Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Psychiatry Research 291 (2020) 113294

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

High depression and anxiety in people with Alzheimer's disease living in retirement homes during the covid-19 crisis

Mohamad El Haj[a,b,c,*], Emin Altintas[b,d], Guillaume Chapelet[e,f], Dimitrios Kapogiannis[g], Karim Gallouj[b]

[a] Nantes Université, Univ Angers, Laboratoire de Psychologie des Pays de la Loire (LPPL - EA 4638), F-44000 Nantes, France
[b] Unité de Gériatrie, Centre Hospitalier de Tourcoing, Tourcoing, France
[c] Institut Universitaire de France, Paris, France
[d] Laboratoire PSITEC – Psychologie: Interactions Temps Émotions Cognition, Université Lille Nord de France – 59000 Lille – France
[e] Department of Geriatric Medicine, Angers University Hospital, Angers, France
[f] CHU Nantes, Inserm CIC04, Département de Neurologie, Centre Mémoire de Ressources et Recherche, Nantes, France
[g] Laboratory of Clinical Investigation, National Institute on Aging, Baltimore, MD, USA

ARTICLE INFO

Keywords:
Alzheimer's disease
Anxiety
Covid-19
Coronavirus
Depression
Mental health

ABSTRACT

To cope with Covid-19 and limits its spread among residents, retirement homes have prohibited physical contact between residents and families and friend and, in some cases, even between residents or between residents and caregivers. We investigated the effects of measures against Covid-19 on the mental health of participants with Alzheimer's disease (AD) who live in retirement homes in France. We instructed on-site caregivers to assess depression and anxiety in participants with mild AD who live in retirement homes. Fifty-eight participants consented to participate in the study. The participants rated their depression and anxiety during and before the Covid-19 crisis. Participants reported higher depression (p = .005) and anxiety (p = .004) during than before the Covid-19 crisis. These increases can be attributed to the isolation of the residents and/or to the drastic changes in their daily life and care they receive. While, in their effort to prevent infections, retirement homes are forced to physically separate residents from the outside world and to drastically reduce residents' activities, these decisions are likely to come at a cost to residents with AD and their mental health.

1. Introduction

Already by mid-spring 2020, Covid-19, the disease caused by the novel coronavirus SARS-CoV-2 that primarily affects the lower respiratory tract, has caused a pandemic affecting the lives and livelihoods of the entire human population around the world. The disease is more severe in older age groups and in the presence of common age-associated comorbidities, such as hypertension, cardiovascular disease and diabetes. Consequently, the Covid-19 crisis is most drastically affecting the quality of life of older adults, especially those residing in retirement homes in North America and Europe, including France. Although retirement homes are used to deal with illnesses and deaths, Covid-19 has shaken up the functioning of these facilities. To cope with the crisis, retirement homes in France have been restricting, since 15 March 2020, all visitations except for end of life situations. Retirement homes have even been forced to restrict all activities considered as non-essential, including restricting access to non-essential personnel (e.g., hairdressers), group activities, and even communal dining. Despite the effort of caregivers to provide the best care possible, they have had to struggle with an increased workload (e.g., due to increased vigilance for potential fever and respiratory symptoms, increased requirement to provide postmortem care) and deal with shortages in equipment and supplies, such as sanitizers, gloves and facemasks, potentially exposing them to higher danger for infection. These challenges may have impacted the quality of care, as well as the wellbeing of retirement home residents. Regarding the consequences of the Covid-19 crisis on mental health of residents of retirement homes, we offer, to the best of our knowledge, the first empirical investigation.

We studied the mental health of participants with Alzheimer's disease (AD) residing in retirement homes during the Covid-19 crisis. More specifically, we investigated their levels of depression and anxiety, since they are among the most prevalent neuropsychiatric symptoms in

* Corresponding author at: Faculté de Psychologie, LPPL – Laboratoire de Psychologie des Pays de la Loire, Université de Nantes, Chemin de la Censive du Tertre, BP 81227, 44312 Nantes Cedex 3, France.
E-mail address: mohamad.elhaj@univ-nantes.fr (M. El Haj).

https://doi.org/10.1016/j.psychres.2020.113294
Received 4 May 2020; Received in revised form 18 June 2020; Accepted 11 July 2020
Available online 13 July 2020

the AD disease spectrum (Ismail et al., 2016) and arguably the ones most likely to be affected by the Covid-19 crisis. While AD is primarily a neurodegenerative dementia and one of its main cognitive features is memory decline (El Haj et al., 2016; McKhann et al., 2011), the disease is also characterized by the early emergence of various neuropsychiatric symptoms, especially depression and anxiety (Ballard et al., 1999; Chi et al., 2014; Ferretti et al., 2001; Gormley and Rizwan, 1998; Ismail et al., 2016).

Regarding depression, nearly up to 50% of people with AD experience some degree of depression during the course of the disease (Starkstein et al., 2005), whereas approximately 20% to 30% of people with AD meet criteria for major depressive disorder during the course of the disease (Ballard et al., 1996; Enache et al., 2011). Risk factors for depression in AD include a personal or family history of depression (Lyketsos and Olin, 2002; Rapp et al., 2006) or ApoE4 positivity (Krishnan et al., 1996; Qiu et al., 2016). Iatrogenic factors may also increase the likelihood of developing depression in AD, such as the use of certain medications, such as benzodiazepines, corticosteroids, and beta-blockers (Burke et al., 2019). Prolonged exposure to dopamine agonists, anticonvulsants, and anticholinergic medications can also increase the likelihood of developing depression in AD (Burke et al., 2019). Regardless of its risk factors, depression in AD increases the risk of behavioral disturbance and accelerates functional decline (Lyketsos and Olin, 2002). Depression in AD also contributes to institutionalization (Gaugler et al., 2009) and mortality (Suh et al., 2005).

Besides depression, another prominent neuropsychiatric symptom in AD is anxiety. Research suggests that 25% to 71% people with AD experience anxiety during the course of the disease (Mintzer et al., 2005). Anxiety has been also considered as a risk factor for AD, especially anxiety occurring at midlife (Gimson et al., 2018). Moreover, anxiety in people with amnestic Mild Cognitive Impairment predicts conversion to AD to a greater degree than memory loss, hippocampal cortex atrophy, or even depression (Mah et al., 2015). The potential pathogenic role of anxiety in AD can be attributed to its negative effects on neuroplasticity and cognitive reserve (i.e., the flexibility or efficiency of cognitive networks) (Santabarbara et al., 2019). Anxiety also shares some underlying etiopathogenic mechanisms with AD, such as inflammation and oxidative damage (Salim et al., 2012). Research has also suggested a bi-directional association between anxiety and amyloid-β, a the main pathogenic protein of AD (Pietrzak et al., 2015). Regardless of its causes, anxiety in AD has been associated with behavioral disturbance and increased caregiver burden (Kaufer et al., 1998).

We hypothesize that symptoms of depression and anxiety are likely to increase in participants with AD who live in retirement facilities during the Covid-19 crisis. In their effort to prevent infections, retirement facilities have been forced to physically separate residents from the outside world and to drastically reduce their residents' activities, decisions which are likely to have come at a cost to the residents' mental health. To investigate this issue, we evaluated symptoms of depression and anxiety in participants with AD who live in retirement homes in France during the Covid-19 crisis. More specifically, we instructed caregivers to ask participants with AD to rate their depression and anxiety before and during the Covid-19 crisis. We expected higher levels of depression and anxiety during than before the Covid-19 crisis.

2. Method

2.1. Participants

Fifty-eight participants with a clinical diagnosis of probable AD (37 women and 21 men; *M* age = 71.79 years, *SD* = 5.54; *M* years of formal education = 9.26, *SD* = 2.33) voluntarily participated in the study. They were recruited from retirement homes in France. Participants provided their consent to participate. This study was designed and conducted in accordance with the Declaration of Helsinki. Recruitment occurred by contacting colleagues (fourteen psychologists, physicians, or nurses) who work in retirement homes in France, either directly or through social networks (e.g., Facebook groups of geriatric caregivers). These on-site caregivers agreed to obtain consent from eligible participants, provide historical information about them and administer study procedures. On-site colleagues were asked to verify, in the medical records, that a diagnosis of probable dementia AD was made by a neurologist or geriatrician according to clinical criteria developed by the National Institute on Aging and the Alzheimer's Association criteria for probable Alzheimer's disease (McKhann et al., 2011) and that the participants had been assessed with the Mini Mental State Exam (Folstein et al., 1975) within three months before the study to provide an recent assessment of their cognitive status. Due to their increased workload during the crisis, we did not ask on-site caregivers to repeat administration of the Mini Mental State Exam or perform any other clinical test. We selected a score of 21/30 points or higher as an inclusion criterion (raw data is provided in Annex, *M* = 23.03, range 21–26, *SD* = 1.18) to limit enrollment to participants with mild AD. We did not include participants with a score < 21 points on the Mini Mental State Exam because our study required some introspection into psychological states (i.e., participants had to compare their own depression/anxiety before and during the Covid-19 crisis). By applying these criteria, we excluded 22 participants from the original sample size (*n* = 80 participants). Twelve participants were excluded because of diagnosis of mixed dementia (e.g., a patient was diagnosed as suffering from both AD and Lewy body) and ten participants were excluded because they did not have a Mini Mental State Exam in the last three months.

2.2. Procedures

On-site caregivers instructed participants to assess their depression and anxiety with the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), which consists of 14 items. Half of the items evaluates depression (e.g., I feel cheerful, I feel as if I am slowed down, I have lost interest in my appearance) and the other half anxiety (e.g., Worrying thoughts go through my mind, I can sit at ease and feel relaxed, I get a sort of frightened feeling like 'butterflies' in the stomach). Each item is scored on a four-point scale ranging from 0 (not present) to 3 (considerable). The maximum score for each subscale is 21 points.

Participants were instructed to rate items on the scale twice. On one occasion, participants were provided with the following instructions: "We would like to evaluate the psychological effects of social distancing implemented to cope with the Covid-19 crisis. We thus invite you to fill the following items referring to the period BEFORE the beginning of social distancing. For instance, for the following item (I feel cheerful), you should consider it as (I felt cheerful before the beginning of social distancing)". On the second occasion, participants were provided with the following instructions "We would like to evaluate the psychological effects of social distancing implemented to cope with the Covid-19 crisis. We thus invite you to fill the following items referring to the period of social distancing. For instance, for the following item (I feel cheerful), you should consider it as (I feel cheerful DURING social distancing)". These instructions were provided orally by on-site caregivers and scores were also provided orally by participants, to minimize the risk of contamination by exchanging paper and pencil materials. To counterbalance the two conditions, half the participants rated the Hospital Anxiety and Depression Scale regarding the period before containment, first, and, then, the period during containment, and vice versa. We invited caregivers to note scores on the depression and anxiety subscales and provide us with these scores by phone or email.

We compared means on the depression and anxiety subscales between the two conditions (i.e., before vs. during the Covid-19 crisis). We used non-parametric tests (i.e., Wilcoxon signed rank tests) due to the scale nature of the variables and their abnormal distribution. We also calculated effect size [*d* = 0.2 can be considered a small effect size,

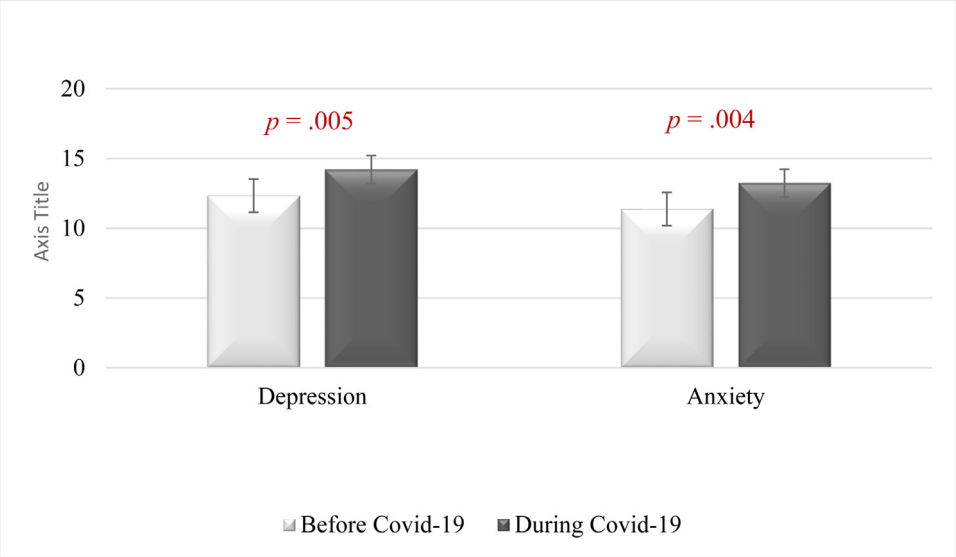

Fig. 1. Depression and anxiety scores (maximum score = 21 points) before and during the Covid-19 crisis. Error bars represent intervals of 95% within-subjects confidence.

$d = 0.5$ represents a medium effect size and $d = 0.8$ refers to a large effect size (Cohen, 1988)] following recommendations by Rosenthal and DiMatteo (2001), and Ellis (2010). Level of significance was set as $p \leq 0.05$.

3. Results

3.1. Higher depression and anxiety during than before the covid-19 crisis

As illustrated in Fig. 1 (raw data is provided in Annex), participants reported higher depression during ($M = 14.21$, $SD = 3.17$) than before ($M = 12.34$, $SD = 4.10$) the Covid-19 crisis ($Z = -2.84$, $p = .005$, Cohen's $d = 0.80$). Participants also reported higher anxiety during ($M = 13.24$, $SD = 3.39$) than before ($M = 11.38$, $SD = 4.36$) the Covid-19 crisis ($Z = -2.86$, $p = .004$, Cohen's $d = 0.81$).

4. Discussion

In their effort to limit the spread of Covid-19, retirement homes have been reducing physical contact of residents with the outside world, and in some cases, even physical contact between residents. We thus evaluated self-reported indicators of depression and anxiety to assess the mental health of participants with AD who have been living in retirement homes during the Covid-19 crisis. Analyses demonstrated higher depression and anxiety during than before the Covid-19 crisis.

Our study offers the first assessment of the mental health of people with AD who live in retirement homes during the Covid-19 crisis. The higher levels of depression and anxiety during than before the Covid-19 crisis, as reported by our participants, may reflect the drastic changes in their daily life in retirement homes during the crisis. Retirement homes in France, as well as in our European and North American countries, are currently prohibiting all visitation. Non-essential activities and services are also being restricted, including social activities, such as communal dining. In some cases, residents are asked to not leave their rooms and, when in wards, to keep a safe distance from other residents to avoid contracting the virus. In addition, they have not been allowed to have physical contact with their family members and friends, even during sickness. Even when not themselves confronted with previously unfathomable situations (i.e., suffering serious physical sickness or being in the end of life without being able to see their families), residents are aware that these situations confront other residents in their facilities. Social distancing measures are naturally difficult to bear, especially in the event of death, e.g., when residents of the same unit cannot even say goodbye to the sufferers. While these restrictions may be deemed necessary, they are likely to come at a cost to residents in retirement facilities and their mental health. Another factor that may contribute to the depression and anxiety of residents of retirement homes during the Covid-19 crisis is the reduced physical contact with caregivers who, despite their efforts to provide the best care, have been dealing with an increased workload, shortages in equipment and supplies, and increased postmortem care.

We should note that participants reported high levels of depression and anxiety both before and during the Covid-19 crisis. Although this may be partly the result of recall bias, these scores reflect the high occurrence of both depression and anxiety in AD (Starkstein et al., 2005). Also, 25% to 71% people with AD experience anxiety during the course of the disease (Mintzer et al., 2005). Both before and during the Covid-19 crisis, the depression and anxiety scores of our participants were above the cutoff of > 10/21 points on the Hospital Anxiety and Depression Scale recommended by Herrmann (1997).

Limitations of our study design include the fact that assessments were carried out by on-site caregivers. Due to visit restrictions, we had to delegate these assessments to on-site physicians, psychologists and nurses. However, these healthcare professionals are typically trained to assess mental health in people with AD and had already established rapport with participants. To avoid overwhelming on-site caregivers, we did not ask them to perform any additional cognitive or clinical assessments. Another limitation of our study is the retrospective assessment of anxiety and depression, with might result in recall bias. That bieng said, the confinement was somehow unpredictable so we were not able to prepare the study and include the pre-assessment.

Regardless of its potential limitations, largely unavoidable in the current situation, this is the first report on the mental health of people with AD who live in retirement homes during the Covid-19 crisis. By demonstrating significant depression and anxiety during the crisis, our study reinforces the calls for clinical interventions to deal with the psychological consequences of this crisis. Ideally, psychological therapies (e.g., cognitive and behavioral therapy, mindfulness-based stress reduction meditation) should be offered to residents at the end of the period of social distancing to help them recover. Also, future training and education programs for caregivers should benefit from lessons learned during the Covid-19 crisis and train caregivers on how to deal with the mental health consequences of similar crises.

CRediT authorship contribution statement

Mohamad El Haj: Conceptualization, Data curation, Writing - review & editing. **Emin Altintas:** Data curation, Writing - review & editing. **Guillaume Chapelet:** Data curation, Writing - review & editing. **Dimitrios Kapogiannis:** Data curation, Writing - review & editing. **Karim Gallouj:** Data curation, Writing - review & editing.

Acknowledgements

The authors would like to thank the caregivers who, despite the increased workload during the Covid-crisis, have dedicated their time to answer the survey. The authors would like to thank the patients who have challenged and continue to challenge their isolation during the Covid-19 crisis and provided their feedback about their experience during this crisis. The first author was supported by the LABEX (excellence laboratory, program investment for the future) DISTALZ (Development of Innovative Strategies for a Transdisciplinary Approach to Alzheimer Disease) and the EU CASCADE Interreg 2 Seas Programme 2014–2020 (co-funded by the European Regional Development Fund). This research was supported in part (for author DK) by the Intramural Research Program of the National Institute on Aging, NIH.

Annex. Raw data

MMSE	Depression before Covid	Depression after Covid	Anxiety before Covid	Anxiety after Covid
23	8	11	11	13
22	12	14	11	12
24	12	14	7	8
21	9	11	6	7
21	15	12	12	10
22	8	12	15	12
23	16	13	6	9
23	18	16	17	19
22	9	17	8	7
23	13	14	6	17
24	18	15	18	16
24	9	7	10	15
22	17	18	17	18
24	14	15	6	9
25	16	14	14	16
26	8	14	7	6
25	12	14	14	16
24	9	6	11	14
22	15	16	14	18
24	19	18	15	11
23	7	17	8	13
23	8	18	6	7
23	8	7	7	8
22	18	17	17	14
22	8	17	5	15
22	14	16	12	15
24	7	17	18	15
23	16	18	15	16
24	15	15	16	14
24	13	12	11	16
23	6	16	12	14
23	15	15	8	13
23	8	7	7	9
22	18	16	18	15
22	14	15	8	15
24	19	16	17	16
21	19	17	19	15
26	8	12	16	14
23	9	14	6	16
22	11	16	14	13
24	14	13	7	17
22	7	10	8	16
23	18	17	18	14
24	8	7	6	15
24	9	19	12	14
24	8	16	7	16
23	7	15	6	8
24	15	16	14	12
21	16	17	19	17
23	15	15	10	16
22	8	14	14	15
23	15	16	16	14
23	8	11	9	13
24	16	15	16	17
21	14	14	8	9
21	19	16	9	7
24	13	16	9	14
23	8	8	7	8
23	8	11	11	13
22	12	14	11	12

24	12	14	7	8
21	9	11	6	7
21	15	12	12	10
22	8	12	15	12
23	16	13	6	9
23	18	16	17	19
22	9	17	8	7
23	13	14	6	17
24	18	15	18	16
24	9	7	10	15
22	17	18	17	18
24	14	15	6	9
25	16	14	14	16
26	8	14	7	6
25	12	14	14	16
24	9	6	11	14
22	15	16	14	18
24	19	18	15	11
23	7	17	8	13
23	8	18	6	7
23	8	7	7	8
22	18	17	17	14
22	8	17	5	15
22	14	16	12	15
24	7	17	18	15

References

Ballard, C., Bannister, C., Solis, M., Oyebode, F., Wilcock, G., 1996. The prevalence, associations and symptoms of depression amongst dementia sufferers. J Affect. Disord. 36 (3–4), 135–144. https://doi.org/10.1016/0165-0327(95)00072-0.

Ballard, C., Holmes, C., McKeith, I., Neill, D., O'Brien, J., Cairns, N., Perry, R., 1999. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. Am. J. Psychiatry 156 (7), 1039–1045. https://doi.org/10.1176/ajp.156.7.1039.

Burke, A.D., Goldfarb, D., Bollam, P., Khokher, S., 2019. Diagnosing and treating depression in patients with Alzheimer's disease. Neurol. Ther. 8 (2), 325–350. https://doi.org/10.1007/s40120-019-00148-5.

Chi, S., Yu, J.T., Tan, M.S., Tan, L., 2014. Depression in Alzheimer's disease: epidemiology, mechanisms, and management. J. Alzheimers Dis. 42 (3), 739–755. https://doi.org/10.3233/JAD-140324.

Cohen, J., 1988. Statistical Power Analysis For the Behavioral Sciences. Erlbaum Associates, Hillsdale, NJ.

Haj, El, M., Antoine, P., Amouyel, P., Lambert, C., J., Pasquier, F., Kapogiannis, D., 2016. Apolipoprotein E (APOE) epsilon4 and episodic memory decline in Alzheimer's disease: a review. Age. Res. Rev. 27, 15–22. https://doi.org/10.1016/j.arr.2016.02.002.

Ellis, P.D., 2010. The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results. Cambridge University Press, New York, NY.

Enache, D., Winblad, B., Aarsland, D., 2011. Depression in dementia: epidemiology, mechanisms, and treatment. Curr. Opin. Psychiatry 24 (6), 461–472. https://doi.org/10.1097/YCO.0b013e32834bb9d4.

Ferretti, L., McCurry, S.M., Logsdon, R., Gibbons, L., Teri, L., 2001. Anxiety and Alzheimer's disease. J. Geriatr. Psychiatry Neurol. 14 (1), 52–58. https://doi.org/10.1177/089198870101400111.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatry Res. 12 (3), 189–198.

Gaugler, J.E., Yu, F., Krichbaum, K., Wyman, J.F., 2009. Predictors of nursing home admission for persons with dementia. Med. Care 47 (2), 191–198. https://doi.org/10.1097/MLR.0b013e31818457ce.

Gimson, A., Schlosser, M., Huntley, J.D., Marchant, N.L., 2018. Support for midlife anxiety diagnosis as an independent risk factor for dementia: a systematic review. BMJ Open 8 (4), e019399. https://doi.org/10.1136/bmjopen-2017-019399.

Gormley, N., Rizwan, M.R., 1998. Prevalence and clinical correlates of psychotic symptoms in Alzheimer's disease. Int. J. Geriatr. Psychiatry 13 (6), 410–414.

Herrmann, C., 1997. International experiences with the hospital anxiety and depression scale–a review of validation data and clinical results. J. Psychosom. Res. 42 (1), 17–41.

Ismail, Z., Smith, E.E., Geda, Y., Sultzer, D., Brodaty, H., Smith, G., Area, I.N.S.P.I., 2016. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement 12 (2), 195–202. https://doi.org/10.1016/j.jalz.2015.05.017.

Kaufer, D.I., Cummings, J.L., Christine, D., Bray, T., Castellon, S., Masterman, D., DeKosky, S.T., 1998. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the neuropsychiatric inventory caregiver distress scale. J. Am. Geriatr. Soc. 46 (2), 210–215. https://doi.org/10.1111/j.1532-5415.1998.tb02542.x.

Krishnan, K.R., Tupler, L.A., Ritchie Jr., J.C., McDonald, W.M., Knight, D.L., Nemeroff, C.B., Carroll, B.J., 1996. Apolipoprotein E-epsilon 4 frequency in geriatric depression. Biol. Psychiatry 40 (1), 69–71. https://doi.org/10.1016/0006-3223(95)00424-6.

Lyketsos, C.G., Olin, J., 2002. Depression in Alzheimer's disease: overview and treatment. Biol. Psychiatry 52 (3), 243–252.

Mah, L., Binns, M.A., Steffens, D.C., Alzheimer's Disease Neuroimaging, I., 2015. Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease. Am. J. Geriatr. Psychiatry 23 (5), 466–476. https://doi.org/10.1016/j.jagp.2014.10.005.

McKhann, G., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack Jr., C.R., Kawas, C.H., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7 (3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.

Mintzer, J.E., Brawman-Mintzer, O., Mirski, D.F., Barkin, K., 2005. Anxiety in the behavioral and psychological symptoms of dementia. Int. Psychogeriatr. 12 (S1), 139–142. https://doi.org/10.1017/S104161020000692X.

Pietrzak, R.H., Lim, Y.Y., Neumeister, A., Ames, D., Ellis, K.A., Harrington, K., Lifestyle Research, G., 2015. Amyloid-beta, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. JAMA Psychiatry 72 (3), 284–291. https://doi.org/10.1001/jamapsychiatry.2014.2476.

Qiu, W.Q., Zhu, H., Dean, M., Liu, Z., Vu, L., Fan, G., Au, R., 2016. Amyloid-associated depression and ApoE4 allele: longitudinal follow-up for the development of Alzheimer's disease. Int. J. Geriatr. Psychiatry 31 (3), 316–322. https://doi.org/10.1002/gps.4339.

Rapp, M.A., Schnaider-Beeri, M., Grossman, H.T., Sano, M., Perl, D.P., Purohit, D.P., Haroutunian, V., 2006. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch. Gen. Psychiatry 63 (2), 161–167. https://doi.org/10.1001/archpsyc.63.2.161.

Rosenthal, R., DiMatteo, M.R., 2001. Meta-analysis: recent developments in quantitative methods for literature reviews. Ann. Rev. Psychol., 52 59–82. https://doi.org/10.1146/annurev.psych.52.1.59.

Salim, S., Chugh, G., Asghar, M., 2012. Chapter one - inflammation in anxiety. In: Donev, R. (Ed.), Advances in Protein Chemistry and Structural Biology 88. Academic Press, pp. 1–25.

Santabarbara, J., Villagrasa, B., Lopez-Anton, R., Olaya, B., Bueno-Notivol, J., de la Camara, C., Lobo, A., 2019. Clinically relevant anxiety and risk of Alzheimer's disease in an elderly community sample: 4.5 years of follow-up. J. Affect. Disord. 250, 16–20. https://doi.org/10.1016/j.jad.2019.02.050.

Starkstein, S.E., Jorge, R., Mizrahi, R., Robinson, R.G., 2005. The construct of minor and major depression in Alzheimer's disease. Am. J. Psychiatry 162 (11), 2086–2093. https://doi.org/10.1176/appi.ajp.162.11.2086.

Suh, G.H., Kil Yeon, B., Shah, A., Lee, J.Y., 2005. Mortality in Alzheimer's disease: a comparative prospective Korean study in the community and nursing homes. Int. J. Geriatr. Psychiatry 20 (1), 26–34. https://doi.org/10.1002/gps.1256.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatry Scand. 67 (6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.