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Cardiovascular Health and Cognitive Functioning Among Centenarians: A Comparison Between the Tokyo and Georgia Centenarian Studies

Peter Martin, Ph.D.¹, Yasuyuki Gondo, Ph.D.², Yasumichi Arai, M.D., Ph.D.³, Yoshiko Ishioka, Ph.D.⁴, Mary Ann Johnson, Ph.D.⁵, L. Stephen Miller, Ph.D.⁵, John Woodard, Ph.D.⁵, Leonard W. Poon, Ph.D.⁵, and Nobuyoshi Hirose, M.D.⁴

¹Iowa State University

²Osaka University

³Keio University

⁴Tokyo Metropolitan Institute of Gerontology

⁵University of Georgia

Abstract

Objectives—Centenarians have survived into very late life but whether they reach very old age in good health remains unclear. The purpose of this study was to compare the cardiovascular health status and cognitive functioning of centenarians in the United States with centenarians in Japan.

Design, Setting, and Participants—This cross-national design compared centenarians from the United States and Japan. The sample of U. S. centenarians was recruited from the Georgia Centenarian Study and included 287 centenarians. The sample of Japanese centenarians was recruited from the Tokyo Centenarian Study and included 304 centenarians.

Measurements—Cognitive functioning was assessed with a mental status questionnaire, and cardiovascular disease by a health history assessment, blood pressure and selected blood parameters.

Results—The results suggest that Tokyo centenarians had lower disease experiences and BMI values when compared to Georgia centenarians but blood pressure was higher among Japanese centenarians. Lower levels of hemoglobin in Japanese centenarians and higher levels of C-reactive protein in Georgia were also found. The positive association of hypertension and albumin levels with cognitive functioning and the negative association of stroke occurrence with cognitive functioning were replicated in both countries. Differential effects were obtained for heart problems, BMI and C-reactive protein (with positive effects for Tokyo centenarians, except for C-reactive protein).

Corresponding Author: Peter Martin, Ph.D., Department of Human Development & Family Studies, 1096 LeBaron Hall, Iowa State University, Ames, IA 50011, Phone: 515-294-5186, FAX: 515-294-2502, pxmartin@iastate.edu.

Conflicts of Interest:

None

Conclusion—For extremely old individuals, some markers of cardiovascular disease are replicable across countries, whereas differential effects for cardiovascular health also need to be considered in cardiovascular health.

Keywords

centenarians; cardiovascular health; cognitive functioning

One of the most important hopes for centenarians is to remain in good health. However, not all centenarians continue to stay in good health and it is not clear to what extent centenarians escape or simply delay or survive diseases. The purpose of this paper is to directly compare the cardiovascular health and cognitive functioning of centenarians in two countries: The United States and Japan.

It is not clear whether the health status of centenarians is consistent across countries and cultures. We compared long-lived individuals in Japan and the United States with specific focus on cardiovascular disease markers. Japan's current life expectancy is the highest in the world (World Health Organization, 2016) and Japan has relatively low prevalence of disability among oldest-old adults (Kinsella & Velkoff, 2001). Very few studies have conducted a direct comparison of centenarians across countries.

Past centenarian studies have investigated specific diseases. Although some reviews of health among centenarians are organized by centenarians study taking a broad perspective on morbidity profiles (Rasmussen & Andersen-Ranberg, 2016), we primarily focus on findings that specifically address cardiovascular health. Furthermore, we will compare several biomarkers typically associated with cardiovascular functioning across countries.

Previous studies assessing hypertension among centenarians report very different prevalence rates, ranging from 19 percent in Finish centenarians to 65 percent in the Hong Kong centenarian study (Rasmussen & Andersen-Ranberg, 2016). Selim et al. (2005) compared centenarians from the Health Survey of Veteran Enrollees to a younger elderly comparison group age 85 to 99 and noted that centenarians had a lower prevalence of hypertension, angina or myocardial infarction, diabetes and chronic lower back pain. Willcox, Willcox, Wang, He, Rosenbaum, and Suzuki (2008) assessed supercentenarians (those at least 110 years of age) in Okinawa and their results suggest that the majority of supercentenarians had minimal clinically apparent diseases until very late in life, with coronary heart disease (8%), stroke, cancer, and diabetes rare or not evident.

A study of Tokyo centenarians (Takayama et al., 2007) reported that more than 95% of their centenarians had chronic diseases. Most frequently reported diseases included hypertension, heart disease, stroke, fractures, and cataracts, whereas diabetes mellitus was relatively uncommon. Centenarians with hypertension showed a higher level of physical function. The Georgia Centenarian Study reported two clusters of chronic diseases: one resembled a cluster including cardiovascular disease, pneumonia, osteoporosis, anemia, and cancer; and a second cluster including dementia, psychiatric disorders, and neurological disorders (Arnold et al., 2010). The Danish Centenarian Study (Andersen-Ranberg et al., 2001) also showed high levels of morbidity, particularly in hypertension (52%) myocardial infarction (27%) and

strokes (22%). A recent centenarian study from Australia reported relatively low prevalences of chronic conditions, with many centenarians escaping osteoporosis, dementia, cardiovascular disease, respiratory illnesses, cancers, anxiety and depression (Richmond, Law, & KayLamkin, 2012). Hypertension was among the most common conditions. In a Polish sample of centenarians, hypertension was found in 29 percent when the criterion of 160/95mmHg was used and 65 percent if the criterion of 140/90mmHg was used (Zyczkowska, Klich-Raczka, Mossakowska, Gasowski, Wieczorowska-Tobis, & Grodzicki, 2004). A morbidity advantage was found in the next generation as the children of centenarians had a much reduced prevalence of heart disease, hypertension and diabetes when compared to offspring from non-centenarians (Terry, Wilcox, McCormick, Lawler, & Perls 2003).

Some centenarian researchers have reported a paradox of physical health for very old adults, particularly with regard to hypertension (Arai, Sasaki, & Hirose, 2017; Forette 1999; Poon, Johnson, Davey, Dawson, Siegler, & Martin, P., 2000; Robine, Forette, Franceschi, & Allard, 1999). They noted that physical health factors considered to be risk factors in midlife could actually be protective factors in very late life (e.g., body weight, blood pressure, and cholesterol levels; higher body fat). Szewieczek et al. (2015) reported that mildly elevated blood pressure was a marker for better health status in Polish centenarians. With regard to cardiovascular disease, Szewieczek et al. noted a positive relationship between higher blood pressure and cognitive functioning up to a systolic blood pressure of 180.

Specific biomarkers may be important markers of cardiovascular disease. Gareri et al. (1996) reported the prevalence of hypertension was about 19 percent for an Italian group of centenarians but they used the higher cutoff definition of 160 mmHg and/or a diastolic blood pressure over 90 or when centenarians had a history of antihypertensive medication for at least 2 years. The reported blood pressure by Polish centenarians was much higher with a prevalence of 65 percent (Zyczkowska et al., 2004).

Other biomarkers may have multiple functions (e.g. albumin and C-reactive protein). Albumin levels, for example, are indicators of poor nutrition, as well as chronic diseases or acute disease burden (Hausman, Fischer, & Johnson, 2012), and have been reported to be lower among centenarians when compared to a younger age group (Chan, Suzuki, and Yamamoto, 1999). A high serum albumin concentration has been linked to further survival among centenarians (Shimizu, Hirose, Arai, Gondo, & Wakida, 2001). Low serum albumin levels have also been linked with increased odds of cognitive impairment in older adults (Llewellyn, Langa, Friedland, & Lang, 2010; Szewieczek et al., 2015).

Hemoglobin levels have also been reported to be low in a Japanese centenarian study (Hirose et al., 1997) and the Georgia Centenarian Study (Haslam et al., 2012). The prevalence of anemia (low hemoglobin) was 52.1% in Georgia Centenarians and was associated with low albumin, but not with biomarkers of mineral or vitamin status (e.g., serum ferritin, folate, or vitamin B12) (Haslam et al., 2012). Hemoglobin values for an Italian study, however, generally fell within the standard ranges for the healthy adult population (The Italian Multicentric Study on Centenarians, IMSC, 1998). Previous studies have linked low and high hemoglobin concentrations in older persons with a lower level of

cognitive function in old age (Shah, Wilson, Tang, Dong, Murray, & Bennett, 2008) but there may not be a significant association between hemoglobin concentration and cognitive impairment after adjustment for demographics, chronic health conditions, health status, and inflammation (Tamura et al., 2010). However, the association between hemoglobin and cognitive functioning may be stronger in older ages (Huang et al., 2011).

C-reactive protein (CRP) is a marker of active inflammation and has been reported to be lower in centenarians when compared to controls in some studies (Arai et al., 2001), but higher in centenarians when compared to octogenarians in other studies (Haslam et al., 2012). Arai et al. (2001) also noted that centenarians with cognitive impairment exhibited increased CRP. Yaffe et al. (2003) also indicated that there was an association of CRP with cognitive functioning. Taken together, CRP appears to be a promising biomarker for cardiovascular disease (Willcox, Abbott, Yano, Rodriguez, Willcox, and Curb, 2004).

A final biomarker used in this study included the body-mass index (BMI, a ratio of weight to height, kg/m^2 , observed and recorded). In the Georgia Centenarian Study, BMI 20 (underweight) and 25 (overweight or obese) was prevalent in 30.9% and 25.3% of study participants, respectively (Hausman, Johnson, Davey, & Poon, 2011). The same study reported that higher body fat was a predictor of survival in centenarians (Poon et al., 2000). A recent Chinese longevity study indicated that BMI and cognitive function were positively associated for study participants with a relatively low average BMI of around 20 (18.9–21.1, Zhou, Flaherty, Huang, Lu, & Dong, 2010). Results from the Framingham Offspring Study noted that an increased BMI was associated with an adverse effect on all major CHD risk factors (Lamon-Fava, Wilson, & Schaefer, 1996).

Because of the very high prevalence of cognitive impairment among centenarians (Gondo & Poon, 2007), the association between cardiovascular disease and cognitive functioning is important to consider (Vogels, Scheltens, Schroeder-Tanka, & Weinstein, (2007). If cardiovascular disease plays an important role in determining who will develop dementia in very old age and who will not, important prevention programs can be designed.

This study had three specific objectives: First, to compare frequency of cardiovascular diseases. Are Japanese and North American centenarians equally healthy or are there major health disparities? In this study, we will focus on cardiovascular disease, the most common disease among centenarian and other age groups. A second objective was to evaluate cultural differences in biomarkers that are often associated with cardiovascular disease. The third objective was to evaluate the association between cardiovascular disease markers and cognitive functioning. The results would inform us whether cardiovascular health characteristics can be generalized across countries or whether there are unique patterns of health span.

METHODS

Participants and Procedures

Participants of the study included centenarians and near centenarians (98 years and older) from Phase 3 of the Georgia Centenarian Study (Poon et al., 2007) and from the Tokyo

Centenarian Study (Hirose, et al., 2004). Informed consent was obtained before interviewing and testing the centenarians. The survey methodology was very similar across countries. Georgia centenarians were individually visited from 2002–2005 and Tokyo centenarians from 2000–2003 by a team of health practitioners and trained interviewers. Participation rates are depicted in Figure 1.

Georgia Centenarian Study (Phase 3).—The centenarians from this study were from a population-based sample of Georgia (GCS; Poon et al., 2007). This study included 287 community-dwelling and institutionalized centenarians and near-centenarians (98 to 109 years), mean age of 100.3 years ($SD=2.01$) from northern Georgia. Participants were recruited from voter registration rolls and from a random subset of care facilities. Table 1 summarizes information about the participants in the study. The U.S. sample also included 242 proxies. Proxies were most likely to be family members such as daughters (40%), sons (15%), granddaughters (8%), nieces (8%) and wives (6%).

Table 1 indicates that most U.S. centenarians were women (82.2%), White/Caucasian (77.4%), and about 44 percent lived in private homes. Proxy information about the centenarians was obtained for the physical function measure.

Tokyo Centenarian Study.—The Tokyo study (TCS; Gondo et al., 2006) included 304 Japanese centenarians (65 men and 239 women) living in 23 wards of Tokyo's metropolitan area. The mean age of centenarians was 101 years ($SD=1.3$) with an age range from 100 to 106 years. The random sample of centenarians was recruited from residential lists. The Japanese study provided information about centenarians' functional states, characteristics and life history. Table 1 displays detailed information about the TCS participants. The majority of the centenarians in the TCS lived in private homes (67.8%), 25.6% lived in skilled care facilities, and 6.6% lived in hospitals. Among proxies, 54% were the centenarians' child, 19% the spouse of their child, 13% facility staff, and 4% a grandchild.

Table 1 also compares some of the demographic variables across countries. The results for the complete sample suggest that significant sample differences were found for education, residence, and marital status, $\chi^2(2, N= 520) = 97.30, p < .001$; $\chi^2(4, N= 591) = 97.32, p < .001$, and $\chi^2(2, N= 562) = 19.06, p < .001$, respectively. A larger number of U.S. centenarians (41.7%) had college/post college education compared to Japanese centenarians (6.1%), whereas a larger number of Japanese centenarians (57.0%) had less than a high school education compared to U.S. centenarians (28.6%). A relatively higher percentage of U.S. centenarians (5.6%) were currently married compared to 1.4% of Japanese centenarians, whereas more Japanese centenarians were widowed (96.4%) when compared to U.S. centenarians (85.9%).

Measures

The measures included several commonly reported cardiovascular diseases that were recorded in both studies. For example, in the Georgia Centenarian Study participants or their proxies were asked: "Do you have any of these conditions: congestive heart failure, myocardial infarction (heart attack), other heart problem, high blood pressure, or stroke?" In the Tokyo study, participants or their proxies were asked to provide the age of onset and

duration of 25 major diseases including myocardial infarction, angina pectoris, other heart problems, high blood pressure, and stroke. Comparable biomarkers in both studies included body-mass index [weight (kg)/height (m²)], systolic and diastolic blood pressure (mm Hg), albumin (serum, g/dL), hemoglobin (g/dL), and C-reactive protein (serum, mg/dL). BMI and blood chemistry were available only for 165 and 252 centenarians in U. S. Georgia and Tokyo, respectively.

Finally, cognitive functioning was assessed with the total MMSE score (Folstein, Folstein, & McHugh, 1975) to measure global cognitive functioning. The MMSE has been validated for the Japanese sample diagnosed with Alzheimer's disease, left and right hemisphere syndrome, and a non-neurological control group (Mori, Mitani, & Yamadori, 1985). Test-retest reliability and validity checks with the WAIS language, performance, and total score were high (Mori et al., 1985).

Statistical Analyses

Item-by-item comparisons on cardiovascular diseases and cognitive impairment were computed by X² cross tabulations. Mean group differences of cognitive functioning by disease categories and country were assessed with univariate analyses of variance, including interaction effects for country and disease. Finally, multiple regression analyses were computed to assess the effect of age, gender, country, and diseases on cognitive functioning. All analyses were computed with SPSS 21.

RESULTS

Table 2 summarizes the disease results of the comparison between Georgia and Tokyo centenarians. The prevalence of most diseases was significantly higher for Georgia centenarians, except for prevalence of stroke. BMI, hemoglobin, and C-reactive protein were higher in Georgia centenarians, but blood pressure was higher in Tokyo centenarians (Table 3). No differences were observed for albumin levels.

The next analyses included analyses of covariance with disease status as independent and cognitive functioning as dependent variable after controlling for age and gender (Table 4). Main effects were found for country indicating that Georgia centenarians had significantly higher MMSE scores. Main effects were also found for self-reported high blood pressure and stroke, suggesting that centenarians who self-reported high blood pressure had higher MMSE scores, whereas centenarians who had experienced a stroke had lower MMSE scores. Participants with diagnosed heart problems had lower MMSE scores in the United States but higher MMSE scores in Japan when compared to participants who had not been diagnosed with heart problems.

Results of the multiple regression analyses with biomarkers predicting MMSE status are summarized in Table 5. To compare results across countries and to test for interaction effects we computed the multiple regressions first for the entire group and then separately by country. After controlling for age, gender, and country, albumin and high systolic high blood pressure were significantly associated with cognitive functioning indicating that centenarians with higher albumin and blood pressure measures also had higher scores in cognitive

functioning. For the Georgia centenarians, however, higher diastolic blood pressure was related to lower cognitive functioning. For Tokyo centenarians, BMI and CRP were also significant predictors of cognition, indicating that centenarians with higher BMI and lower CRP had higher cognitive scores.

DISCUSSION

Although a number of centenarian studies have reported morbidity profiles of centenarians, a direct comparison of centenarian studies between different countries has not been conducted. We compared centenarians in Tokyo with centenarians in Georgia and compared the prevalence of cardiovascular diseases. We also assessed cultural differences in biomarkers that are often associated with cardiovascular disease and evaluated the association between cardiovascular diseases, biomarkers, and cognitive functioning.

With regard to specific cardiovascular diseases, centenarians from Georgia showed higher prevalence in a number of reported diseases: self-reported high blood pressure, heart disease, and myocardial infarction. Japanese centenarians, on the other hand, had higher prevalence of stroke. The obtained differences in heart diseases may be a result of different lifestyles or particular nutritional differences, in each country. Stroke used to be the leading cause of death in the Japanese population but is now the third-ranked cause of death in Japan (Iso, 2011). Relatively high sodium intake, low calcium and animal protein intakes, and, for middle-aged men, high alcohol consumption, may have contributed to higher mortality from stroke among Japanese populations (Iso, 2011).

The morbidity profile of heart disease is more similar for Georgia and Australian centenarians, whereas the stroke prevalence is more similar between Tokyo and Australian centenarians (Richmond et al., 2012). In comparison to the New England Centenarian Study, the Georgia and Tokyo centenarians reported fewer heart diseases but higher prevalence of hypertension (Evert et al., 2003). The prevalence of myocardial infarction was equivalent for the Georgia and New England studies. The Danish study (Andersen-Ranberg et al., 2001) reported a relatively high stroke prevalence (22 percent), and a high prevalence of hypertension (52 percent) compared to the findings in this study. Prevalence of myocardial infarction (27%) was also relatively high in the Danish study.

The reported hypertension prevalence rates for Georgia and Tokyo centenarians were quite high (48 and 31 percent, respectively) when compared to Gareri et al. (1996) who had reported a prevalence of hypertension of about 19 percent for an Italian group of centenarians. However, these authors had used the higher cutoff definition of 160 mmHg and/or a diastolic blood pressure over 90 or when centenarians had a history of antihypertensive medication for at least 2 years. Lifestyle correlates to higher blood pressure include higher sodium intake, and lower calcium and potassium intake (Gareri et al., 1996). Compared to the Georgia and the Tokyo centenarians, Polish centenarians had a higher prevalence of hypertension (65%, defined as using antihypertensive therapy or systolic blood pressure $\geq$ 140 mm Hg and diastolic $\geq$ 90 mm Hg, Zyzkowska et al., 2004).

With regard to biomarkers, Tokyo centenarians had lower BMI when compared to Georgia centenarians, but measured blood pressure was higher among Japanese centenarians. Lower BMI in Tokyo centenarians could be related to a number of factors such as lower food and energy intake and/or more frailty (e.g., Tokyo centenarians had lower hemoglobin and a higher prevalence of stroke). The higher measured blood pressure values are puzzling, particularly in light of the fact that fewer centenarians in Japan reported hypertension. Perhaps much of the hypertension among Japanese centenarians is unnoticed. Lower levels of hemoglobin may point to higher prevalence of anemia in Japanese centenarians. Anemia levels among centenarians are quite high reaching more than 50 percent in the Georgia sample (Haslam, Hausman, Johnson, Davey, Poon, Allen, & Stabler, 2011). Among Georgia centenarians, higher levels of C-reactive protein may point to higher prevalence of inflammation.

When assessing main and interaction effects of disease and country on cognitive functioning, three results stood out. First, main effects were obtained for country, indicating that centenarians in Tokyo had lower cognitive functioning scores when compared to centenarians in Georgia. Second, stroke was associated negatively with cognitive functioning, whereas measured blood pressure or self-reported hypertension were associated positively with cognitive functioning. Finally, heart problems had a negative effect only among Japanese but not U.S. centenarians.

It is unclear why centenarians in Japan have lower cognitive functioning scores. Perhaps the difference could be explained by lower educational attainment levels among Tokyo centenarians. In addition, the more comprehensive health care system allows older adults to survive longer into very late life with all its negative consequences (Deeg, van Vliet, Kardaun, & Huisman, 2013; Nakagawa & Gondo, 2013). It is no surprise that a history of stroke is negatively associated with cognitive functioning, but the relationship between hypertension and cognitive function may be more surprising. However, some studies did point out that hypertension could have a beneficial effect for cognitive functioning among very old adults (Forette, 1999). Finally, our results on interactive effects of disease and culture also warrant more future research. Diagnosed heart problems might be treated differently in Japan placing very old people at an advantage when compared to U.S. centenarians. Obviously, these findings raise more questions calling for more research.

Some of the effect sizes, even when main effects were obtained, were relatively small (e.g., differences in diastolic blood pressure; differences in effect of stroke on cognitive functioning). These results need to be replicated with larger samples to be confident about the clinical implications of these results. Other effect sizes were larger, such as country differences in systolic blood pressure and BMI. These areas suggest that intervention programs in the United States might be helpful to achieve the same levels as they were obtained in Japan.

The positive association between blood pressure and cognitive function in the combined sample is noteworthy and unique in the oldest old. Similar results have been reported in the past. For example, Nilsson, Read, Berg, Johansson, Melander, and Lindblad (2007) noted that low systolic blood pressure was associated with impaired cognitive function in

longitudinal observations in a population-based sample 80 years and older. Sabayan, van Vliet, de Ruijter, Gussekloo, de Craen, and Westendorp (2013) reported high blood pressure and physical and cognitive function as risk factors of stroke in the Leiden 85-plus Study. However, the results of the combined sample were not replicated for diastolic blood pressure or reported hypertension. Diastolic blood pressure related negatively to cognitive function in the Georgia sample, pointing to potentially different mechanisms of these two blood pressure measures. A positive association of albumin levels with cognitive functioning and the negative association of stroke occurrence with cognitive functioning were replicated in both countries.

Limitations of the current study include different samples in Georgia and Tokyo. The sample in Georgia was somewhat younger, as the inclusion criteria were over 98 years of age. The Georgia sample was better educated, less likely to be widowed, and more likely to live in care facilities. The data in both countries were collected more than 10 years ago, and it is unclear to what extent there are period or cohort effects that may show different health patterns (e.g., Cho, Martin, Margrett, MacDonald, Poon, & Johnson, 2012; Engberg, Andersen-Ranberg, & Jeune, 2008, Suzuki, Akisaka, Ashitomi, Higa, & Nozaki, 1995).

When comparing different studies, it is also not completely assured that the same diagnostic criteria were used or there may be cultural differences in participants' awareness of their diagnosed diseases. Perhaps the patient-physician interaction accounts for some of the differences as well. This should be assessed in future studies. Earlier reports on morbidity (Takayama et al., 2007) used a very comprehensive definition of hypertension (including a diagnosis of the physician, blood pressure measures or treatment for hypertension). In order to make studies comparable across samples, we included self-reported hypertension and actual blood pressure was used as a separate measure. All of these differences may have resulted in differences when comparing countries.

In spite of these limitations, it is important to compare morbidity profiles across cultures. In general, the morbidity profile of Tokyo centenarians may be somewhat better than that of Georgia centenarians (with lower prevalence of common diseases), but some biomarkers are more favorable in the Georgia sample. These results underline the importance of differential survivorship profiles across countries.

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REFERENCES

- Andersen-Ranberg K, Schroll M, & Jeune B (2001). Healthy centenarians do not exist, but autonomous do: A population-based study of morbidity among Danish centenarians. *Journal of Geriatrics Society*, 49, 900–908. doi: 10.1046/j.1532-5415.2001.49180.x
- Arai Y, Hirose N, Nakazawa S, Yamamura K, Shimizu K-I, Takayama M, Ebihara Y, Osono Y, & Homma S (2001). Lipoprotein metabolism in Japanese centenarians: Effects of Apolipoprotein E polymorphism and nutritional status. *Journal of the American Geriatrics Society*, 49, 1434–1441. [PubMed: 11890580]
- Arai Y Sasaki T, & Hirose N (2017). Demographic, phenotypic, and genetic characteristics of centenarians in Okinawa and Honshu, Japan: Part 2 Honshu, Japan. *Mechanisms of Ageing and Development*, 165, 80–85. [PubMed: 28214534]
- Arnold J, Dai J, Nahapetyan L, Arte A, Johnson MA, Hausman D, Rodgers WL, Hensley R, Martin P, MacDonald M, Jazwinski SM, & Poon LW (2010). Predicting successful aging in a population-based sample of Georgia centenarians. *Current Gerontology and Geriatrics Research*, 2010, 1–9. doi:10.1155/2010/989315
- Chan Y-C, Suzuki M, & Yamamoto S (1999). A comparison of anthropometry, biochemical variables and plasma amino acids among centenarians, elderly and young subjects. *Journal of the American College of Nutrition*, 18, 358–365. doi: 10.1080/07315724.1999.10718876. [PubMed: 12038480]
- Cho J, Martin P, Margrett J, MacDonald M, Poon LW, & Johnson MA (2012N). Cohort comparisons in resources and functioning among centenarians: Findings from the Georgia Centenarian Study. *International Journal of Behavioral Development*, 36(4), 271–278.
- Deeg DJH, van Vliet MJG, Kardaun JWPF, & Huisman M Understanding the mortality decline of older age: Improved life course or improved present period? Robine J-M, Jagger C, & Crimmins EM eds. *Annual Review of Gerontology and Geriatrics: Healthy longevity: A global approach* (vol. 33, pp.). New York: Springer, 2013: 261–291.
- Engberg HC, K. Andersen-Ranberg K, & Jeune B (2008). Cohort Changes in Cognitive Function among Danish Centenarians. *Dementia and Geriatric Cognitive Disorders*, 26, 153–160. [PubMed: 18679030]
- Evert J, Lawler E, Bogan H, Perls TT (2003). Morbidity profiles of centenarians: Survivors, delayers, and escapers. *Journal of Gerontology, Series A: Biological Sciences and Medical Sciences*, 58A, 232 – 237.
- Folstein MF, Folstein SE, & McHugh PR (1975). “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198. [PubMed: 1202204]
- Forette B 1999 Are common risk factors relevant in the eldest old? In Robine J-M, Forette B, Franceschi C, & Allard M (Eds.), *The paradoxes of longevity* (pp.73–79). Berlin: Springer.
- Franke H (1987). *Hoch und Höchstbetagte* [Old- and oldest old adults]. Berlin: Springer.
- Gareri P, Lacava R, Rossi MG, Lorio C, Galasso MA, Pansini L, Curti A, Mercurio M, Olivo D, & Mattace R (1996). Hypertension in a group of centenarians. *Archives of Gerontology and Geriatrics*, 22, 373–376. [PubMed: 18653059]
- Gondo Y, Hirose N, Arai Y, Inagaki H, Masui Y, Yamamura K, Shimizu K-I, Takayama M, Ebihara Y, Nakazawa S, & Kitagawa K (2006). Functional status of centenarians in Tokyo, Japan: Developing better phenotypes of exceptional longevity. *Journal of Gerontology: Medical Sciences*, 61A(3), 305–310.
- Gondo Y & Poon LW (2007). Cognitive function of centenarians and its influence on longevity. *Annual Review of Gerontology and Geriatrics*, 27, 129–150.
- Haslam A, Hausman DB, Johnson MA, Davey A, Poon LW, Allen RH, & Stabler SP (2011). Prevalence and predictors of anemia in a population-based study of octogenarians and centenarians in Georgia. *Journal of Gerontology: Medical Sciences*, 67A, 100–106. doi: 10.1093/gerona/glr151
- Hausman DB, Johnson MA, Davey A, & Poon LW (2010). Body mass index is associated with dietary patterns and health conditions in Georgia centenarians. *Journal of Aging Research*, 2011, 1–10. doi: 10.4061/2011/138015

- Hausman DB, Fisher JG, & Johnson MA (2012). Protein, lipid, and hematological biomarkers in centenarians: definitions, interpretation and relationships with health. *Maturitas*, 71, 205–212. [PubMed: 22209200]
- Hirose N, Arai Y, Gondo Y, Nakazawa S, Takayama M, Ebihara Y, ... Kojima T (2004). Tokyo Centenarian Study: Aging inflammation hypothesis. *Geriatrics and Gerontology International* 4: S182–S185. doi: 10.1111/j.1447-0594.2004.00194.x
- Hirose N, Arai Y, Kawamura M, Homma S, Hasegawa H, Ishida H, Shimizu K, Osono Y, Takeda S, Noji H, Homma A, & Nakamura Y (1997). Tokyo Centenarian Study. 5. Nutritional status of Japanese centenarians. *Nihon Ronen Igakkai Zasshi*, 34, 324–330. [PubMed: 9212688]
- Holtsberg PA, Poon LW, Noble CA, & Martin P (1995). Mini-Mental State Exam Status of community dwelling, cognitively intact centenarians. *International Psychogeriatrics*, 7, 417–427. [PubMed: 8821349]
- Huang J, Schmeidler J, Beeri MS, Rosendorff C, Bhatia S, West RK, Bepalova IN, Mavris R, Silverman JM (2012). Haemoglobin A_{1c} and cognitive function in very old, cognitively intact men. *Age and Ageing*, 41, 125–128. doi: 10.1093/ageing/afr124 [PubMed: 21930529]
- Iso H (2011). A Japanese health success story: trends in cardiovascular diseases, their risk factors, and the contribution of public health and personalized approaches. *European Association for Predictive, Preventive and Personalised Medicine*, 2, 49–57. doi: 10.1007/s13167-011-0067-0
- Lamon-Fava S, Wilson PWF, & Schaefer EJ (1996). Impact of body mass index on coronary heart disease risk factors in men and women. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 16, 1509–1515. doi: 10.1161/01.ATV.16.12.1509.
- Llewellyn DJ, Langa KM, Friedland RP, & Lang IA (2010). Serum albumin concentration and cognitive impairment. *Current Alzheimer's Research*, 7, 91–96.
- Mori E, Mitani Y, & Yamadori (1985). Usefulness of a Japanese version of the Mini-Mental State Test in neurological patients. *Shinkei Shinrigaku*, 1, 2–10.
- Nakagawa T, & Gondo Y Health care system and policy implications for older adults in Japan. Scharlach AE, & Hoshino K Healthy aging in sociocultural context New York: Routledge 2013: 53–61.
- Nilsson SE, Read S, Berg S, Johansson B, Melander A, & Lindblad U (2007). Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older. *Aging Clinical and Experimental Research*, 19(1):41–47. [PubMed: 17332720]
- Poon LW, Jazwinski SM, Green RC, Woodard JL, Martin P, Rodgers WL, Johnson MA, Hausman D, Arnold J, Davey A, Batzer MA, Markesbery WR, Gearing M, Siegler IC, Reynolds S, & Dai J (2007). Methodological considerations in studying centenarians: Lessons learned from the Georgia Centenarian Studies. In Poon LW & Perls TT (Eds.), *Annual Review of Gerontology and Geriatrics*, Vol. 27. Biopsychosocial approaches to longevity (pp. 231–264). New York: Springer.
- Poon LW, Johnson MA, Davey A, Dawson DV, Siegler IC, Martin P (2000) Psycho-social predictors of survival among centenarians. In Martin P, Rott C, Hagberg B, & Morgan K (Eds.), *Centenarians: Autonomy versus dependence in the oldest old* (pp. 77–89). New York: Springer Publishing Company.
- Rasmussen SH, & Andersen-Ranberg K (2016). Health in centenarians. In: Pacana NA (Ed.), *Encyclopedia of geropsychology* (pp. 1005–1018). Singapore: Springer.
- Richmond RL, Law J, & KayLambkin F (2012). Morbidity profiles and lifetime health of Australian centenarians. *Australasian Journal on Ageing*, 31(4), 227–232. doi: 10.1111/j.1741-6612.2011.00570.x [PubMed: 23252980]
- Robine J-M, Forette B, Franceschi C, & Allard M (1999). *The paradoxes of longevity* Berlin: Springer.
- Sabayan B, van Vliet P, de Ruijter W, Gussekloo J, de Craen AJ, Westendorp RG. (2013). High blood pressure, physical and cognitive function, and risk of stroke in the oldest old. *Stroke*, 44, 15–20. doi: 10.1161/STROKEAHA.112.663062. [PubMed: 23132780]
- Selim AJ, Fincke G, Berlowitz DR, Miller, Qian SX, Lee A, ... Kazis LE (2005). Comprehensive health status assessment of centenarians: Results from the 1999 large health survey of veteran enrollees." *Journal of Gerontology, Series A: Biological Sciences and Medical Sciences*, 60, 515–519.

- Shah RC, Wilson RS, Tang Y, Dong X, Murray A, & Bennett DA (2009). Relation of hemoglobin to level of cognitive function in older persons. *Neuroepidemiology* 32, 40–46. doi: 10.1159/000170905 [PubMed: 19001795]
- Shimizu K, Hirose N, Arai Y, Gondo Y, & Wakida Y (2001). Determinants of further survival in centenarians. *Geriatrics & Gerontology International*, 1, 14–17.
- Suzuki M, Akisaka M, Ashitomi I, Higa K, & Nozaki H (1995). Chronological study concerning ADL among Okinawan centenarians. *Dementia and Geriatric Cognitive Disorders*, 26, 153–160.
- Szewieczek J, Dulawa J, Francuz T, Legierska K, Hornik B, Włodarczyk-Sporek I... Batko-Szwaczka A (2015). Mildly elevated blood pressure is a marker for better health status in Polish centenarians. *Age*, 37, 4. Doi: 10.1007/s11357-014-9738-9
- Takayama M, Hirose N, Arai Y, Gondo Y, Shimizu K, Ebihara Y, Yamamura K, Nakazawa S, Inagaki M, Masui Y, & Kitagawa K (2007). Morbidity of Tokyo-area centenarians and its relationship to functional status. *Journal of Gerontology: Medical Sciences*, 62A, 774–782.
- Tamura MK, Wadley VG, Newsome BB, Zakai NA, McClure LA, Howard G, Warnock DG, & McClellan W (2010). Hemoglobin concentration and cognitive impairment in the Renal Reasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *Journal of Gerontology: Series A, Biological Sciences and Medical Sciences*, 65, 1380–1386. doi: 10.1093/gerona/gdq126
- Terry DF, Wilcox M, McCormick MA, Lawler E, & Perls TT (2003). Cardiovascular advantages among the offspring of centenarians. *Journal of Gerontology: Series A: Biological Sciences and Medical Sciences*, 58A, M425–M431.
- The Italian Multicentric Study on Centenarians (IMSC) (1998). Laboratory parameters of Italian centenarians. *Archives of Gerontology and Geriatrics*, 27, 67–74. [PubMed: 18653152]
- Vogels RLC, Scheltens P, Schroeder-Tana JM, & Weinstein HC (2007). Cognitive impairment in heart failure: A systematic review of the literature. *European Journal of Heart Failure*, 9, 440–449. doi: 10.1016/j.ejheart.2006.11.001 [PubMed: 17174152]
- Willcox BJ, Abbott RD, Yano K, Rodriguez BL, Willcox DC, & Curb JD (2004). C-reactive protein, cardiovascular disease and stroke: new roles for an old biomarker. *Expert Review in Neurotherapeutics*, 4, 507–518.
- Willcox DC, Willcox BJ, He Q, Wang N, & Suzuki M (2008). They really are that old: A validation study of centenarian prevalence in Okinawa. *Journal of Gerontology: Series A: Biological Sciences and Medical Sciences*, 63, 338–349.
- Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky Kuller L, Rubin S, & Harris T (2003). Inflammatory markers and cognitive functioning African-American and white elders. *Neurology*, 61, 76–80. [PubMed: 12847160]
- Zhou Y, Flaherty JH, Huang CQ, Lu ZC, & Dong BR (2010). Association between body mass index and cognitive function among Chinese nonagenarians/centenarians. *Dementia and Geriatric Cognitive Disorders*, 30, 517–24. doi: 10.1159/000322110. [PubMed: 21252546]
- Zyczkowska J, Klich-Raczka A, Mossakowska M, Gasowski J, Wieczorowska-Tobis K, & Grodzicki T (2004). Blood pressure in centenarians in Poland. *Journal of Human Hypertension*, 18(10), 713–716. doi: 10.1038/sj.jhh.1001728 [PubMed: 15085168]

Figure 1.
Flowchart of study participants.

Table 1

Demographic Characteristics of Complete Sample

Demographic Characteristics	United States (GCS)	Japan (TCS)	χ^2
Number of Centenarians	<i>N</i> =289	<i>N</i> =304	--
Age in years <i>M</i> (<i>SD</i>)	100.3 (2.00)	101.1 (1.74)	--
Gender			1.22
Women	82.2%	78.6%	--
Men	17.8%	21.4%	--
Ethnicity			--
White/Caucasian	77.4%	--	--
Black/African-American	22.6%	--	--
Asian	--	100%	--
Education			97.30 ***
Less than High School	28.6%	57.0%	--
High School	30.4%	36.9%	--
College/Post-Graduate	41.7%	6.1%	--
Residential Status			97.32 ***
Private Home	44.3%	67.8%	--
Personal Care Home	19.2%	--	--
Nursing Home	36.6%	25.7%	--
Hospital	--	6.6%	--
Marital Status			19.06 ***
Married/Partner	5.6%	1.4%	--
Widowed	85.9%	96.4%	--
Other	8.5%	2.2%	--
Cognitive Functioning			
MMSE, Mean (<i>SD</i>)	16.83 (8.80)	12.45 (8.64)	5.92 ***

Note. Because of rounding, percentages may not add to 100. GCS= Georgia Centenarian Study; and TCS= Tokyo Centenarian Study.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 2

Comparison of Cardiovascular Problems for Georgia and Tokyo Centenarians

Disease	Georgia		Tokyo		χ^2
	<i>N</i>	Percent	<i>N</i>	Percent	
Reported High Blood Pressure	117	48.1	94	31.1	16.44 ***
Heart Problems	69	30.3	55	18.2	10.53 **
Myocardial Infarction	26	10.8	13	4.3	8.45 **
Stroke	18	9.3	48	15.9	4.48 *

*
 $p < .05$.**
 $p < .01$.***
 $p < .001$.

Table 3

Mean Group Differences for BMI, Blood Pressure and Biomarkers Comparing Georgia and Tokyo Centenarians

	Georgia <i>M</i>	Tokyo <i>M</i>	<i>F</i>	η^2
BMI	22.61 (0.27)	19.70 (0.31)	50.32 ***	.11
Systolic Blood Pressure	127.75 (1.29)	142.09 (1.25)	64.14 ***	.12
Diastolic Blood Pressure	73.79 (0.73)	77.10 (0.72)	10.44 **	.02
Albumin (g/dl)	3.67 (0.03)	3.63 (0.03)	1.15	.00
Hemoglobin (g/dl)	12.01 (0.10)	11.24 (0.10)	31.04 ***	.06
C-Reactive Protein (mg/dL)	9.27 (1.12)	6.46 (1.05)	3.38	.01

Note. Standard errors are included in the parentheses.

**
 $p < .01$.

 $p < .001$.

Table 4
Mean Group Differences for Cognitive Functioning (MMSE) By Country and Disease Category

	GCS		TCS		F_c	η^2	F_d	η^2	$F_{c \times d}^*$
	no	yes	no	yes					
Reported									
High Blood Pressure	15.88	16.54	11.77	14.33	16.64 ^{***}	.03	4.35 [*]	.04	1.55
Heart Problems	17.14	13.68	11.93	15.27	4.19 [*]	.01	0.01		14.77 ^{***}
Myocardial Infarction	15.88	17.88	12.67	10.82	10.79 [*]	.02	0.00		1.52
Stroke	16.48	12.15	13.14	9.55	6.32 [*]	.01	11.54 ^{**}	.02	0.10

Note. F_c refers to main effects of culture, F_d refers to main effect of disease, $F_{c \times d}$ refers to interaction effect of culture and disease. Age and gender were included as covariates.

* $p < .05$.

** $p < .01$.

*** $p < .001$

Table 5
Association Between Biomarkers and Cognitive Functioning for Georgia and Tokyo Centenarians

	Total			Georgia			Tokyo		
	B	SE	β	B	SE	β	B	SE	β
Age	-0.72 (-1.15; -0.29)	0.22	-.15 ^{**}	-1.23 (-1.77; -0.69)	0.27	-.28 ^{***}	-0.12 (-0.85; 0.60)	0.37	-.03
Gender	-3.68 (-5.66; -1.70)	1.00	-.16 ^{***}	-2.78 (-5.59; -0.02)	1.42	-.12 ⁺	-4.60 (-7.55; -1.64)	1.50	-.22 ^{**}
Country	-4.34 (-6.19; -2.49)	0.94	-.24 ^{***}						
BMI	0.11 (-0.09; 0.31)	0.10	.05	0.10 (-0.14; 0.34)	0.12	.05	0.44 (0.06; 0.82)	0.19	.17 [*]
Blood Pressure ¹									
Systolic Blood Pressure	0.05 (0.01; 0.09)	0.02	.11 [*]	0.02 (-0.05; 0.09)	0.04	.03	0.04 (-0.03; 0.09)	0.03	.12
Diastolic Blood Pressure	-0.01 (-0.09; 0.06)	0.04	-.02	-0.12 (-0.23; 0.00)	0.06	-.12 [*]	0.04 (-0.05; 0.14)	0.05	.06
Hypertension	0.97 (-0.70; 2.64)	0.85	.05	-0.10 (-2.26; 2.05)	1.09	-.01	1.81 (-0.80; 4.42)	1.32	.10
Albumin	7.08 (4.79; 9.30)	1.15	.31 ^{***}	8.06 (4.80; 11.33)	1.66	.33 ^{***}	5.91 (2.58; 9.25)	1.69	.29 ^{**}
C-Reactive Protein	-0.04 (-0.09; 0.01)	0.03	-.08 ⁺	-0.02 (-0.08; 0.05)	0.03	-.03	-0.10 (-0.18; -0.01)	0.04	-.18 [*]
Hemoglobin	-0.32 (-0.86; 0.23)	0.28	-.06	-0.15 (-0.90; 0.61)	0.38	-.02	-0.37 (-1.17; 0.43)	0.41	-.07
Adjusted R ²	.26			.23			.24		
F	13.61 ^{***}			6.44 ^{***}			8.63 ^{***}		

Note. Blood pressure variables were entered separately. Values in parentheses are lower- and upper-bound confidence intervals. *F* is explained variance after controlling for age, gender, and country.

$p < .001$
 $***$
 $p < .01$
 $**$
 $p < .05$
 $*$
 $p > .10$
 $+$

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