Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
SEP. 2024 VOL.3, NO.3

Investigating Alzheimer's Disease Resistance in Okinawan Centenarians' Offspring: A Population Study in a Blue Zone

Justin Lu[1]

[1] St. Mark's School, Southborough, MA 01772, USA

Correspondence: Justin Lu, St. Mark's School, Southborough, MA 01772, USA.

doi:10.56397/JIMR/2024.09.07

Abstract

Alzheimer's disease (AD) is a neurodegenerative condition characterized by cognitive decline and the accumulation of amyloid-β plaques and neurofibrillary tangles in the brain. Although developing the disease becomes increasingly common as people age, centenarians — individuals who reach the age of 100 — have shown an unexpected resilience to AD, and these individuals are more prevalent in regions known as blue zones, where people experience exceptional longevity and health. This study focuses on the offspring of centenarians in one of these blue zones, Okinawa, Japan, to investigate what potential protective factors they may possess against AD. By screening this unique population using a questionnaire and the Mini-Mental State Examination (MMSE) and tracking AD pathology through advanced biomarker assays following the A/T/N criteria, A: Aβ40/42 ratio, T: phosphorylated tau (pT217-tau), and N: neurofilament light chain (NfL) levels, we aim to uncover genetic, environmental, or lifestyle-related factors that contribute to the decreased incidence of AD in these populations. This study seeks to identify key factors contributing to their resilience by comparing the results of centenarian offspring with age-matched non-centenarians. The spouses of these offspring of centenarians will also be included in the study, acting as a control group of individuals who are likely to share many of the lifestyle and environmental factors with the centenarian offspring but with different genetics. These findings could provide valuable insights for the future development of public health strategies and approaches to mitigate AD risk in the broader population.

Keywords: Alzheimer's Disease (AD), Okinawan centenarians' offspring, research

1. Introduction

AD is the most common form of dementia, affecting over 50 million people worldwide, a number which is expected to double every 20 years (ADI — Dementia Statistics, n.d.). As the life expectancy of humans continues to grow, so too does the rate of AD diagnosis and death, making researching the disease increasingly urgent. The disease is often clinically characterized by a progressive decline in cognitive function, memory, and reasoning. Pathologically, AD is characterized by the buildup of abnormal protein aggregates in the brain made of amyloid β-protein (Aβ) and hyperphosphorylated tau (p-tau). Amyloid plaques are abnormal clumps of Aβ that accumulate extracellularly, while neurofibrillary tangles are twisted fibers of p-tau that build up inside cells. Both of these contribute to cell death and the loss of brain function characteristic of AD.

Research has shown that as individuals age, the likelihood of AD developing increases drastically, with the chance doubling every five years past 65, and over one-third of people over 85 have AD (Jorm & Jolley, 1998). Interestingly, the risk of developing AD no longer increases beyond a certain age. In reality, people who are over 100 years of age, known as centenarians, have a decreased chance of developing AD (Corrada et al., 2010). Studying and understanding the health and longevity of these centenarians offers valuable insights into aging, particularly in relation to neurodegenerative diseases such as AD due to their currently enigmatic and unique resilience and/or resistance to these diseases. Their unexpectedly decreased risk suggests that these centenarians

may possess protective genetic factors or are shielded by environmental or lifestyle-related factors that contribute to this decreased risk. The offspring of these centenarians can provide even further insight into AD resilience and resistance, which is often linked to genetics. The link between centenarianism and genetics is so strong that the siblings of centenarians are nine times more likely to become centenarians than the average population, and their offspring have 62% lower all-cause mortality rates compared to age-matched individuals (Anderson, 2020). Studying these offspring is also incredibly beneficial because they can be compared with control groups of similar-aged people who are not the offspring of centenarians. On the other hand, their parents do not have any control group to which they can be compared because, as the name centenarian suggests, those who are not centenarians never live to the same age. Certain areas known as blue zones contain exceptional levels of health and longevity, lower disease rates, including Alzheimer's, and a higher proportion of these centenarians.

Blue zones are described as regions of the world where people live significantly longer and healthier lives than the global average. Five regions are currently widely considered as blue zones: Ikaria, Greece; Nicoya, Costa Rica; Loma Linda, US; Sardinia, Italy; and Okinawa, Japan. Although Japan already has a higher percentage of centenarians within the country than other countries, Okinawa has an even higher percentage of centenarians than other prefectures (Nakanishi et al., 2021). This fact means that Okinawan centenarians can more easily be compared to the centenarians from other regions of Japan due to the higher number of Japanese centenarians. While some blue zones have studies researching various rates of diseases and other health factors of their older populations, none except for Okinawa has a specific study to track its centenarians. Okinawa centenarians are tracked by the Okinawa Centenarian Study, the most extensive centenarian study in the world, which has examined over 600 centenarians over the years (OCS ORCLS, n.d.). Also, all Japanese centenarians receive a certificate from the prime minister of Japan on the "Respect for the Aged Day," meaning that the centenarians in Japan are tracked in a database (Respect for the Aged Day, 2021). In conjunction, these two factors make studying and gathering data on these centenarians, and by extension, their offspring, much more accessible in Okinawa than in other blue zones because of access to large databases containing information on these centenarians. I hypothesize that the Okinawan centenarians' offspring will continue to show protection from AD, and their protection will be caused by environmental and lifestyle factors. By researching the Okinawan centenarians and their offspring, I aim to uncover potential factors that contribute to their resilience and resistance to AD.

Various past studies on the prevalence of AD and other neurodegenerative diseases are based on clinical symptoms and diagnoses by medical professionals to determine whether or not individuals have the disease. The problem with these methods is that they are subjective and inevitably somewhat affected by the personal biases and previous experiences of those conducting the diagnoses. Therefore, this study will use biomarkers, a more objective method that will not falsely diagnose individuals with neurodegeneration caused by factors outside of the diseases of interest. This method is even more relevant now than ever due to the significant recent improvements in AD biomarkers.

Recent progress in AD research, allowed by new ultrasensitive detection methods, has led to the development of significantly improved biomarkers, enhancing our ability to diagnose and monitor the disease. These biomarker tests will focus on the A/T/N criteria — Amyloid, Tau, and Neurodegeneration — pivotal in identifying AD and tracking its progression. The amyloid component in the A/T/N ratio refers to the Aβ40/42 ratio. Aβ42 has been shown through research to be more likely to cause amyloid plaque build-up, meaning a lower ratio of Aβ40/42 below a certain threshold will be evidence of AD (Doecke et al., 2020). This is possibly because Aβ40/42 aggregates more easily and is more likely to be found in aggregates, where the biomarker assay will not measure it as part of the Aβ40/42 ratio, meaning that since Aβ40 levels remain similar, the ratio will lower. This ratio can now be measured in blood plasma, with research showing these new tests have a strong correlation with amyloid PET imaging. This breakthrough led to the FDA approval of a CSF test measuring the Aβ40/42 ratio in 2022, followed by the launch of the AD-Detect™ blood test in 2023 (Pais et al., 2023). The Tau component of A/T/N has been discovered through research, mainly by chance. Scientists discovered that the phosphorylated form of tau (pTau) at position 217 (pT217-tau) has emerged as a highly specific and promising biomarker for AD, both as a diagnostic biomarker and progression biomarker, thanks to its close correlation with AD plaque build-up, leading to the availability of a commercial assay by AlzPath, Inc. in 2024 (Noëlle Warmenhoven et al., 2024). Finally, the neurofilament light chain (NfL) is the Neurodegeneration component of the A/T/N criteria. The NfL is a very stable marker of neurodegeneration, which can now be measured much more easily and less intrusively than before through blood tests thanks to the consistent correlation between the more invasive cerebral spinal fluid measurements (CSF) and plasma/serum NfL concentrations. NfL concentrations have now also been shown in research to predict familial AD up to 15 years before symptom onset (Weston et al., 2019). Familial AD is a form of AD that is often caused by autosomal dominant genetic inheritance of the APP, PSEN1, and PSEN2 genes. It is also a form that often exhibits symptoms in the patients' 40s and 50s, much earlier than normal

(Bekris et al., 2010). Further research is necessary before this data on familial AD can be applied to other AD forms. However, changes to pTau occur much earlier and level off later on, and NfL changes occur later, meaning both biomarkers are important. These huge advancements in biomarkers for the diagnosis and tracking of the progression of AD have paved the way for future developments.

AD is a growing global health issue, with millions affected and no known cure. As populations age, the urgency to find preventative strategies increases. This study focuses on a unique population — Okinawan centenarians — who exhibit a lower incidence of AD despite advanced age. This research could reveal insights into AD prevention by exploring the genetic, environmental, and lifestyle factors contributing to centenarians' resilience through their offspring. Identifying protective factors in these individuals may lead to the development of public health strategies to reduce AD risk in the general population, offering new hope for combating this neurodegenerative disease.

2. Experimental Design

In my study, the included subjects must each have at least one biological parent to have made it to the age of 100 and lived in Okinawa. The population of centenarians in Japan, as recorded by the national government in 2023, was 92,139, which is about 73 per 100,000 individuals living in Japan (Japan's Centenarians Reach a Record 92,000, 2023). In Okinawa, the number of centenarians per 100,000 is almost double that of the rest of Japan, according to the Okinawa Centenarian Study (Willcox et al., 2006). Although Japan currently has quite a low birth rate of 1.3 births per woman compared to the United States, 1.6 births per woman, Okinawa has the highest birth rate compared to all other regions of Japan, being the only prefecture to have an increasing population in Japan in 2021 and previous years, according to the Ministry of Internal Affairs and Communications (Japanese Birth Rates Highest in Okinawa and Kyūshū Municipalities, 2024). The offspring of the centenarians were likely born 60-80 years ago when the birth rate was significantly higher, with over three births per woman. I can use these data to calculate a safe estimate of approximately 240 offspring of centenarians from Okinawa that will be willing to participate in the study, given that about 75% agree to participate, which is reasonably accurate based on older studies of centenarians (Yamada et al., 2002).

In phase 1 of the study, I will send out a brief online questionnaire examination for all subjects. The questionnaire will be emailed to the offspring directly to gather information on their daily activities, psychological and medical symptoms, and medical history. To ensure more responses from the targeted subjects, I will also make phone calls to individuals who did not respond to the questionnaire after three days, and I will also offer a $20 incentivization reward to all participants of this stage. The screening will also be extended to the subjects' spouses if they have one and live together. The spouse group will act as a control group as they are more likely to share similar lifestyles and be influenced by environmental factors similar to the centenarian, given they live together. This survey will be modeled after a past study on centenarians of Ikaria, Greece, another blue zone (Legrand et al., 2019). The questions will include (1) Identity: name, birth date, place of birth, and father's name (to distinguish potential namesakes); (2) Location of primary and secondary residences. For the principal residence, participants defined their primary home as isolated; within a village; or within a nursing home; (3) Number of years living in Okinawa; (4) Educational level: abilities in reading, writing, and calculation, all will be scored from 1 to 100 based on standardized tests; (5) School: primary, secondary or higher; (6) Profession before retirement; (7) Monthly income and source: personal, family or state; (8) Family status: single, widow(er), cohabitant, married or divorced; (9) Family environment: number of siblings, number of children, number of people living in the home of the participant; (10) Habits: current or past smoking with the year of cessation, equivalent alcohol consumption in glasses of wine per day. Both smoking and drinking habits will be rated by the participants from 1 (No consumption) to 10 (Heavy daily consumption). In addition to the questions from the Ikaria study, I will include questions about personal health and lifestyle, including the makeup of their diets (consumption of various food types numerically expressed on a scale based on the amount consumed per week), quality, duration, and consistency of their sleep (based on hours slept on average per day and rated from 1 to 10 of sleep quality), as well as about their consumption of Okinawan Propolis (whether they use it and how much they use it). Propolis is a material produced naturally by honey bees and used to treat wounds and other skin issues. It was found to possibly have links to protection from health problems, including AD (Shahinozzaman et al., 2018). Each subject will also complete the Mini-Mental State Examination (MMSE) to screen for cognitive impairment, administered by personnel trained to administer this examination. The local screenings for the MMSE will be held at any local testing center available in Okinawa. However, for screenings for the offspring who have since left Okinawa, the administrator will be sent to each individual's home to conduct the test. Based on previous studies, a cutoff of below 24 out of 30 in the MMSE was chosen to show cognitive impairment (Gluhm et al., 2013).

In phase 2 of the study, all cases (including spouses) that show questionable or definite cognitive impairment in phase 1, according to the MMSE, will be examined for biomarkers of AD. In this phase, all subjects from Phase

1 who demonstrate questionable or definite cognitive impairment based on the MMSE scores will undergo further analysis using advanced biomarkers to diagnose and monitor AD more precisely. The biomarker tests will focus on the A/T/N criteria.

Blood samples will be collected from all participants who scored below 24 on the MMSE. This blood will be analyzed for the Aβ40/42 ratio, phosphorylated tau at position 217 (pT217-tau), and neurofilament light chain (NfL) levels using the previously mentioned biomarker tests. The Aβ 40/42 ratio in serum and plasma will be analyzed, and the results will be compared to normative data from other populations to identify any protective or risk factors. An Aβ 40/42 ratio higher than or equal to 0.170 shows evidence of low risk of AD, a ratio between 0.150-0.169 shows intermediate risk, and a ratio below 0.150 shows evidence of high risk of AD (Quest Diagnostics: Test Directory, 2023). The presence of amyloid plaques will also be confirmed through amyloid PET imaging for those with abnormal ratios. The pT217-tau levels will also be measured in the blood and CSF. Elevated levels will indicate tau pathology, which is a hallmark of AD. Plasma p-tau217 levels of greater than 0.15 pg/mL are often consistent with those who have AD and may be indicative of AD, while those with levels lower than or equal to 0.15 pg/mL are more likely not to have AD (Quest Diagnostics: Test Directory, 2024). NfL levels will be assessed to evaluate the extent of neurodegeneration. High levels of NfL may indicate a higher rate of neuron loss, which is associated with AD progression. One study found control groups to have a mean level of plasma NfL of 34.7 ng/L, while those with AD had mean levels of 51.0 ng/L (Mattsson et al., 2017).

The biomarker data will be integrated with the questionnaire responses to identify patterns and correlations between lifestyle, environmental factors, and AD biomarkers. Statistical models will be used to determine the significance of these relationships and control for potential confounding factors.

Before starting the study, a power analysis will be conducted to determine the minimum sample size needed to detect significant differences between the groups. This ensures the study has enough participants to produce reliable results.

This study will employ various statistical techniques to analyze the relationships between biomarkers, cognitive test scores, and the questionnaire data. Given the different types of data, continuous (e.g., biomarker levels) and categorical (e.g., lifestyle factors), several statistical approaches will be applied to ensure accurate and meaningful results. Statistical analysis will help identify significant protective factors against Alzheimer's disease (AD) in the offspring of Okinawan centenarians and compare them with the control group of spouses. I will use descriptive statistics to summarize the data, including the mean, standard deviation, and range. Frequency and percentages will summarize categorical variables like diet, smoking status, and alcohol consumption. I will then use the Shapiro-Wilk test to determine if the data for continuous variables (e.g., biomarker levels and MMSE scores) follow a normal distribution. If the data are normally distributed, parametric tests will be used. If they are not, non-parametric tests will be employed. These values and tests will describe and detail continuous variables' shape, outliers, center, and spread, including Aβ40/42 ratio, pT217-tau, NfL levels, and MMSE scores.

The cognitive performance (MMSE scores) between groups will be compared using a t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data (Mishra et al.). This will help determine if there is a significant difference in cognitive function between the groups. To explore relationships between continuous variables like biomarkers (Aβ40/42, pT217-tau, NfL) and lifestyle factors (e.g., sleep duration, diet), we will use Pearson's correlation for normally distributed data and Spearman's correlation for non-normally distributed data. This will help identify possible connections between these factors and AD risk found from the biomarker data. For categorical data (e.g., smoking status, alcohol consumption, and Propolis use), a chi-square test will be employed to examine if there are any significant differences in these lifestyle factors between centenarian offspring and non-centenarians.

3. Possible Outcomes

One possible outcome of the study is that the results show a significantly higher level of protection from AD in Okinawa centenarian descendants compared to the general population and that the evidence also leans towards environmental factors being the source of this protection. If the data show that centenarian offspring have a higher level of protection against AD, and the questionnaire reveals specific lifestyle or environmental factors (e.g., diet, sleep quality, or Propolis consumption) that are significantly more common in healthy individuals, this would suggest that these factors play a crucial role in AD resistance. My next steps would involve testing other populations, particularly in other blue zones, to see if similar protective factors are present. Additionally, interventions or public health recommendations could be developed based on these findings to promote these protective factors in broader populations. Further research could explore the mechanisms by which these factors confer protection against AD, potentially leading to new preventative strategies or treatments.

On the other hand, the data could indicate that centenarian offspring have a higher level of protection against AD,

but the questionnaire factors do not significantly correlate with AD resistance. This would suggest that either inherited genetic protective factors might be responsible for their resilience or some other lifestyle or environmental factors that were not covered by my questionnaire are responsible. The next logical step would be to conduct a genetic study of the subjects, focusing on sequencing their genomes to identify potential protective genes or variants that correlate with higher protection from AD. This could involve pinpointing specific genetic differences by comparing the genetic data of the centenarian offspring with those of non-centenarians and the general population as a control group.

If the study fails to recruit enough participants or the participation rate is lower than expected (e.g., fewer than the anticipated 240 offspring of centenarians agree to participate), the study may lack the statistical power needed to draw meaningful conclusions. A smaller sample size can lead to inconclusive results or increased variability, making it challenging to identify significant correlations among the biomarkers, questionnaire factors, and AD resistance. Something I could do to change future studies and achieve higher participation would be to broaden the recruitment criteria to include centenarian offspring from other blue zones or regions with similar characteristics to increase the sample size. I could also implement additional outreach strategies, such as partnering with local healthcare providers or community organizations to boost participation.

If the questionnaire responses are highly variable or inconsistent, it may be challenging to identify clear correlations between lifestyle factors and AD resistance. This could be due to differences in how participants interpret the questions or recall bias in reporting past behaviors. High variability could obscure potential relationships and make it difficult for me to draw definitive conclusions about the role of lifestyle or environmental factors in AD resistance. Although the probability of this outcome is lower because, in this study, I mainly used questions from a previously successful questionnaire for my questionnaire, it is still a possibility. If this happens, I would refine my questions to create questions with multiple-choice answers or force participants to answer using a scale from 1-10.

Another possibility is technical difficulties in conducting the biomarker assays, such as equipment malfunctions, reagent shortages, or inconsistent lab results. These technical issues can lead to data loss, unreliable results, or the need for repeated testing, which can delay the study and increase costs. Ultimately, these problems can lead to complete failure in the study results. To address this challenge, I could establish rigorous quality protocols to ensure the accuracy and reliability of the biomarker assays and invest in higher-quality assays. This could include running pilot tests, using multiple labs for cross-validation, and ensuring consistent reagent supply. I could also have backup biomarker assays or alternative methods available to mitigate the impact of any technical failures. If technical issues arise, I could also consider sending samples to external organizations with high-level laboratories and specialized expertise in AD biomarkers to confirm results and ensure data integrity.

References

ADI — Dementia statistics, (n.d.). Alzint. https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/#:~:text=This%20number%20will%20almost%20double

Anderson, S., (2020). Centenarians as Models of Resistance and Resilience to Alzheimer's Disease and Related Dementias. *Advances in Geriatric Medicine and Research*. https://doi.org/10.20900/agmr20200018

Bekris, L. M., Yu, C.-E., Bird, T. D., & Tsuang, D. W., (2010). Genetics of Alzheimer Disease. *Journal of Geriatric Psychiatry and Neurology*, *23*(4), 213-227. https://doi.org/10.1177/0891988710383571

Breijyeh, Z., & Karaman, R., (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*, *25*(24), 5789. https://doi.org/10.3390/molecules25245789

Corrada, M. M., Brookmeyer, R., Paganini-Hill, A., Berlau, D., & Kawas, C. H., (2010). Dementia Incidence Continues to Increase with Age in the Oldest Old The 90+ Study. *Annals of Neurology*, *67*(1), 114-121. https://doi.org/10.1002/ana.21915

Doecke, J. D., Pérez-Grijalba, V., Fandos, N., Fowler, C., Villemagne, V. L., Masters, C. L., Pesini, P., & Sarasa, M., (2020). Total $A\beta_{42}/A\beta_{40}$ratio in plasma predicts amyloid-PET status, independent of clinical AD diagnosis. *Neurology*, *94*(15), e1580-e1591. https://doi.org/10.1212/wnl.0000000000009240

Gluhm, S., Goldstein, J., Loc, K., Colt, A., Liew, C. V., & Corey-Bloom, J., (2013). Cognitive Performance on the Mini-Mental State Examination and the Montreal Cognitive Assessment Across the Healthy Adult Lifespan. *Cognitive and Behavioral Neurology*, *26*(1), 1-5. https://doi.org/10.1097/wnn.0b013e31828b7d26

Japan's Centenarians Reach a Record 92,000, (2023, September 29). Nippon.com. https://www.nippon.com/en/japan-data/h01786/

Japanese Birth Rates Highest in Okinawa and Kyūshū Municipalities, (2024, May 7). Nippon.com. https://www.nippon.com/en/japan-data/h01975/

Jorm, A. F., & Jolley, D., (1998). The incidence of dementia: a meta-analysis. *Neurology*, *51*(3), 728-733. https://doi.org/10.1212/wnl.51.3.728

Legrand, R., Manckoundia, P., Nuemi, G., & Poulain, M., (2019). Assessment of the Health Status of the Oldest Olds Living on the Greek Island of Ikaria: A Population Based-Study in a Blue Zone. *Current Gerontology and Geriatrics Research*, *2019*, 1-8. https://doi.org/10.1155/2019/8194310

Mattsson, N., Andreasson, U., Zetterberg, H., & Blennow, K., (2017). Association of Plasma Neurofilament Light with Neurodegeneration in Patients With Alzheimer Disease. *JAMA Neurology*, *74*(5), 557. https://doi.org/10.1001/jamaneurol.2016.6117

Mishra, P., Singh, U., Pandey, C. M., Mishra, P., & Pandey, G., (2019). Application of student's t-test, analysis of variance, and covariance. *Annals of cardiac anesthesia*, *22*(4), 407-411. https://doi.org/10.4103/aca.ACA_94_19

Nakanishi, Y., Tsugihashi, Y., Akahane, M., Noda, T., Nishioka, Y., Myojin, T., Kubo, S., Higashino, T., Okuda, N., Robine, J.-M., & Imamura, T., (2021). Comparison of Japanese Centenarians' and Noncentenarians' Medical Expenditures in the Last Year of Life. *JAMA Network Open*, *4*(11), e2131884. https://doi.org/10.1001/jamanetworkopen.2021.31884

Noëlle Warmenhoven, Salvadó, G., Shorena Janelidze, Niklas Mattsson-Carlgren, Bali, D., Anna Orduña Dolado, Kolb, H., Gallen Triana-Baltzer, Barthélemy, N. R., Schindler, S. E., Aschenbrenner, A. J., Raji, C. A., Tammie L.S. Benzinger, Morris, J. C., Ibanez, L., Jigyasha Timsina, Cruchaga, C., Bateman, R. J., Ashton, N., & Arslan, B., (2024). A Comprehensive Head-to-Head Comparison of Key Plasma Phosphorylated Tau 217 Biomarker Tests. *MedRxiv (Cold Spring Harbor Laboratory)*. https://doi.org/10.1101/2024.07.02.24309629

OCS — Part 1 — ORCLS, (n.d.). Okinawa Centenarian Study. https://orcls.org/ocs/

Pais, M. V., Forlenza, O. V., & Diniz, B. S., (2023). Plasma Biomarkers of Alzheimer's Disease: A Review of Available Assays, Recent Developments, and Implications for Clinical Practice. *Journal of Alzheimer's Disease Reports*, *7*(1), 355-380. https://doi.org/10.3233/adr-230029

Quest Diagnostics: Test Directory, (n.d.). Testdirectory.questdiagnostics.com. https://testdirectory.questdiagnostics.com/test/test-guides/TS_AD_Detect_BetaRatioPlasma/quest-ad-detect

Quest Diagnostics: Test Directory, (2024). Questdiagnostics.com. https://testdirectory.questdiagnostics.com/test/test-guides/TS_AD_Detect_Ptau217Plasma/quest-ad-detect-phosphorylated-tau217-p-tau217-plasma

Respect For The Aged Day—Japan's Unique Holiday For Honoring The Elderly, (2021, September 9). More than Tokyo. https://www.morethantokyo.com/elderly-honored-respect-for-the-aged-day/

Shahinozzaman, M., Taira, N., Ishii, T., Halim, M., Hossain, M., & Tawata, S, (2018). Anti-Inflammatory, Anti-Diabetic, and Anti-Alzheimer's Effects of Prenylated Flavonoids from Okinawa Propolis: An Investigation by Experimental and Computational Studies. *Molecules*, *23*(10), 2479. https://doi.org/10.3390/molecules23102479

Terry, D. F., Wilcox, M. A., McCormick, M. A., Pennington, J. Y., Schoenhofen, E. A., Andersen, S. L., & Perls, T. T, (2004). Lower All-Cause, Cardiovascular, and Cancer Mortality in Centenarians' Offspring. *Journal of the American Geriatrics Society*, *52*(12), 2074-2076. https://doi.org/10.1111/j.1532-5415.2004.52561.x

Weston, P. S. J., Poole, T., O'Connor, A., Heslegrave, A., Ryan, N. S., Liang, Y., Druyeh, R., Mead, S., Blennow, K., Schott, J. M., Frost, C., Zetterberg, H., & Fox, N. C., (2019). Longitudinal measurement of serum neurofilament light in presymptomatic familial Alzheimer's disease. *Alzheimer's Research & Therapy*, *11*(1). https://doi.org/10.1186/s13195-019-0472-5

Willcox, D. C., Willcox, B. J., Hsueh, W.-C., & Suzuki, M., (2006). Genetic determinants of exceptional human longevity: insights from the Okinawa Centenarian Study. *AGE*, *28*(4), 313-332. https://doi.org/10.1007/s11357-006-9020-x

Yamada, T., Kadekaru, H., Matsumoto, S., Inada, H., Tanabe, M., Moriguchi, E. H., Moriguchi, Y., Ishikawa, P., Ishikawa, A. G., Taira, K., & Yamori, Y., (2002). Prevalence of dementia in the older Japanese-Brazilian population. *Psychiatry and Clinical Neurosciences*, *56*(1), 71-75. https://doi.org/10.1046/j.1440-1819.2002.00931.x

Copyrights

Copyright for this article is retained by the author(s), with first publication rights granted to the journal.

This is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/).