



Please cite the Published Version

Didikoglu, Altug , Guler, Esin Simge, Turk, Halil Kaan, Can, Kubilay, Erim, Aleyna Nur, Payton, Antony, Murgatroyd, Chris , Pakpahan, Eduwin, Minshull, James, Robinson, Andrew C and Maharani, Asri (2024) Depression in older adults and its associations with sleep and synaptic density. *Journal of Affective Disorders*, 366. pp. 379-385. ISSN 0165-0327

DOI: <https://doi.org/10.1016/j.jad.2024.08.186>

Publisher: Elsevier

Version: Accepted Version

Downloaded from: <https://e-space.mmu.ac.uk/635526/>

Usage rights:  [Creative Commons: Attribution 4.0](https://creativecommons.org/licenses/by/4.0/)

Additional Information: This is an accepted manuscript of an article which appeared in final form in *Journal of Affective Disorders*

Enquiries:

If you have questions about this document, contact openresearch@mmu.ac.uk. Please include the URL of the record in e-space. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from <https://www.mmu.ac.uk/library/using-the-library/policies-and-guidelines>)

Depression in older adults and its associations with sleep and synaptic density

Altug Didikoglu , Esin Simge Guler , Halil Kaan Turk , Kubilay Can , Aleyna Nur Erim , Antony Payton , Chris Murgatroyd , Eduwin Pakpahan , James Minshull , Andrew C Robinson , Asri Maharani

Abstract

Background: Depression among older adults is a global concern, contributing to disability and overall illness burden. Understanding its trajectory, associated risk factors, and implications for mortality is essential for effective intervention. Moreover, the relationship between depression, sleep disturbances, and synaptic density in the ageing brain remains complex and poorly understood.

Methods: Using data from the University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age cohort, comprising 6375 participants, we conducted comprehensive assessments of depression trajectories using generalized linear mixed models and mortality risks using Cox mixed-effects models. Generalized structural equation modelling was performed to explore longitudinal associations between sleep duration and depression. Lastly, associations between post-mortem synaptic density and depression were investigated.

Results: Our findings revealed that depression rates declined until age 80 before increasing again. Depression was associated with a 10 % increased risk of mortality in older adults. Reduced sleep was correlated with depression, and depression measured early in the study predicted future reduced sleep. Post-mortem analysis showed a global reduction in synaptic density associated with depression, particularly pronounced in the frontal lobe.

Limitations: Limitations include recall bias, limiting generalizability due to dominantly including White British participants and difficulty in establishing causation between synaptic density and depression.

Conclusion: Our study underscores the significance of addressing depression in older adults, not only for mental health but also for mortality risk and neurobiological health. Early detection and intervention strategies are crucial for improving outcomes in elderly populations, potentially mitigating adverse effects on sleep, synaptic density, cognitive health, and longevity.

Keywords: Depression; Longitudinal study; Mortality; Older adults; Sleep; Synaptic density.

1. Introduction

Depression is a significant global challenge, prominently ranking among the leading causes of disability and significantly contributing to the overall burden of illness worldwide (Ferrari et al., 2013; Liu et al., 2020; Vos T. et al., 2020). Previous large-scale global meta-studies have revealed that the prevalence of depression in older populations ranges from 7.7% to 81.1%, based on data collected from various countries (Zenebe et al., 2021). With the ageing population projected to increase, depression in older people poses considerable risks to their well-being and longevity (Rodda J. et al., 2011). Several factors contribute to late-life depression, including marital status, social isolation, financial problems, cognitive impairment, retirement, loss of loved ones, or declining health (Zenebe et al., 2021). Studies have shown that depression in older adults is associated with up to a 50% increased risk of mortality (Walker et al., 2015). Understanding the developmental trajectories and the social and biological factors that influence this progression is crucial for further research and intervention.

Synaptic density is an important factor in healthy ageing, with a loss of density observed in cognitive decline and neurodegeneration (Holmes et al., 2023). There is evidence from post-mortem (Duman et al., 2016; Rajkowska et al., 2005), animal model (Csabai et al., 2018) and human imaging studies (Holmes et al., 2019) suggesting that depression also reduces synaptic density. In old age, synaptic density steadily decreases (Huttenlocher, 1979), while sleep disturbances brought on by ageing (Cirelli, 2012) also have a detrimental effect on synaptic density (Raven et al., 2018). Sleep plays a critical role in both synaptic downscaling and synaptic plasticity (Raven et al., 2018). Older people commonly experience various types of sleep problems, including difficulty falling asleep, frequent awakenings during the night, early morning awakenings, changes in sleep architecture, and overall poor sleep quality (Leblanc et al., 2015). Considering sleep and circadian rhythm disruptions are one of the factors causing psychiatric disorders, addressing sleep issues in the older people becomes crucial not only for improving sleep quality but also for potentially mitigating the adverse effects on synaptic density and overall cognitive and mental health (Costa et al., 2013). To complicate the understanding further, both depression and sleep are associated with genetic markers (e.g., Brain-Derived Neurotrophic Factor (BDNF)) that are linked to synaptic density (Alsina et al., 2001; Giese et al., 2013; Shimizu et al., 2003). It is not fully understood how this complex relationship manifests in older people, nor the sequence in which these factors influence each other.

In this study, we aim to explore several key aspects related to depression in older population. First, we seek to identify depression trajectories among older people and understand their implications for mortality rates. Second, we aim to investigate the correlation and temporal structure between sleep duration and depression among older adults. Another aspect of our investigation involves assessing

the effects of both depression and sleep duration on synaptic density in the ageing brain. Lastly, we aim to explore the role of BDNF in the relationship between depression, sleep, and synaptic density in elderly individuals. Through this comprehensive examination, we aim to gain a deeper understanding of the complex interplay between depression, sleep, and synaptic markers in older adults.

2. Methods

2.1. Population

From 1982, 6375 participants were recruited in Greater Manchester and Newcastle upon Tyne by the University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age (UMLCHA) cohort. The aim of the cohort was to recruit healthy participants and collect a comprehensive set of data on health, physiology, psychology, behavior, and lifestyle to investigate neurodegeneration and cognition (Rabbitt et al., 2004). Upon commencement of the study, written informed approval was acquired from all participants. The University of Manchester Research Ethics Committee approved the gathering of the self-report and questionnaire data from the participants. Recruitment lasted for approximately 10 years, with every participant over the age of 40, recruited at different dates and different ages. Therefore, every participant has different assessment periods. In this study, we utilize the depression data from this extensive longitudinal database (n = 5490). All self-report survey assessments were administered either face-to-face by trained clinicians or via postal mail, approximately two to three years apart, respectively (see timeline in **Figure S1**). Over 30 years until 2017, participants completed eleven depression assessments (The earliest first depression data were collected in 1982, and the latest first depression data were collected in 2005. For details on the years of data collection and the sequence of assessments, please refer to **Table S1**), including two Beck Depression Inventory (BDI) (Beck et al., 1988) assessments and the Geriatric Depression Scale (GDS) with 30 items for four assessments, and a 15-item short version of the GDS for five assessments (Alden et al., 1989). In addition, five sleep assessments (Didikoglu et al., 2019) using the study-specific survey of Personal Details Questionnaire (PDQ), one negative life events assessment (Accurso et al., 2015), and one life satisfaction assessment (Diener et al., 1985) were performed. Death registration data for 5075 participants were accessed from the National Health Service (NHS) digital (<https://digital.nhs.uk>).

2.2. Survey and measures

Sex (female/male), socioeconomic status (low/high; Standard Occupational Classification professional and intermediate were coded as high), and education level (low/high; International Standard Classification of Education tertiary stages were coded as higher education) were noted at the beginning. For the assessment of sleep, the PDQ was performed, which contains information about

sleep duration (hours): “On average, how many hours of sleep do you get every night?” (Didikoglu et al., 2019). To standardize depression scores, all different survey measures were categorized as either ‘no depression’ or ‘mild to severe depression’. Scores between 10 and 63 are classified as indicating depression in the BDI (Beck et al., 1988). The GDS long classifies depression as a score above 11, while the GDS short classifies depression as a score above 5 (Alden et al., 1989). These three self-report assessments of depression have demonstrated successful validity in older adults, effectively distinguishing between normal and mild-to-severe depression, and the specified cutoff values are significantly comparable across these surveys (Beck AT et al., 1988; Hyer & Blount, 1984; Leshner & Berryhill, 1994). Age of participants (years) was recorded in every sleep and depression assessments.

2.3. Post-mortem measures

Participants were invited to donate their brains and 312 participants underwent brain donation after their death. The donated brains were collected at The Manchester Brain Bank (<https://sites.manchester.ac.uk/manchester-brain-bank/>). Approval for this study was obtained from the Manchester Brain Bank Management Committee (REC reference 19/NE/0242). Data was obtained from the brain bank database for the following experiment used frozen hippocampus, occipital, parietal, and frontal lobe tissue chunks. Light transmittance measurements of Synaptic Vesicle Glycoprotein 2A (SV2A) immunoreactivity were obtained from the images of scanned slide-mounted sections. The following equation was used for the calculation of adjusted optical density values from the mean light transmittance values: adjusted optical density = $\log(\text{light transmittance in white matter} / \text{light transmittance in cortex})$ (Glantz et al., 2007). From the frontal lobe tissue chunk, total BDNF relative gene expression was measured using a qPCR system (Aarson et al., 2019).

2.4. Statistical analysis

Data analyses were performed using R version 4.3.1, GraphPad Prism version 10.1.1. R, and Mplus version 8.10. R packages “lme4 1.1-35.1”, “lmerTest 3.1-3”, “survival 3.5-5”, and “coxme 2.2-18.1” were utilized for longitudinal analyses (Muthén & Muthén, 2017). The prevalence of depression was reported as the percentage of participants falling into the mild-to-severe depression category. Longitudinal depression trajectory was investigated using Generalized Linear Mixed Models (GLMM) with bivariate logistic depression outcomes and quadratic aging trends. Random slopes and intercepts were included in the models with sex, education level and social class covariates. Associations between depression and number of negative life events and satisfaction with life score were examined using simple logistic models. Survival analysis then performed using the Cox Mixed-Effect Model fitted by fit by maximum likelihood. GLMM analysis was performed to investigate longitudinal associations

between depression and sleep duration. Next, using a subgroup of the sample, we used a cross-lagged panel model to investigate the temporal structure between sleep duration and depression (performed using Mplus 8.10). This generalized structural equation modelling (GSEM) subgroup included those surveyed twice within a maximum of 5 years and who had simultaneous depression and sleep assessments. In a second model, age, age-squared, sex, social class, and education control variables were added to analyses. In the last part, linear mixed models were used to investigate whether sleep duration or depression predict synaptic densities of four target brain region and gene expression level. These models included age at death and interaction term with duration since the survey performed.

3. Results

The cohort comprised of 70.4% females at the baseline. The prevalence of higher education was 21.2%, and 38.8% of the sample were classified as having high social status (**Table 1**). The average age at the first depression assessment was 65.3 years (SD = 7.28). The cohort were healthy older adults on recruitment and the majority of the participants were already retired and able to select their own sleep schedules without occupational and educational constraints (Didikoglu et al., 2022). Depression assessments were completed by 5490 volunteers with 3758 people participating in at least two sessions. 5217 participants had data of at least one depression and all covariates. A total of 17,049 depression data points were collected, with 16,867 data points containing age information, and 16,541 data points including all covariates (please see **Table S2** for selection of cases).

3.1. Change of depression with age

At first assessment, depression with any kind of severity (mild, moderate, or severe) was found in 29.4% of the cohort and 6.3% showed severe depression (**Table 1**). The Depression rate was lowest (9.3%) in the eighth depression assessment (after approximately 20 years). In the last depression assessment after approximately 30 years from the beginning, the depression rate was 17.6%, with a large volunteer drop-out due to mortality (n = 204). To answer how the depression rate changes with ageing in older people, a GLMM was performed (**Table S3**) and results showed that there is a significant U-shape relationship between depression and age ($p < 0.0001$) after adjusting for the effects of sex, education and social class. From age 40 to 80 years, depression decreased by 20% in the model. By the age of 80 years, the trend inversed and started to increase. **Figure 1A** illustrates the change in incidence density of depression over the follow-up years within our study period. **Figure 1B** displays the associations between the probability of depression and age within the cohort.

We then investigated the cross-sectional associations between age, life satisfaction, and negative life events. Low life satisfaction was associated with a 12% higher risk of depression ($p < 0.0001$; **Figure**

S2A). Similarly, a high number of stressful life events, following a comparable aging pattern, was associated with an 11% increased risk of depression ($p = 0.0003$; **Figure S2B**).

Figure 2: A) Change in the probability of mild to severe depression over the follow-up years in the study ($n = 16,867$). **B)** Associations between the probability of mild to severe depression and age in the full cohort ($n = 16,867$). **C)** Associations between the probability of mild to severe depression and age in participants who were alive at the end of the study ($n = 4,334$). In both graphs, the blue lines represent the quadratic fit used to estimate the probability of depression by age, with the grey areas indicating the 95% confidence intervals.

Table 1: Study description

Depression assessments	Sample size (n)	Age (years) Mean(SD)	Depression prevalence (%)
1	5311	65.3(7.3)	29.4
2	3103	69.8(6.5)	20.8
3	2023	72.8(6.2)	20.2
4	1096	75.9(5.9)	19.8
5	2131	69.3(7.6)	27.7
6	378	77.5(5.4)	17.7
7	863	78.9(5.4)	10.5
8	765	80.8(5.1)	9.3
9	662	82.5(5.0)	11.9
10	513	84.6(5.0)	13.6
11	204	86.6(4.4)	17.6
Sleep assessments	Sample size (n)	Age (years) Mean(SD)	Sleep duration Mean(SD)
1	5557	65.19(7.5)	7.0(1.2)
2	2925	67.88(6.8)	6.9(1.2)
3	571	76.24(5.7)	6.9(1.2)
4	693	80.56(5.3)	6.6(1.2)
5	551	82.87(5.2)	6.7(1.3)

3.2. Mortality of depression

Since depression trajectories can provide insights into mortality, and to assess the significance of depression in older age as well as to evaluate potential dropout effects in previous trajectory analyses, we conducted survival analyses. Date of death provided by NHS Digital death registration data was available for 4510 (84.6%) participants, while 820 participants were still alive amongst those who had depression data. The average age at death was 83.8 years (SD = 8.55). The Cox mixed-effects model showed that there is a 10% increased risk of mortality (OR = 1.096, $p < 0.0001$) if depression was reported during the study period (**Table S4**). Since drop-out due to depression mortality would influence the trajectory, we ran the same GLMM using the subgroup of those who were alive in the mortality analysis. The U-shape trend was still observed with the turning point of 80 years of age (**Figure 1C, Table S3**).

3.3. Longitudinal associations between sleep and depression

Previous study using sleep data from this cohort reported decreasing sleep duration with ageing (Didikoglu et al., 2020). Here we compared sleep duration with depression. Sleep duration is reduced in old age and shorter sleep was associated with higher depression (OR = 0.71, $p < 0.0001$). We then looked at whether sleep problems precede depression or depression results in inappropriate sleep (**Figure 2**). GSEM cross-lagged analysis was performed for those who present in two assessments with time differences below 5 years between surveys. The models comprised 2500 individuals. The first model investigated depression and sleep duration (**Table 2**). Recent reduced sleep was associated with recent depression. Recent depression was weakly and directly associated with previous long sleep before 5 years. Previous depression was directly associated with recent reduced sleep. The addition of age, sex, social class, and education level in the model as controls yielded similar results except for the direct effect between previous sleep and recent depression; the direct effect between previous depression and recent short sleep was robust.

Figure 2: Basic concept of the association between depression and sleep duration. Sleep1 and Sleep2 represent any sleep duration assessments taken a maximum of 5 years apart. Depression1 and Depression2 represent any depression assessments taken a maximum of 5 years apart. Depression1 - Sleep1 and Depression2 - Sleep2 are simultaneous depression and sleep assessments.

Table 2: GSEM Depression and sleep duration

Parameter (outcome ON predictor)	Sleep duration			Sleep duration (adjusted for age, sex, education, social status)		
	Std. Estimate	SE	<i>p</i> -value	Std. Estimate	SE	<i>p</i> -value
Depression1 ON Sleep1	-0.242	0.024	<0.0001	-0.220	0.024	<0.0001
Depression2 ON Depression1	0.690	0.023	<0.0001	0.695	0.024	<0.0001
Depression2 ON Sleep2	-0.122	0.032	<0.0001	-0.104	0.034	0.002
Depression2 ON Sleep1	0.078	0.032	0.016	0.064	0.033	0.053
Sleep2 ON Depression1	-0.059	0.018	0.001	-0.050	0.02	0.011
Sleep2 ON Sleep1	0.713	0.009	<0.0001	0.704	0.009	<0.0001
Model fit information	Chi-square=3594.40			Chi-square= 1899.828		
WLSMV estimator	<i>p</i> -value=0.00			<i>p</i> -value=0.00		
	RMSEA=0.026			RMSEA= 0.032		
	CFI=0.998			CFI= 0.987		
	TLI=0.995			TLI= 0.950		
	SRMR=0.078			SRMR= 0.279		

3.4. Post-mortem synaptic density after depression or short sleep

We then investigated associations between depression in older adults, sleep duration and synaptic density. Post-mortem synaptic density measurements were available for 61 participants. The average age at death of those who donated their brains was 87.5 years (SD = 6.20). There were 440 depression data reported from this post-mortem subgroup. Adjusting for age at death and interaction between depression and duration since the survey, depression significantly predicted the synaptic density in the hippocampus ($p = 0.015$), frontal lobe ($p = 0.004$), parietal lobe ($p = 0.003$), and occipital lobe ($p = 0.012$). The frontal lobe showed the steepest decline in synaptic density with old age depression, and this reduction is more apparent if depression was assessed recently (**Figure 3A**). Sleep duration was not significantly associated with synaptic density.

Figure 3: A) Comparison of Frontal Lobe Postmortem Synaptic Density Between Depressed (Red) and Healthy (Blue) Individuals. Data were categorized based on the duration from the depression survey to death (recent or older than 10 years). Groups were compared using one-way ANOVA with Tukey's multiple comparisons test ($p < 0.001$; ns, not significant). Error bars represent 95% confidence intervals. **B)** Associations between BDNF gene expression (log-normalized) and frontal lobe synaptic density. Blue line shows quadratic fit line to estimate synaptic density by gene expression. Grey area represents 95% confidence intervals.

3.5. BDNF gene expression and synaptic density

We then collected BDNF gene expression levels in the frontal lobe and compared with synaptic density of the same region. There was a weak quadratic relationship ($p = 0.027$) between gene transcript and synaptic density levels, where both low and high levels of BDNF expression were associated with lower synaptic density (**Figure 3B**). There was no significant relationship between BDNF transcription level and depression or sleep.

4. Discussion

There is substantial experimental evidence indicating that depression adversely affects health and well-being (Liu et al., 2020). However, the progression of depression in older adults and its contribution to mortality is not well-established. We utilized a large cohort of individuals of advanced age, followed over more than 30 years, with a high incidence of mortality during the follow-up period. Data collected from the study participants included depression inventories and self-reported sleep durations. We integrated this data with post-mortem measurements of synaptic density and gene transcription

analyses. Our findings demonstrated a general trend of lower depression levels until the age of 80, followed by a deterioration in mood. Additionally, depression between the ages of 40 and 100 was associated with an increased risk of mortality. We observed that inadequate sleep duration did not precede the onset of depression, but being depressed was linked to future reduced sleep duration. Finally, we identified a global decrease in synaptic density associated with depression.

We observed a 10 to 20% prevalence of mild to severe depression in older adults, consistent with the prevalence rate in individuals over 65 years old (Rodda J. et al., 2011; Murthy et al., 2001). However, the shape of ageing trajectories was inconsistent in the literature. Some studies showed a linear increase in age effects on composite mental health measures from the 20s to the 90s, while others demonstrated a decline in depressive symptoms until age 70, similar to our findings of a U-shaped curve (Tampubolon & Maharani, 2017; Thomas et al., 2016). Older adults might experience better mental health due to several factors, such as being more adept at coping with stress, increased wisdom with age, enhanced emotional regulation, life satisfaction, and positive information processing (MacLeod et al., 2016; Thomas et al., 2016). Supporting these findings, we showed that the number of negative life events increased after 80 years, and satisfaction with life decreased, both of which correlated with depression in our sample.

Depression has been associated with increased mortality, with more than 50% higher likelihood of death (van den Berg et al., 2021; Walker et al., 2015). It is linked to an approximately 15% increased risk of suicide (Orsolini et al., 2020). Depression is also associated with negative health-related behaviours, including smoking, poor diet, and low physical activity (Jerstad et al., 2010). Furthermore, other studies have shown that depression is related to poor health outcomes such as obesity, type II diabetes, and cardiovascular disease (Luppino et al., 2010; Musselman et al., 1998), all demonstrating the relationship between survival and depression. However, the impact of depression specifically in older people on mortality has not been extensively studied. Our findings indicate a 10% increased risk of mortality associated with late-life depression. Previous studies have consistently revealed similar effects, though our study extends the knowledge to a population aged up to 100 years (Schulz et al., 2000; Tsai et al., 2022; Walker et al., 2015; Wei et al., 2019).

Sleep problems are common in older people (Leblanc et al., 2015). It is unclear whether old-age depression causes sleep decline or if sleep problems lead to mental health issues in older people. Evidence suggests reciprocal effects between the two. Most psychiatric disorders are associated with sleep problems, where circadian and sleep disruptions contribute to low mood (Wulff et al., 2010). Furthermore, the circadian sleep-wake system and mood regulation are intertwined through genetic, neural and hormonal systems (Costa et al., 2013; Lane et al., 2017). Previous studies examining the

temporal structure of these relationships (using structural equation modelling and cross-lagged models of sleep and depression) have shown intricate connections. For example, a study focusing on sleep disruption demonstrated that insomnia is a primary factor in developing depression (Oh et al., 2019). Additionally, children's depression at age 10 was predicted by sleep disruption at age 8, though there were no significant results for depression predicting sleep disturbance (Gregory et al., 2009). Treating sleep disorders early might prevent depression and offer some protection against it (Gregory et al., 2009). Moreover, older women who showed little or no depression but reported sleep disruptions were likely to experience worse depression symptoms five years later (Maglione et al., 2014). In our sample, a cross-lagged model showed that depression can directly affect sleep duration in the future. This is critical because, similar to depression, sleep problems can also independently escalate health problems and mortality.

With regards to synaptic density, we demonstrated that synaptic density is reduced in older individuals with depression compared to non-depressed older adults. However, a recent *in vivo* PET imaging study proposed that synaptic density is preserved in late-life depression, but grey matter volume decreases (Vande Castele et al., 2024). Other studies utilizing post-mortem measurements have provided evidence that major depressive disorder during a person's lifetime leads to a reduction in the number of synapses, as well as alterations in synaptic function-related genes, within the prefrontal cortex (Kang et al., 2012). We also observed the strongest effect of synaptic density decrease in the frontal lobe. Some proposed biological mechanisms for this reduction include low levels of BDNF. Despite inconsistencies in the literature, reduced BDNF levels are correlated with cognitive impairment in individuals with late-life depression (Diniz et al., 2010, 2014). This reduction contributes to disruptions in synaptic function and synaptogenesis due to the loss of neurotrophic support (Diniz et al., 2010, 2014). We could not find any association between BDNF and depression, but we observed a weak non-linear correlation between synaptic density and BDNF expression levels.

A previous study using this cohort demonstrated that old age depression was associated with Alzheimer's pathology and cognitive status at death within cognitively healthy individuals (Robinson et al., 2021). However, it remains unclear whether depressive symptoms among older people act as a risk factor, a consequence, or an early symptom of dementia (Kaup et al., 2016; Savva et al., 2009; A. J. Thomas et al., 2002; Wiels et al., 2020). Synaptic density is already expected to decrease in cognitively healthy individuals over the age of 65 (Masliah et al., 2006). Primate models have indicated that age-related cognitive decline is linked to a decrease in synaptic density as well as a reduction in overall dendritic spine size (Dumitriu et al., 2010). Additionally, lower synaptic density has been consistently shown to correlate with cognitive decline in neurodegenerative diseases in several neuroimaging

studies (Mecca et al., 2022; Zhang et al., 2023). A study also showed that lower synaptic density is linked to the severity of depression and suggested that a decrease in synaptic density may lead to cognitive decline by causing dysfunctions in certain neural circuits (Holmes et al., 2019). Overall, understanding the complex relationships between synaptic function, old-age depression, and cognitive decline may pave the way for prevention strategies targeted at vulnerable elderly populations.

The novelty of the present study includes a large sample size, an old age cohort, over 30 years of follow-up to generate ageing trajectories, a high number of mortality events for survival analysis, and the availability of post-mortem tissues with life history records connected to genetic and clinical observations. However, there are some possible limitations of the study. These include recall bias in older people and recording errors due to subjective record data, the use of data from decades ago that may not represent current social conditions, limited ethnic and cultural variation (predominantly White British participants), a sex bias with more female participants, and missing data due to the nature (selective dropout and mortality) of an old age longitudinal study design. Moreover, depression is influenced by a multitude of social and biological factors throughout later life, and an accurate assessment of its trajectory and mortality should take all these factors into account. However, our study lacks a comprehensive set of covariates to fully capture this complexity. Although these depression surveys are highly valid among older adults, including those with cognitive impairments, the use of three different assessments could introduce inconsistencies in categorizing mild to severe depression. Additionally, it is challenging to establish causation in synaptic density results; it is also possible that both synaptic density and cognitive decline contribute towards depression.

In conclusion, our longitudinal study offers significant insights into the progression of depression among older adults and its impact on mortality. By analysing a large cohort over a span of more than 30 years, we identified a pattern of mood stability until the age of 80, followed by a subsequent decline. The data indicate that depression in older adults is linked to an increased risk of mortality. Finally, our findings revealed a global reduction in synaptic density correlated with depression, underscoring the profound neurobiological effects of this condition. These results highlight the importance of early detection and intervention in managing depression to potentially improve sleep, cognitive health, quality of life, and longevity in older people.

References

Aarson T., Bradburn S., Robinson A., Payton A., Pendleton N., & Murgatroyd C. (2019). Dysregulation of BDNF in prefrontal cortex in Alzheimer's disease. *Journal of Alzheimer's Disease*.

- Accurso E. C., Garland A. F., Haine-Schlagel R., Brookman-Frazee L, & Baker-Erziczen M. J. (2015). Life Events Questionnaire. . *Journal of Emotional and Behavioral Disorders*.
- Alden, D., Austin, C., & Sturgeon, R. (1989). A correlation between the Geriatric Depression Scale Long and Short Forms. *Journals of Gerontology*, *44*(4). <https://doi.org/10.1093/geronj/44.4.P124>
- Alsina, B., Vu, T., & Cohen-Cory, S. (2001). Visualizing synapse formation in arborizing optic axons in vivo: Dynamics and modulation by BDNF. *Nature Neuroscience*, *4*(11). <https://doi.org/10.1038/nn735>
- Beck AT, Steer RA, & Carbin MG. (1988). Psychometric proper- ties of the beck depression inventory: twenty-five years of evaluation. *Clin Psychol Rev*.
- Bhandari, A., Lissemore, J. I., Rajji, T. K., Mulsant, B. H., Cash, R. F. H., Noda, Y., Zomorodi, R., Karp, J. F., Lenze, E. J., Reynolds, C. F., Daskalakis, Z. J., & Blumberger, D. M. (2018). Assessment of neuroplasticity in late-life depression with transcranial magnetic stimulation. *Journal of Psychiatric Research*, *105*. <https://doi.org/10.1016/j.jpsychires.2018.08.022>
- Cirelli, C. (2012). Brain plasticity, sleep and aging. *Gerontology*, *58*(5). <https://doi.org/10.1159/000336149>
- Costa, I. C., Carvalho, H. N., & Fernandes, L. (2013). Aging, circadian rhythms and depressive disorders: A review. In *American Journal of Neurodegenerative Diseases* (Vol. 2, Issue 4).
- Csabai, D., Wiborg, O., & Czéh, B. (2018). Reduced synapse and axon numbers in the prefrontal cortex of rats subjected to a chronic stress model for depression. *Frontiers in Cellular Neuroscience*, *12*. <https://doi.org/10.3389/fncel.2018.00024>
- Didikoglu, A., Maharani, A., Payton, A., Pendleton, N., & Canal, M. M. (2019). Longitudinal change of sleep timing: association between chronotype and longevity in older adults. *Chronobiology International*, *36*(9). <https://doi.org/10.1080/07420528.2019.1641111>
- Didikoglu, A., Maharani, A., Tampubolon, G., Canal, M. M., Payton, A., & Pendleton, N. (2020). Longitudinal sleep efficiency in the elderly and its association with health. *Journal of Sleep Research*, *29*(3). <https://doi.org/10.1111/jsr.12898>
- Didikoglu, A., Walker, B., Maharani, A., Pendleton, N., Canal, M. M., Payton, A., Gibson, J., & Brown, T. (2022). Associations between chronotype and employment status in a longitudinal study of an elderly population. *Chronobiology International*, *39*(8). <https://doi.org/10.1080/07420528.2022.2071158>
- Diener, E., Emmons, R. A., Larsen, R. J., & Griffin, S. (1985). The Satisfaction With Life Scale. *Journal of Personality Assessment*, *49*(1). https://doi.org/10.1207/s15327752jpa4901_13
- Diniz, B. S., Reynolds, C. F., Begley, A., Dew, M. A., Anderson, S. J., Lotrich, F., Erickson, K. I., Lopez, O., Aizenstein, H., Sibille, E. L., & Butters, M. A. (2014). Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: A longitudinal study. *Journal of Psychiatric Research*, *49*(1). <https://doi.org/10.1016/j.jpsychires.2013.11.004>
- Diniz, B. S., Teixeira, A. L., Talib, L. L., Mendonça, V. A., Gattaz, W. F., & Forlenza, O. V. (2010). Serum brain-derived neurotrophic factor level is reduced in antidepressant-free patients with late-life depression. *World Journal of Biological Psychiatry*, *11*(3). <https://doi.org/10.3109/15622970903544620>
- Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants. In *Nature Medicine* (Vol. 22, Issue 3). <https://doi.org/10.1038/nm.4050>

- Dumitriu, D., Hao, J., Hara, Y., Kaufmann, J., Janssen, W. G. M., Lou, W., Rapp, P. R., & Morrison, J. H. (2010). Selective changes in thin spine density and morphology in monkey prefrontal cortex correlate with aging-related cognitive impairment. *Journal of Neuroscience*, *30*(22). <https://doi.org/10.1523/JNEUROSCI.6410-09.2010>
- Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., Vos, T., & Whiteford, H. A. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Medicine*, *10*(11). <https://doi.org/10.1371/journal.pmed.1001547>
- Giese, M., Unternaehrer, E., Brand, S., Calabrese, P., Holsboer-Trachsler, E., & Eckert, A. (2013). The Interplay of Stress and Sleep Impacts BDNF Level. *PLoS ONE*, *8*(10). <https://doi.org/10.1371/journal.pone.0076050>
- Glantz, L. A., Gilmore, J. H., Hamer, R. M., Lieberman, J. A., & Jarskog, L. F. (2007). Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. *Neuroscience*, *149*(3). <https://doi.org/10.1016/j.neuroscience.2007.06.036>
- Gregory, A. M., Rijdsdijk, F. V., Lau, J. Y. F., Dahl, R. E., & Eley, T. C. (2009). The direction of longitudinal associations between sleep problems and depression symptoms: A study of twins aged 8 and 10 years. *Sleep*, *32*(2). <https://doi.org/10.1093/sleep/32.2.189>
- Holmes, S. E., Abdallah, C., & Esterlis, I. (2023). Imaging synaptic density in depression. In *Neuropsychopharmacology* (Vol. 48, Issue 1). <https://doi.org/10.1038/s41386-022-01368-4>
- Holmes, S. E., Scheinost, D., Finnema, S. J., Naganawa, M., Davis, M. T., DellaGioia, N., Nabulsi, N., Matuskey, D., Angarita, G. A., Pietrzak, R. H., Duman, R. S., Sanacora, G., Krystal, J. H., Carson, R. E., & Esterlis, I. (2019). Lower synaptic density is associated with depression severity and network alterations. *Nature Communications*, *10*(1). <https://doi.org/10.1038/s41467-019-09562-7>
- Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex - Developmental changes and effects of aging. *Brain Research*, *163*(2). [https://doi.org/10.1016/0006-8993\(79\)90349-4](https://doi.org/10.1016/0006-8993(79)90349-4)
- Hyer, L., & Blount, J. (1984). Concurrent and discriminant validities of the geriatric depression scale with older psychiatric inpatients. *Psychological Reports*, *54*(2). <https://doi.org/10.2466/pr0.1984.54.2.611>
- Jerstad, S. J., Boutelle, K. N., Ness, K. K., & Stice, E. (2010). Prospective Reciprocal Relations Between Physical Activity and Depression in Female Adolescents. *Journal of Consulting and Clinical Psychology*, *78*(2). <https://doi.org/10.1037/a0018793>
- Kang, H. J., Voleti, B., Hajszan, T., Rajkowska, G., Stockmeier, C. A., Licznarski, P., Lepack, A., Majik, M. S., Jeong, L. S., Banasr, M., Son, H., & Duman, R. S. (2012). Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nature Medicine*, *18*(9). <https://doi.org/10.1038/nm.2886>
- Kaup, A. R., Byers, A. L., Falvey, C., Simonsick, E. M., Satterfield, S., Ayonayon, H. N., Smagula, S. F., Rubin, S. M., & Yaffe, K. (2016). Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry*, *73*(5). <https://doi.org/10.1001/jamapsychiatry.2016.0004>
- Lane, J. M., Liang, J., Vlasac, I., Anderson, S. G., Bechtold, D. A., Bowden, J., Emsley, R., Gill, S., Little, M. A., Luik, A. I., Loudon, A., Scheer, F. A. J. L., Purcell, S. M., Kyle, S. D., Lawlor, D. A., Zhu, X., Redline, S., Ray, D. W., Rutter, M. K., & Saxena, R. (2017). Genome-wide association analyses of sleep disturbance

traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. *Nature Genetics*, 49(2). <https://doi.org/10.1038/ng.3749>

- Leblanc, M. F., Desjardins, S., & Desgagné, A. (2015). The relationship between sleep habits, anxiety, and depression in the elderly. *Nature and Science of Sleep*, 7. <https://doi.org/10.2147/NSS.S77045>
- Leshner, E. L., & Berryhill, J. S. (1994). Validation of the geriatric depression scale-short form among inpatients. *Journal of Clinical Psychology*, 50(2). [https://doi.org/10.1002/1097-4679\(199403\)50:2<256::AID-JCLP2270500218>3.0.CO;2-E](https://doi.org/10.1002/1097-4679(199403)50:2<256::AID-JCLP2270500218>3.0.CO;2-E)
- Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., & Lyu, J. (2020). Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. *Journal of Psychiatric Research*, 126. <https://doi.org/10.1016/j.jpsychires.2019.08.002>
- Luppino, F. S., De Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W. J. H., & Zitman, F. G. (2010). Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. In *Archives of General Psychiatry* (Vol. 67, Issue 3). <https://doi.org/10.1001/archgenpsychiatry.2010.2>
- MacLeod, S., Musich, S., Hawkins, K., Alsgaard, K., & Wicker, E. R. (2016). The impact of resilience among older adults. *Geriatric Nursing*, 37(4). <https://doi.org/10.1016/j.gerinurse.2016.02.014>
- Maglione, J. E., Ancoli-Israel, S., Peters, K. W., Paudel, M. L., Yaffe, K., Ensrud, K. E., & Stone, K. L. (2014). Subjective and objective sleep disturbance and longitudinal risk of depression in a cohort of older women. *Sleep*, 37(7). <https://doi.org/10.5665/sleep.3834>
- Masliah, E., Crews, L., & Hansen, L. (2006). Synaptic remodeling during aging and in Alzheimer's disease. *Journal of Alzheimer's Disease*, 9(SUPPL. 3). <https://doi.org/10.3233/jad-2006-9s311>
- Mecca, A. P., O'Dell, R. S., Sharp, E. S., Banks, E. R., Bartlett, H. H., Zhao, W., Lipior, S., Diepenbrock, N. G., Chen, M. K., Naganawa, M., Toyonaga, T., Nabulsi, N. B., Vander Wyk, B. C., Arnsten, A. F. T., Huang, Y., Carson, R. E., & van Dyck, C. H. (2022). Synaptic density and cognitive performance in Alzheimer's disease: A PET imaging study with [11C]UCB-J. *Alzheimer's and Dementia*, 18(12). <https://doi.org/10.1002/alz.12582>
- Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. In *Archives of General Psychiatry* (Vol. 55, Issue 7). <https://doi.org/10.1001/archpsyc.55.7.580>
- Muthén, L. K., & Muthén, B. O. (2012). Statistical analysis with latent variables using Mplus. *Los Angeles, CA: Muthén & Muthén*.
- Oh, C. M., Kim, H. Y., Na, H. K., Cho, K. H., & Chu, M. K. (2019). The effect of anxiety and depression on sleep quality of individuals with high risk for insomnia: A population-based study. *Frontiers in Neurology*, 10(JUL). <https://doi.org/10.3389/fneur.2019.00849>
- Orsolini, L., Latini, R., Pompili, M., Serafini, G., Volpe, U., Vellante, F., Fornaro, M., Valchera, A., Tomasetti, C., Fraticelli, S., Alessandrini, M., La Rovere, R., Trotta, S., Martinotti, G., Di Giannantonio, M., & De Berardis, D. (2020). Understanding the complex of suicide in depression: From research to clinics. In *Psychiatry Investigation* (Vol. 17, Issue 3). <https://doi.org/10.30773/pi.2019.0171>
- Rabbitt, P. M. A., McInnes, L., Diggle, P., Holland, F., Bent, N., Abson, V., Pendleton, N., & Horan, M. (2004). The University of Manchester longitudinal study of cognition in normal healthy old age, 1983 through 2003. In *Aging, Neuropsychology, and Cognition* (Vol. 11, Issues 2–3). <https://doi.org/10.1080/13825580490511116>

- Rajkowska, G., Miguel-Hidalgo, J. J., Dubey, P., Stockmeier, C. A., & Krishnan, K. R. R. (2005). Prominent reduction in pyramidal neurons density in the orbitofrontal cortex of elderly depressed patients. *Biological Psychiatry*, *58*(4). <https://doi.org/10.1016/j.biopsych.2005.04.013>
- Raven, F., Van der Zee, E. A., Meerlo, P., & Havekes, R. (2018). The role of sleep in regulating structural plasticity and synaptic strength: Implications for memory and cognitive function. In *Sleep Medicine Reviews* (Vol. 39). <https://doi.org/10.1016/j.smr.2017.05.002>
- Robinson, A. C., Roncaroli, F., Davidson, Y. S., Minshull, J., Heal, C., Montaldi, D., Payton, A., Horan, M. A., Pendleton, N., & Mann, D. M. A. (2021). Mid to late-life scores of depression in the cognitively healthy are associated with cognitive status and Alzheimer's disease pathology at death. *International Journal of Geriatric Psychiatry*, *36*(5). <https://doi.org/10.1002/gps.5470>
- Rodda J., Walker Z., & Carter J. (2011). Depression in older adults. *Bmj*, *343*.
- Savva, G. M., Zaccai, J., Matthews, F. E., Davidson, J. E., McKeith, I., & Brayne, C. (2009). Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *British Journal of Psychiatry*, *194*(3). <https://doi.org/10.1192/bjp.bp.108.049619>
- Schulz, R., Beach, S. R., Ives, D. G., Martire, L. M., Ariyo, A. A., & Kop, W. J. (2000). Association between depression and mortality in older adults: The Cardiovascular Health study. *Archives of Internal Medicine*, *160*(12). <https://doi.org/10.1001/archinte.160.12.1761>
- Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., Nakazato, M., Watanabe, H., Shinoda, N., Okada, S. I., & Iyo, M. (2003). Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biological Psychiatry*, *54*(1). [https://doi.org/10.1016/S0006-3223\(03\)00181-1](https://doi.org/10.1016/S0006-3223(03)00181-1)
- Tampubolon, G., & Maharani, A. (2017). When Did Old Age Stop Being Depressing? Depression Trajectories of Older Americans and Britons 2002–2012. *American Journal of Geriatric Psychiatry*, *25*(11). <https://doi.org/10.1016/j.jagp.2017.06.006>
- The World Health Report 2001: Mental health: new understanding, new hope.* (2001). World Health Organization.
- Thomas, A. J., O'Brien, J. T., Davis, S., Ballard, C., Barber, R., Kalaria, R. N., & Perry, R. H. (2002). Ischemic basis for deep white matter hyperintensities in major depression: A neuropathological study. *Archives of General Psychiatry*, *59*(9). <https://doi.org/10.1001/archpsyc.59.9.785>
- Thomas, M. L., Kaufmann, C. N., Palmer, B. W., Depp, C. A., Martin, A. S., Glorioso, D. K., Thompson, W. K., & Jeste, D. V. (2016). Paradoxical trend for improvement in mental health with aging: A Community-Based study of 1,546 adults aged 21-100 years. *Journal of Clinical Psychiatry*, *77*(8). <https://doi.org/10.4088/JCP.16m10671>
- Tsai, S. J., Hsiao, Y. H., Liao, M. Y., & Lee, M. C. (2022). The Influence of Depressive Mood on Mortality in Elderly with Different Health Status: Evidence from the Taiwan Longitudinal Study on Aging (TLISA). *International Journal of Environmental Research and Public Health*, *19*(11). <https://doi.org/10.3390/ijerph19116922>
- van den Berg, K. S., Wiersema, C., Hegeman, J. M., van den Brink, R. H. S., Rhebergen, D., Marijnissen, R. M., & Oude Voshaar, R. C. (2021). Clinical characteristics of late-life depression predicting mortality. *Aging and Mental Health*, *25*(3). <https://doi.org/10.1080/13607863.2019.1699900>

- Vande Castele, T., Laroy, M., Van Cauwenberge, M., Koole, M., Dupont, P., Sunaert, S., Van den Stock, J., Bouckaert, F., Van Laere, K., Emsell, L., & Vandenbulcke, M. (2024). Preliminary evidence for preserved synaptic density in late-life depression. *Translational Psychiatry, 14*(1). <https://doi.org/10.1038/s41398-024-02837-8>
- Vos T., Lim SS, Abbafati C, Abbas KM, Abbasi M, & Abbasifard M. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*.
- Walker, E. R., McGee, R. E., & Druss, B. G. (2015). Mortality in mental disorders and global disease burden implications a systematic review and meta-analysis. *JAMA Psychiatry, 72*(4). <https://doi.org/10.1001/jamapsychiatry.2014.2502>
- Wei, J., Hou, R., Zhang, X., Xu, H., Xie, L., Chandrasekar, E. K., Ying, M., & Goodman, M. (2019). The association of late-life depression with all-cause and cardiovascular mortality among community-dwelling older adults: Systematic review and meta-analysis. In *British Journal of Psychiatry* (Vol. 215, Issue 2). <https://doi.org/10.1192/bjp.2019.74>
- Wiels, W., Baeken, C., & Engelborghs, S. (2020). Depressive symptoms in the elderly—an early symptom of dementia? A systematic review. *Frontiers in Pharmacology, 11*. <https://doi.org/10.3389/fphar.2020.00034>
- Wulff, K., Gatti, S., Wettstein, J. G., & Foster, R. G. (2010). Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. In *Nature Reviews Neuroscience* (Vol. 11, Issue 8). <https://doi.org/10.1038/nrn2868>
- Zenebe, Y., Akele, B., W/Selassie, M., & Necho, M. (2021). Prevalence and determinants of depression among old age: a systematic review and meta-analysis. In *Annals of General Psychiatry* (Vol. 20, Issue 1). <https://doi.org/10.1186/s12991-021-00375-x>
- Zhang, J., Wang, J., Xu, X., You, Z., Huang, Q., Huang, Y., Guo, Q., Guan, Y., Zhao, J., Liu, J., Xu, W., Deng, Y., Xie, F., & Li, B. (2023). In vivo synaptic density loss correlates with impaired functional and related structural connectivity in Alzheimer's disease. *Journal of Cerebral Blood Flow and Metabolism, 43*(6). <https://doi.org/10.1177/0271678X231153730>