



Underweight Nutritional Status as a Predictor of Mortality in Alzheimer's Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Study

Kemal Akbar Suryoadji, Muhammad Faruqi, Vincentius Juan Aryaputra
Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

ABSTRACT

Purpose: The research was conducted to determine the risk of mortality in underweight Alzheimer's patients and consider nutritional maintenance as an important management approach in Alzheimer's patients. **Methods:** This review used publications found in Pubmed, Scopus, Cochrane, and ScienceDirect. The keywords were "(Alzheimer's Disease) AND (Underweight) AND (Mortality)". A meta-analysis review with Revman 5 software calculated the average relative risk from all selected cohort studies. **Result:** The process identified 230 articles; only three studies with 1423 patients were included. The meta-analysis result showed that underweight patients have a higher risk of mortality than normal weight patients based on their BMI status. (RR: 1.65, 95% CI: 1.32-2.06). **Conclusion:** Underweight nutritional status in Alzheimer's patients increases the risk of mortality compared to the individuals with normal nutritional status.

Keywords: Alzheimer's disease, nutritional, underweight

ABSTRAK

Tujuan: Penelitian ini dilakukan untuk menentukan risiko kematian pasien penyakit Alzheimer yang memiliki berat badan kurang dan mempertimbangkan pemeliharaan nutrisi sebagai bagian dari pendekatan tata laksana pasien Alzheimer. **Metode:** Tinjauan dalam publikasi ini diambil dari Pubmed, Scopus, Cochrane, dan ScienceDirect. Kata kunci yang digunakan ialah "(Alzheimer Disease) AND (Underweight) AND (Mortality)". Tinjauan meta-analisis menggunakan perangkat lunak Revman 5 menghitung rata-rata risiko relatif dari semua studi kohort yang dipilih. **Hasil:** Dari 230 artikel yang berhasil diidentifikasi, 3 studi dengan 1423 pasien dimasukkan dalam studi. Hasil meta-analisis menunjukkan berdasarkan status indeks massa tubuh, bahwa pasien dengan berat badan kurang memiliki risiko mortalitas lebih tinggi daripada pasien dengan berat badan normal (RR: 1,65; 95% CI: 1,32-2,06). **Simpulan:** Kondisi nutrisi dengan berat badan kurang pada pasien Alzheimer meningkatkan risiko mortalitas dibandingkan dengan individu yang memiliki berat badan normal. **Kemal Akbar Suryoadji, Muhammad Faruqi, Vincentius Juan Aryaputra. Status Berat Badan Kurang sebagai Prediktor Mortalitas Penyakit Alzheimer: Tinjauan Sistematis dan Meta-Analisis Studi Kohort Prospektif.**

Kata kunci: Berat badan kurang, nutrisi, penyakit Alzheimer



Mermin Dunia Kedokteran is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

INTRODUCTION

The United Nations reported 703 million people aged sixty-five years or over in the world in 2019, which is nine percent of the global population.¹ Ageing is a predisposing factor for several diseases such as arthritis, heart disease, and Alzheimer's.² Alzheimer's disease is the most common type of dementia. WHO data (2017) showed 30-35 million Alzheimer's cases globally.³ In Indonesia, current statistics suggest there are 1.2 million cases across the nations,⁴ and a projection of a 400% case increase within the next 30 years if no serious prevention measures are taken.⁴

Currently, no proven drugs are available for treating Alzheimer's disease completely. The general approaches help patients

to maintain their physical function and wellbeing.⁵ Drugs containing cholinesterase inhibitors, commonly prescribed for mild to moderate cases, act as a temporary reliever in controlling and reducing symptoms.⁶ Other activities such as memory training, social and mental stimulation, and physical exercises are suggested to maintain independence and cognitive performance.⁷

Kivimaki, *et al*, (2018) mentioned an association between dementia, including Alzheimer's, and BMI. Its incidence is higher among people with high BMI levels, considered overweight and obese.⁸ Several publications suggest that underweight condition also contributes to Alzheimer's progression. This research will analyze the impact of underweight nutritional

status on Alzheimer's mortality.

METHOD

This systematic review and meta-analysis were conducted by searching through online journal databases: PubMed, Scopus, Cochrane, and ScienceDirect with the keywords "(Alzheimer's Disease) AND (Underweight) AND (Mortality)". The inclusion criteria consisted of suitability with PICO, type of research (systematic review and meta-analysis, cohort study, and case control study), and research conducted on humans. The exclusion criteria consisted of no available article's full text, use of languages other than Indonesian or English, and publications over ten years. A duplication check was conducted, followed by selection according to inclusion and

Alamat Korespondensi email: kemal.akbar@ui.ac.id



ANALYSIS



Table. Details of the selected studies

Author and Year	Study Design	Location	Sample Size	Range/Mean of Sample Age	Intervention	Duration of Follow Up	Risk Ratio M-H, Fixed, 95% CI
Chen, <i>et al</i> , 2019	Prospective cohort	Taiwan	84	86.6	Underweight BMI ≤18.5	2.1 years	1.20 [0.65, 2.22]
de Sousa, <i>et al</i> , 2020	Prospective cohort	Portugal	79	65-93	Underweight BMI ≤18,5	60 months	3.37 [1.71, 6.63]
Jang, <i>et al</i> , 2015	Prospective cohort	South Korea	2,490	73.4	Underweight BMI <18.5	43.7 months	1.59 [1.23, 2.05]

exclusion criteria. From those four databases, 228 articles related to our topic (Pubmed (9), Cochrane (1), Scopus (13), ScienceDirect (205)) were found. Title and abstract screening were conducted, resulting in 6 articles in total. A flowchart of the literature search strategy can be seen in **Figure 1**. A meta-analysis review was done with Revman 5 software to calculate the average relative risk from all selected cohort studies.

RESULT

Based on the criteria, three case-control studies from 4 journal databases (228 subjects) were selected. Two studies showed a significant risk ratio on the increased mortality risk of Alzheimer's patients with underweight status compared to normal weight. In contrast, one study doesn't indicate any significant risk ratio.^{9,10} De Sousa, *et al*, (2020)¹⁰ and Jang, *et al*, (2015)⁹ showed significant results with RR>1 with the precision limit below 1. However, Chen, *et al*, (2019)¹¹ show an insignificant result.

All subjects included subjects aged 65 or above. Follow-ups were between 25 months and 60 months. All studies used the same BMI's underweight cut-off value, which is below 18.5. Specific detail on the selected studies can be seen in **Table**.

DISCUSSION

Chen, *et al*, (2019) involved 14 subjects with underweight and 53 subjects with normal weight;⁷ of 14 underweight subjects (50%) died, and 22 of 53 normoweight subjects (41.5%) died. The risk ratio is not insignificant with wide precision (RR 1.20, 95% confidence interval 0.65-2.22).¹¹

de Sousa, *et al*, (2020) is a novel study with 13 underweight subjects and 35 normal weight subjects. After follow-up, there were 77% deaths in underweight subjects and 22.8% deaths in normal weight subjects. There is a significant risk ratio (RR 3.37, 95% confidence interval 1.71-6.63) with a wide precision range due to relatively few subjects.¹⁰

Jang, *et al*, (2015) study involved more subjects. There are 181 underweight subjects with a 29.2% death rate compared to 1127 normal weight subjects with an 18.4% death rate. The study shows a more significant percentage of underweight death than normal weight (RR 1.65, 95% confidence interval 1.32-2.06) categorized as narrow precision.⁹

We combined outcomes from three studies based on the total death among underweight and normal weight patients as the output. The calculation and analysis with Revman 5 Software resulted in RR 1.65 with 95% CI 1.32-2.06. The measures mean that patients with underweight nutritional status have a 1.65 x mortality risk; chi2 P value in this study was 0.07, indicating no significant (>0.05) heterogeneity in the studies included in this meta-analysis.

Several scientific reasons may explain the increased mortality risk in underweight Alzheimer's patients. Patients with lower BMI tend to have small muscle mass, known as sarcopenia. Patients with sarcopenia possess limited training capacity and mobility, which correlates to the total mortality rate increase.^{12,13} The second reason is that lower BMI is an indirect biomarker for malnutrition.^{14,15}

CONCLUSION

The underweight condition increases mortality risk among Alzheimer's patients.

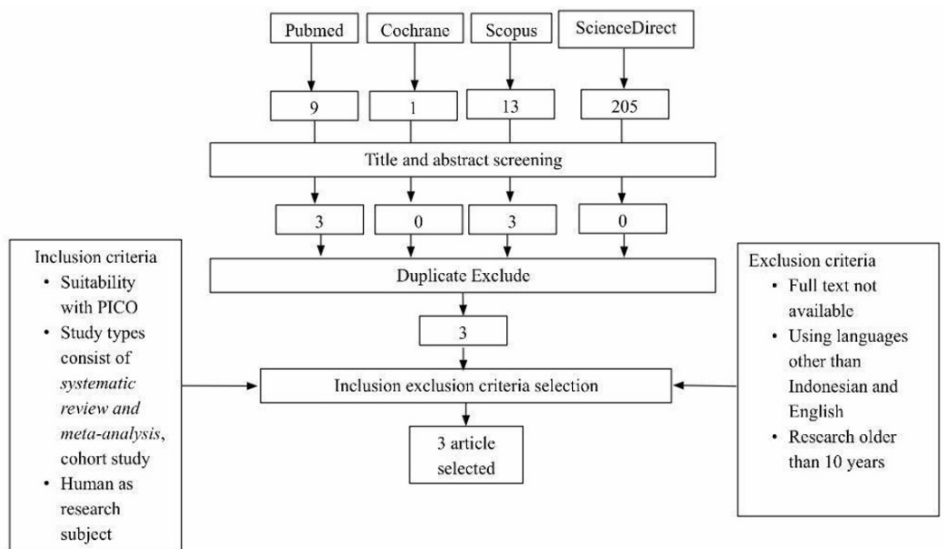


Figure 1. Search strategy flowchart



Figure 2. Forest plot of three studies



ANALISIS



REFERENCE

1. Department of Economics and Social Affairs United Nations. World Population Ageing 2019. New York: United Nations; 2019. pp. 7-8.
2. MacNee W, Rabinovich R, Choudhury G. Ageing and the border between health and disease. *Eur Respir J*. 2014;44:1332-52.
3. World Health Organization. Global action plan on the public health response to dementia. Geneva: World Health Organization; 2017 pp. 2-34.
4. Turana Y, Tengkawan J, Suswanti I, Suharya D, Riyadina W, Pradono J. Primary prevention of Alzheimer's disease in Indonesia. *Internat J Aging Res*. 2019;2(3):2.
5. 2020 Alzheimer's disease Facts and Figures. *Alzheimer's & dementia*. 2021;16(3):391-460.
6. Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics. *Mol Med Rep*. 2019;20(2):1479-87.
7. Berg-Weger M, Stewart D. Non-pharmacologic interventions for persons with dementia. *Missouri Med*. 2017;114(2):116-9.
8. Kivimaki M, Luukkonen R, Batty G, Ferrie J, Pentti J, Nyberg S, et al. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer's & Dementia*. 2018;14(5):601-9.
9. Jang H, Kim JH, Choi SH, Lee Y, Hong CH, Jeong JH, et al. Body mass index and mortality rate in Korean patients with Alzheimer's disease. *J Alzheimers Dis*. 2015;46(2):399-406.
10. de Sousa OV, Mendes J, Amaral TF. Nutritional and functional indicators and their association with mortality among older adults with Alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2020;35:1533317520907168.
11. Chen TB, Weng SC, Chou YY, Lee YS, Liang CK, Lin CS, et al. Predictors of mortality in the oldest old patients with newly diagnosed Alzheimer disease in a residential aged care facility. *Dement Geriatr Cogn Disord*. 2019;48(1-2):93-104.
12. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia. *J Appl Physiol*. 2003;95:1851-60.
13. Bouchonville MF, Villareal DT. Sarcopenic obesity: How do we treat it? *Curr Opin Endocrinol Diabetes Obes*. 2013;20:412-9.
14. Persson MD, Brismar KE, Katzarski KS, Nordenstrom J, Cederholm TE. 2002) Nutritional status using mini nutritional assessment and subjective global assessment predict mortality in geriatric patients. *J Am Geriatr Soc*. 2002;50(12):1996-2002. doi: 10.1046/j.1532-5415.2002.50611.x.
15. Rivière S, Lauque S, Boisard A, Guyonnet S, Vellas B. La nutrition dans la maladie d'Alzheimer [Nutrition in Alzheimer's disease]. *Soins Gerontol*. 1999;(16):9-11.