevated concentrations inflammatory of the cytokine, including interleukin 6 (IL-6), tumor necrosis factor, and C-reactive protein in several studies. These inflammatory markers are increased in frail elderly, indicating chronic, low-level activation of inflammatory and systems. immunological Inflammatory cytokines are correlated with reduced muscle strength and muscle mass and contrarily affect central dopaminergic function, which induces the signs of frailty such as fatigue, depressed mood, and decelerated cognition and movement.<sup>21</sup> Inflammatory processes are hypothesized to produce alterations in the brain's neural circuits, which activate development of geriatric depression. IL-6 levels have persistently been linked to major depressive symptoms and depression disorders in the elderly among the proinflammatory cytokines.19,21

Third overlapping mechanism is regulated poorly hypothalamicthat pituitary-adrenal well axis. as as abnormalities in other mediators, including insulin-like growth factor and testosterone. have been studied in frail individuals with depression and may explain the correlations observed here. Frailty is linked to inadequate concentrations of the adrenal androgen dehydroepiandrosterone sulfate and insulin-like growth factor 1. Inadequate insulin-like growth factor 1 levels might be linked to widespread late-life depression, particularly in women.

Furthermore, testosterone depletion with age is assumed to be linked to a loss of muscle mass in males, which is a significant factor in frailty syndrome. Intriguingly, depleted testosterone concentrations have been found in older males with dysthymic disease. Cortisol dysregulation has been discovered in bereaved elderly with depression, and a related discovery of cortisol dysregulation has been discovered in the elderly who fracture their hip and afterward develop into frail and depressed. These discoveries propose that poorly regulated neuroendocrine system could be a typical underlying process of frailty and late-life depression, while more research is needed to determine if the hormonal anomalies reported in these diseases are the same or different.<sup>19,22,23</sup>

The last overlapping mechanism is mitochondrial disruption. Mitochondrial dysfunction is also found in many neurodegenerative diseases and depression. Muscle biopsies from depressed patients show reduced ATP creation and compromised mitochondrial respiration in peripheral blood mononuclear cells from adult depressed patients, most strongly associated with symptoms of fatigue. The cycle between deleterious decreased activity, energy, and mobility similar to the clinical manifestations of depression and frailty syndromes.18

Furthermore. the strategies for avoiding depression or frailty may help to eliminate the other. For instance, successful treatment of depression can improve behavior and social activation, resulting in escalated amount of physical and social activity, muscle strength and mass, and overall energy quantities in the elderly, which means lowering frailty. Increased physical exercise is also an efficacious therapeutic for frailty in elderly, and it may shield and manage depressive symptoms in older adults by underlying neurobiological changes as well as social and physical involvement. Other approaches, including strengthening muscle strength and balance and taking vitamin D supplements, could help prevent or treat frailty. Depressive symptoms can lead to lack of vitamin D through reduced sun exposure, reduced food intake, and more smoking.<sup>8,18</sup>

Caring for people with frailty and depression is a challenge in clinical setting. Proactive health encouragement for frail elderly in nursing home can improve quality of life and decrease depressive symptoms in frail elderly without increasing overall health care costs.<sup>3</sup>

### Conclusion

In conclusion, our findings

contribute to a better knowledge of the multifactorial association between frailty and depression in later life. Our findings imply that there was a significant positive relation between depression and frailty among elderly in nursing home. Interdisciplinary research is also needed to better understand the connections between frailty and depression and to promote health and well-being in later life.

## Acknowledgment

The authors would like to thank all of the person who contribute to this study, including all of the subjects and nursing home administrators who allow us to perform this research in their facility.

#### References

1. Mayerl H, Stolz E, Freidl W. Frailty and depression: Reciprocal influences or common causes? Social Science & Medicine 2020; 263: 113273.

2. Perna S, Francis MD, Bologna C, et al. Performance of Edmonton Frail Scale on frailty assessment: its association with multi-dimensional geriatric conditions assessed with specific screening tools. BMC Geriatrics 2017; 17: 2.

3. Buigues C, Padilla-Sánchez C, Garrido JF, et al. The relationship between depression and frailty syndrome: a systematic review. Aging & Mental Health 2015; 19: 762–772.

4. Zhang C, Zhang H, Zhao M, et al. Psychometric properties and modification of the 15item geriatric depression scale among Chinese oldest-old and centenarians: a mixed-methods study. BMC Geriatrics 2022; 22: 144.

5. Acosta Quiroz CO, García-Flores R, Echeverría-Castro SB. The Geriatric Depression Scale (GDS-15): Validation in Mexico and Disorder in the State of Knowledge. The International Journal of Aging and Human Development 2021; 93: 854–863.

6. Brown PJ, Roose SP, O'Boyle KR, et al. Frailty and Its Correlates in Adults with Late Life Depression. The American Journal of Geriatric Psychiatry 2020; 28: 145–154.

7. Potter GG, McQuoid DR, Whitson HE, et al. Physical frailty in late-life depression is associated with deficits in speed-dependent executive functions. International Journal of Geriatric Psychiatry 2016; 31: 466–474.

8. Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing Research Reviews 2017; 36: 78–87.

9. He Y, Li LW, Hao Y, et al. Assessment of predictive validity and feasibility of Edmonton Frail Scale in identifying postoperative complications among elderly patients: a prospective observational study. Scientific Reports 2020; 10: 14682.

10. Navarro-Flores E, de Bengoa Vallejo RB,

Losa-Iglesias ME, et al. The reliability, validity, and sensitivity of the Edmonton Frail Scale (EFS) in older adults with foot disorders. Aging 2020; 12: 24623–24632.

11. Faller JW, Pereira D do N, de Souza S, et al. Instruments for the detection of frailty syndrome in older adults: A systematic review. PLOS ONE 2019; 14: e0216166.

12. Novitasari D, Awaludin S. Geriatric Depression Scale Short Form (GDS-SF) to assess depression in elderly with hypertension. Jurnal Aisyah: Jurnal Ilmu Kesehatan 2020; 5: 101–106.

13. Krishnamoorthy Y, Rajaa S, Rehman T. Diagnostic accuracy of various forms of geriatric depression scale for screening of depression among older adults: Systematic review and meta-analysis. Archives ofGerontology and Geriatrics 2020; 87:104002.

14. Ribeiro O, Duarte N, Teixeira L, et al. Frailty and depression in centenarians. International Psychogeriatrics 2018; 30: 115–124.

15. Mezuk B, Edwards L, Lohman M, et al.

Depression and frailty in later life: a synthetic review. International Journal of Geriatric Psychiatry 2012; 27: 879–892.

16. da Mata FAF, Miranda Forte Gomes M, Lício Ferreira Santos J, et al. Depression and frailty in older adults: A population-based cohort study. PLOS ONE 2021; 16: e0247766.

17. Hajek A, Brettschneider C, Posselt T, et al.

Predictors of frailty in old age–results of a longitudinal study. J Nutr Health Aging 2016; 20: 952–957.

18. Brown PJ, Roose SP, Fieo R, et al. Frailty and Depression in Older Adults: A High-Risk Clinical Population. The American Journal of Geriatric Psychiatry 2014; 22: 1083–1095.

19. Vaughan L, Goveas J, Corbin A. Depression and frailty in later life: a systematic review. Clinical Interventions in Aging 2015; 1947.

20. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Research Reviews 2016; 31: 1–8.

21. Fernández-Garrido J, Ruiz-Ros V, Buigues C, et al. Clinical features of prefrail older individuals and emerging peripheral biomarkers: A systematic review. Archives of Gerontology and Geriatrics 2014; 59: 7–17.

22. Johar H, Emeny RT, Bidlingmaier M, et al. Blunted Diurnal Cortisol Pattern Is Associated With Frailty: A Cross-Sectional Study of 745 Participants Aged 65 to 90 Years. The Journal of Clinical Endocrinology & Metabolism 2014; 99: E464– E468.

23. van Varsseveld NC, van Bunderen CC, Sohl E, et al. Serum insulin-like growth factor 1 and late-life depression: A population-based study. Psychoneuroendocrinology 2015; 54: 31–40.