



Original Investigation | Geriatrics

Association Between Adverse Childhood Experiences and Dementia in Older Japanese Adults

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Abstract

IMPORTANCE The prevalence of dementia in Japan has been increasing. Childhood poverty has been associated with increased risk of cognitive impairment, possibly mediated by individuals' educational paths. However, the associations between dementia and adverse childhood experiences other than poverty and education have not been well documented.

OBJECTIVE To examine the association between adverse childhood experiences and dementia onset among Japanese individuals born before 1948 who grew up during and after World War II.

DESIGN, SETTING, AND PARTICIPANTS A 3-year (2013-2016) follow-up was performed of 17 412 participants in the Japan Gerontological Evaluation Study, a population-based cohort study of adults aged 65 years or older. Data were analyzed in December 2019.

MAIN OUTCOMES AND MEASURES Dementia onset was assessed through the public long-term care insurance system. Adverse childhood experiences before the age of 18 years were assessed by survey at baseline. Seven adverse childhood experiences were assessed: parental death, parental divorce, parental mental illness, family violence, physical abuse, psychological neglect, and psychological abuse. Participants were classified according to whether they had 0, 1, 2, or 3 or more adverse childhood experiences. Cox regression models were used to estimate hazard ratios for the risk of dementia.

RESULTS Among 17 412 participants (9281 women [53.3%]; mean [SD] age, 73.5 [6.0] years), dementia occurred in 703 participants (312 men and 391 women) during a mean follow-up of 3.2 years (range, 2.4-3.3 years). Among all participants, 6804 (39.1%) were older than 75 years; 10 968 (63.0%) reported 0 adverse childhood experiences, 5129 (29.5%) reported 1 adverse childhood experience, 964 (5.5%) reported 2 adverse childhood experiences, and 351 (2.0%) reported 3 or more adverse childhood experiences. Participants who experienced 3 or more adverse childhood experiences had a greater risk of developing dementia compared with those who grew up without adverse childhood experiences, after adjustment for age, sex, childhood economic hardship, nutritional environment, and education (hazard ratio, 2.18; 95% CI, 1.42-3.35). After successive adjustment for adult sociodemographic characteristics, social relationships, health behavior, and health status, this hazard ratio was attenuated but remained statistically significant (1.78; 95% CI, 1.15-2.75; $P = .009$).

CONCLUSIONS AND RELEVANCE This study found that having 3 or more adverse childhood experiences was associated with increased dementia risk among older Japanese adults.

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Key Points

Question Are adverse childhood experiences associated with the onset of dementia later in life?

Findings In a large-scale cohort study of 17 412 older Japanese adults, the cumulative number of adverse childhood experiences was associated with an increased risk of developing dementia.

Meaning Having 3 or more adverse childhood experiences was associated with increased dementia risk among older Japanese adults.

+ Supplemental content

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Introduction

With population aging, dementia is a major public health concern globally.^{1,2} Approximately 47 million people had dementia in 2015 worldwide, and this number is expected to triple by 2050.² To address the dementia epidemic, an appropriate evidence-based prevention strategy is needed. A recent review² examined the life-course model of the contributions of modifiable risk factors associated with dementia, including education, hearing loss, hypertension, obesity, smoking, depression, physical inactivity, social isolation, and diabetes. In that model, education showed the second highest percentage in terms of the contribution to the onset of dementia,² suggesting that childhood environment is crucial to developing enough cognitive reserve to prevent dementia.³ Previous studies^{4,5} reported that childhood poverty is associated with cognitive impairment, perhaps mediated by individual's educational path. However, the associations between dementia and adverse childhood experiences other than education and poverty are not well documented.

Early life exposure to adverse childhood experiences, including parental loss, family psychopathology, and child maltreatment, may be associated with dementia. Direct associations of adverse childhood experiences with dementia can be explained by studying the brain. For example, individuals who experienced adverse childhood experiences show deficits in brain structure and function.^{6,7} An indirect outcome of adverse childhood experiences on dementia is also possible—that is, adverse childhood experiences are associated with smoking, obesity, and depression, which are well known to be associated with dementia.^{8,9} Several epidemiological studies¹⁰⁻¹⁶ have demonstrated an association between the components of adverse childhood experiences, such as parental death, and cognitive function or dementia in later life. However, comprehensive assessments of the associations of adverse childhood experiences with dementia are scarce, despite multiple types of adverse childhood experiences often co-occurring.^{8,17} Most of the studies investigating the association between each component of adverse childhood experiences and dementia have small sample sizes of fewer than 500 people and are cross-sectional studies. Moreover, to our knowledge, no study of whether sex differences exist has ever been performed. Dementia prevalence and risk factors vary by sex, possibly because of sex differences in brain development and biological responses to environmental factors, such as adversities, and sex disparities in the level of risk factors of dementia, such as educational attainment.¹⁸ Sex differences have been identified for adverse childhood experiences and other subsequent adulthood outcomes, such as physical health problems and well-being.¹⁹⁻²² Therefore, the association between adverse childhood experiences and dementia incidence may also differ between men and women.

Japan is in a unique case for the investigation of the association between adverse childhood experiences and dementia for 2 reasons. First, Japanese people have the greatest longevity; thus, we can include a large number of older-old (ie, ≥ 75 years old) individuals in this investigation.²³ Second, older Japanese people experienced World War II (1937-1945), which might be associated with adverse childhood experiences. More than one-fifth of Japanese older adults (born before 1948) experienced parental death before the age of 18 years, and the cumulative number of adverse childhood experiences has been associated with a higher level of functional limitations in later life.²⁴ Therefore, older Japanese adults who experienced harmful events resulting from the war might have an increased risk of onset of dementia later in life.

The Japan Gerontological Evaluation Study is a large-scale cohort study of community-dwelling older Japanese people. Baseline surveys were administered in 2013 to individuals aged 65 years and older who were physically and cognitively independent and then were linked to data on the incidence of dementia until 2016. The participants were born during the period from 1915 to 1948 and grew up during and after World War II. Using these data, we examined the association between adverse childhood experiences and the subsequent emergence of dementia among older adults separately in men and women.

Methods

Study Design and Participants

The Japan Gerontological Evaluation Study was established to evaluate the social determinants of healthy aging in Japan.^{25,26} The baseline survey was conducted between October and December 2013 for older people living in 24 municipalities throughout Japan. Self-reported questionnaires were distributed by mail to 151 324 people aged 65 years or older without functional disabilities, which was defined as not being certified as eligible for benefits from the long-term care insurance system.²⁷ Participants were informed that participation in the study was voluntary and that completing and returning the questionnaire via mail indicated their consent to participate in the study. The protocol of this study was approved by the Ethics Committees on Research on Human Subjects at Nihon Fukushi University. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

A simple random sample was obtained in large municipalities, as well as a complete census of older residents in smaller municipalities. A total of 107 183 participants returned the questionnaire (response rate, 71%), and data for 98 803 of them (92%) were linked to information on dementia onset during the 3-year follow-up period. One-fifth of the sample (19 842 participants) was randomly selected to receive the survey module inquiring about adverse childhood experiences. The following participants were excluded: 100 participants receiving treatment for dementia at baseline survey, 2286 participants missing responses to the questions regarding adverse childhood experiences, and 44 participants who reported that they received care and assistance during walking, bathing, and toileting in their daily lives.

Dementia Outcome

Dementia incidence was ascertained during the follow-up period, from 2013 to 2016 (mean [range], 3.2 [2.4-3.3] years), by linking the cohort participants to the standardized in-home assessment and medical examination conducted under Japan's public long-term care insurance registry.²⁷ The details of the assessment of dementia have been reported elsewhere.²⁸ In brief, trained investigators determined the eligibility for benefits (eg, a home helper or day care) for the applicants by evaluating the following statuses: physical function, activities of daily living, cognitive function, mental and behavioral disorders, adaptation to social life, and past medical treatment.^{29,30} Investigators classified the applicants on a dementia scale according to the severity of their cognitive impairment.^{28,31,32} A validation study showed a high correlation with the Mini-Mental State Examination (Spearman rank correlation $\rho = -0.74$).³³ In this study, dementia was defined as level II or higher on the dementia scale—that is, a condition with manifesting at least some symptoms, behaviors, or communication difficulties that hinder daily activities (level II corresponds to a 16-point rating on the Mini-Mental State Examination),³³ as described elsewhere.^{28,32,34}

Adverse Childhood Experiences

Adverse childhood experiences were assessed using a self-reported questionnaire at baseline. We developed the adverse childhood experience questionnaire for older Japanese people^{24,35} on the basis of the Adverse Childhood Experiences Study.⁸ The adverse childhood experience questionnaire consists of 7 questions, querying whether participants had the following experiences before the age of 18 years: interpersonal loss (parental loss or parental divorce), family psychopathology (parental mental illness or family violence), and abuse and neglect (physical abuse, psychological neglect, or psychological abuse). Participants were classified according to whether they had experienced 0, 1, 2, or 3 or more total adverse childhood experiences. Participants who experienced 4 or more adverse childhood experiences accounted for only 0.65% of the sample; therefore, we combined the participants who had 3 or more experiences into 1 category.

Covariates

Covariates were assessed by a self-administered questionnaire. Age at baseline was categorized into 4 groups (65-69, 70-74, 75-79, and ≥ 80 years; corresponding birth years are 1944-1948, 1939-1943, 1934-1938, and 1933 and before, respectively). We included childhood economic hardship and height as other childhood environmental factors. Childhood economic hardship was assessed by a question about whether the family's financial condition was difficult during childhood (yes or no response).²⁴ Height was used as a proxy for childhood nutritional environment³⁶ and was categorized into 5 groups at 5-cm intervals for each sex (for men, <155, 155-159.9, 160-164.9, 165-169.9, and ≥ 170 cm; for women, <145, 145-149.9, 150-154.9, 155-159.9, and ≥ 160 cm).^{37,38} We included education as an environmental factor from childhood to adolescence and categorized it into 3 groups by years of schooling (≤ 9 , 10-12, or ≥ 13 years).³⁸ We included adult sociodemographic characteristics (current annual household income and longest held occupation), current social relationships (marital status, frequency of meeting friends, social participation, and employment status), health behavior (smoking), and health status (body mass index [calculated as the weight in kilograms divided by height in meters squared], depressive symptoms, hypertension, diabetes, and hearing loss) as potential mediators. The longest held occupation was categorized as nonmanual (professional, technical, or managerial), manual (clerical, sales or service, skilled labor, agricultural, forestry, fishery, or other), and no occupation.³⁸ The assessment of current social relationships included frequency of meeting friends and acquaintances and social participation in a variety of groups or activities, including volunteer groups, sports groups, leisure activity groups, senior citizens' clubs, and neighborhood or residents' associations.³⁸ Depressive symptoms were assessed by the 15-item short form of the Geriatric Depression Scale (Japanese version).³⁹ For hypertension, diabetes, stroke, heart disease, and hearing loss, participants were asked whether they were currently being treated or had sequelae. Covariates with missing data were categorized as missing, and participants with missing data on the covariates were included in the analysis.

Statistical Analysis

Cox proportional hazards models were estimated, yielding hazard ratios (HRs) and 95% CIs for dementia incidence during the 3-year follow-up period. Model 1 was adjusted for age, sex, other childhood environmental factors (economic hardship and height), and education. Model 2 was also adjusted for adult health status associated with cardiovascular risk (hypertension, diabetes, stroke, and heart disease). Model 3 was further adjusted for adult sociodemographic characteristics (annual income and longest occupation), social relationships (marital status, frequency of meeting friends, social participation, and employment status), and health behavior (smoking). Model 4 was further adjusted for health status (body mass index, depressive symptoms, and hearing loss). Subsequently, data were analyzed separately for men and women because the interaction term between sex and adverse childhood experiences showed marginal interaction effect ($P = .17$), and sex differences were reported in studies that examined adverse childhood experiences and subsequent health outcomes.¹⁹⁻²² We applied the multiple imputation methods for adequately addressing missing data on covariates. We generated 50 imputed data sets using the multiple imputation by chained equations with the `mi impute chained` command in Stata. We performed a mediation analysis to evaluate the mediation effects of adult sociodemographic characteristics, social relationships, health behavior, and health status using the binary mediation command in Stata. All analyses were conducted using Stata statistical software version 14 (StataCorp). Two-sided $P < .05$ (Pearson χ^2 test) was considered statistically significant. Data were analyzed in December 2019.

Results

The analytic sample for the present study included 17 412 participants (8131 men [46.7%] and 9281 women [53.3%]; mean [SD] age, 73.5 [6.0] years). **Table 1** shows the characteristics of participants. Among all participants, 6804 (39.1%) were older than 75 years, 12 653 (72.7%) were married, 4106

Table 1. Baseline Characteristics of Older Japanese Men and Women

| Characteristic | Participants, No. (%) | | |
|--|-----------------------|----------------|------------------|
| | Total (N = 17 412) | Men (n = 8131) | Women (n = 9281) |
| Age, y | | | |
| 65-69 | 5201 (29.9) | 2495 (30.7) | 2706 (29.2) |
| 70-74 | 5407 (31.1) | 2503 (30.8) | 2904 (31.3) |
| 75-79 | 3794 (21.8) | 1783 (21.9) | 2011 (21.7) |
| ≥80 | 3010 (17.3) | 1350 (16.6) | 1660 (17.9) |
| Adverse childhood experiences | | | |
| Interpersonal loss | | | |
| Parental death | 3929 (22.6) | 1881 (23.1) | 2048 (22.1) |
| Parental divorce | 326 (1.9) | 185 (2.3) | 141 (1.5) |
| Family psychopathology | | | |
| Parental mental illness | 121 (0.7) | 74 (0.9) | 47 (0.5) |
| Family violence | 638 (3.7) | 359 (4.4) | 279 (3.0) |
| Abuse and neglect | | | |
| Physical abuse | 221 (1.3) | 155 (1.9) | 66 (0.7) |
| Psychological neglect | 2121 (12.2) | 1182 (14.5) | 939 (10.1) |
| Psychological abuse | 899 (5.2) | 463 (5.7) | 436 (4.7) |
| No. of adverse childhood experiences | | | |
| 0 | 10 968 (63.0) | 4872 (59.9) | 6096 (65.7) |
| 1 | 5129 (29.5) | 2523 (31.0) | 2606 (28.1) |
| 2 | 964 (5.5) | 529 (6.5) | 435 (4.7) |
| ≥3 | 351 (2.0) | 207 (2.5) | 144 (1.6) |
| Other childhood environmental factors | | | |
| Economic hardship | | | |
| No | 9528 (54.7) | 3847 (47.3) | 5681 (61.2) |
| Yes | 7762 (44.6) | 4238 (52.1) | 3524 (38.0) |
| Missing | 122 (0.7) | 46 (0.6) | 76 (0.8) |
| Height ^a | | | |
| Short | 1535 (8.8) | 532 (6.5) | 1003 (10.8) |
| Middle-short | 3667 (21.1) | 1208 (14.9) | 2459 (26.5) |
| Middle | 5733 (32.9) | 2515 (30.9) | 3218 (34.7) |
| Middle-tall | 4098 (23.5) | 2275 (28.0) | 1823 (19.6) |
| Tall | 2090 (12.0) | 1500 (18.4) | 590 (6.4) |
| Missing | 289 (1.7) | 101 (1.2) | 188 (2.0) |
| Education, y | | | |
| ≤9 (Low) | 6926 (39.8) | 2961 (36.4) | 3965 (42.7) |
| 10-12 (Middle) | 6557 (37.7) | 2875 (35.4) | 3682 (39.7) |
| ≥13 (High) | 3646 (20.9) | 2190 (26.9) | 1456 (15.7) |
| Other or missing | 283 (1.6) | 105 (1.3) | 178 (1.9) |
| Adult socioeconomic status | | | |
| Annual income (million yen) ^b | | | |
| <2.00 (Low) | 7297 (41.9) | 3429 (42.2) | 3868 (41.7) |
| 2.00-3.99 (Middle) | 5770 (33.1) | 3004 (36.9) | 2766 (29.8) |
| ≥4.00 (High) | 1670 (9.6) | 861 (10.6) | 809 (8.7) |
| Missing | 2675 (15.4) | 837 (10.3) | 1838 (19.8) |
| Longest occupation | | | |
| Nonmanual | 3898 (22.4) | 2973 (36.6) | 925 (10.0) |
| Manual | 11 104 (63.8) | 4671 (57.4) | 6433 (69.3) |
| No occupation | 818 (4.7) | 28 (0.3) | 790 (8.5) |
| Missing | 1592 (9.1) | 459 (5.6) | 1133 (12.2) |

(continued)

Table 1. Baseline Characteristics of Older Japanese Men and Women (continued)

| Characteristic | Participants, No. (%) | | |
|-------------------------------------|-----------------------|----------------|------------------|
| | Total (N = 17 412) | Men (n = 8131) | Women (n = 9281) |
| Adult social relationships | | | |
| Marital status | | | |
| Married | 12 653 (72.7) | 7021 (86.3) | 5632 (60.7) |
| Widowed | 3403 (19.5) | 560 (6.9) | 2843 (30.6) |
| Divorced, unmarried, or other | 1027 (5.9) | 442 (5.4) | 585 (6.3) |
| Missing | 329 (1.9) | 108 (1.3) | 221 (2.4) |
| Frequency of meeting friends | | | |
| ≥1 Time/wk | 8646 (49.7) | 3368 (41.4) | 5278 (56.9) |
| ≥1 Time/mo | 3731 (21.4) | 1781 (21.9) | 1950 (21.0) |
| Rarely | 4299 (24.7) | 2693 (33.1) | 1606 (17.3) |
| Missing | 736 (4.2) | 289 (3.6) | 447 (4.8) |
| Social participation | | | |
| Yes | 12 015 (69.0) | 5648 (69.5) | 6367 (68.6) |
| No | 3950 (22.7) | 1885 (23.2) | 2065 (22.2) |
| Missing | 1447 (8.3) | 598 (7.4) | 849 (9.1) |
| Employment status | | | |
| Working | 4106 (23.6) | 2464 (30.3) | 1642 (17.7) |
| Retired | 10 398 (59.7) | 5184 (63.8) | 5214 (56.2) |
| Never worked | 1899 (10.9) | 290 (3.6) | 1609 (17.3) |
| Missing | 1009 (5.8) | 193 (2.4) | 816 (8.8) |
| Health behaviors | | | |
| Smoking | | | |
| Nonsmoker | 12 677 (72.8) | 4050 (49.8) | 8627 (93.0) |
| Current or former smoker | 4499 (25.8) | 3988 (49.0) | 511 (5.5) |
| Missing | 236 (1.4) | 93 (1.1) | 143 (1.5) |
| Health status | | | |
| Body mass index ^c | | | |
| <18.5 (Underweight) | 1165 (6.7) | 402 (4.9) | 763 (8.2) |
| 18.5-24.9 (Normal) | 11 834 (68.0) | 5622 (69.1) | 6212 (66.9) |
| 25.0-29.9 (Overweight) | 3300 (19.0) | 1690 (20.8) | 1610 (17.3) |
| ≥30.0 (Obese) | 415 (2.4) | 158 (1.9) | 257 (2.8) |
| Missing | 698 (4.0) | 259 (3.2) | 439 (4.7) |
| Disease | | | |
| Hypertension | 7526 (43.2) | 3476 (42.7) | 4050 (43.6) |
| Diabetes mellitus | 2286 (13.1) | 1344 (16.5) | 942 (10.1) |
| Stroke | 508 (2.9) | 338 (4.2) | 170 (1.8) |
| Heart disease | 1825 (10.5) | 1117 (13.7) | 708 (7.6) |
| Hearing loss | 1056 (6.1) | 527 (6.5) | 529 (5.7) |
| Depressive symptoms ^d | | | |
| No depression | 11 298 (64.9) | 5442 (66.9) | 5856 (63.1) |
| Moderate depression | 2767 (15.9) | 1405 (17.3) | 1362 (14.7) |
| Depression | 815 (4.7) | 421 (5.2) | 394 (4.2) |
| Missing | 2532 (14.5) | 863 (10.6) | 1669 (18.0) |
| Dementia incidence during follow-up | 704 (4.0) | 312 (3.8) | 392 (4.2) |

^a Height categories are defined as less than 155 cm, 155 to 159.9 cm, 160 to 164.9 cm, 165 to 169.9 cm, and greater than or equal to 170 cm for men and less than 145 cm, 145 to 149.9 cm, 150 to 154.9 cm, 155 to 159.9 cm, and greater than or equal to 160 cm for women.

^b As of December 17, 2019, 1 Japanese yen equals 0.0091 US dollar.

^c Body mass index is calculated as the weight in kilograms divided by height in meters squared.

^d Depressive symptoms were assessed by the 15-item short form of the Geriatric Depression Scale (Japanese version),³⁹ where a score of less than 5 indicates no depression, a score of 5 to less than 10 indicates moderate depression, and a score of 10 or higher indicates depression.

(23.6%) were working, 12 677 (72.8%) were nonsmokers, 7526 (43.2%) were receiving treatment for hypertension, and 2286 (13.1%) were receiving treatment for diabetes. Approximately 1% of participants had 3 cognitive complaints at baseline. Overall, 10 968 (63.0%) reported 0 adverse childhood experiences, 5129 (29.5%) reported 1 adverse childhood experience, 964 (5.5%) reported 2 adverse childhood experiences, and 351 (2.0%) reported 3 or more adverse childhood experiences

(Table 1). The prevalence of each adverse childhood experience was similar for men and women. The adverse childhood experience with the highest prevalence was parental death (1881 men [23.1%] vs 2048 women [22.1%]), and that with the second highest prevalence was psychological neglect (1182 men [14.5%] vs 939 women [10.1%]). Only 326 participants overall (1.9%) experienced parental divorce (185 men [2.3%] vs 141 women [1.5%]), and 121 participants overall (0.7%) experienced parental mental illness (74 men [0.9%] vs 47 women [0.5%]). Approximately one-half of participants (7762 [44.6%]) reported that they had economic hardship during childhood, and 39.8% of the participants (6926 participants) had been in school for less than 9 years.

The percentages of missing values were higher among women than men possibly because of older age—that is, older women may have been reluctant to complete the questionnaire. In particular, for current household income, longest occupation, and employment status, in a national survey conducted in the 1980s,⁴⁰ 40% of working women retired after marriage and 60% of the remaining women retired after the birth of their first child. Thus, women may tend to fail to report their income and occupation. For annual income, data were missing for 1938 women (19.8%) vs 837 men (10.3%); for longest occupation, data were missing for 1133 women (12.2%) vs 459 men (5.6%); and for employment status, data were missing for 816 women (8.8%) vs 193 men (2.4%). The missing responses to the adverse childhood experience questionnaires were similar between men and women (1016 men vs 1260 women; 2276 participants total) (eTable 1 in the Supplement).

eTable 2 in the Supplement shows the probability that participants who experienced 1 adverse childhood experience would have also experienced other adverse childhood experiences. Among those who experienced only 1 adverse childhood experience, 61% experienced parental death. Approximately one-half of the participants who experienced physical abuse also experienced family violence, psychological neglect, and psychological abuse among both men and women. Similarly, approximately 40% of those who experienced psychological abuse also experienced psychological neglect. Participants who experienced interpersonal loss (parental death or divorce) were more likely to experience psychological neglect compared with other components of adverse childhood experiences. For those with 3 or more adverse childhood experiences, 52% of men and 59% of women (55% overall) had experienced parental death, 84% of men and 88% of women had experienced psychological neglect, 45% of men and 31% of women had experienced physical abuse, and 69% of men and 88% of women had experienced psychological abuse. The proportion of physical abuse was less than 8% for men with fewer than 2 adverse childhood experiences, but 45% for men with 3 or more adverse childhood experiences (eTable 2 in the Supplement). We found that participants who experienced adverse childhood experiences had a lower education level, were more likely to be unmarried, had less social participation, were more likely to have a history of smoking, and were more likely to have depression (all $P < .001$) (eTable 3 in the Supplement).

During the 3-year follow-up period, dementia was present in 703 participants (312 men and 391 women) among the analytical sample (cumulative dementia rate: 4.0% in all participants, 3.8% in men, and 4.2% in women). The incidence rate of dementia was 3.4 cases per 100 000 person-years (95% CI, 3.1-3.7 cases per 100 000 person-years) for those who grew up without adverse childhood experiences and 6.0 cases per 100 000 person-years (95% CI, 4.0-9.1 cases per 100 000 person-years) for those who experienced 3 or more adverse childhood experiences (Table 2).

Table 2 shows the association between the total number of adverse childhood experiences and dementia incidence. The proportional hazards assumption for model was checked by examining log minus log-transformed Kaplan-Meier estimates of the survival plots, and we confirmed no serious violation of the proportional hazards assumption. Participants who experienced 3 or more adverse childhood experiences had a greater risk of developing dementia compared with those who grew up without adverse childhood experiences after adjustment for age, sex, other childhood environmental factors (economic hardship and height), and education (model 1) (HR, 2.18; 95% CI, 1.42-3.35). After successive adjustment for adult sociodemographic characteristics, social relationships, health behavior, and health status (model 4), this HR was attenuated but remained statistically significant (HR, 1.78; 95% CI, 1.15-2.75; $P = .009$). When we performed a mediation analysis, adult

sociodemographic characteristics, social relationships, health behavior, and health status mediated 67% of the association between the adverse childhood experiences and dementia. When stratified by sex, there were associations with dementia for 3 or more adverse childhood experiences for men (HR, 2.20; 95% CI, 1.24-3.90), for 2 adverse childhood experiences for women (HR, 1.66; 95% CI, 1.12-2.48), and for 3 or more adverse childhood experiences for women (HR, 2.17; 95% CI, 1.13-4.15).

Table 3 shows the association between individual adverse childhood experiences and dementia incidence. Physical abuse (HR, 2.61; 95% CI, 1.65-4.14), psychological neglect (HR, 1.26; 95% CI, 1.02-1.55), and psychological abuse (HR, 1.65; 95% CI, 1.23-2.20) were associated with dementia incidence (model 1). The associations between physical abuse (HR, 2.42; 95% CI, 1.52-3.86) and psychological abuse (HR, 1.35; 95% CI, 1.01-1.81) and dementia remained after adjustment for potential mediators (model 4). When stratified by sex, physical abuse was associated with dementia in men, whereas psychological neglect and abuse were associated with dementia in women. Men who experienced physical abuse had a greater risk of developing dementia after adjustment for age, other childhood environmental factors (economic hardship and height), and education (model 1) (HR, 2.82; 95% CI, 1.64-4.85). This association remained in the final model (HR, 2.70; 95% CI, 1.56-4.70). Women who experienced psychological neglect had a greater risk of developing dementia (HR, 1.51; 95% CI, 1.14-2.00), and those who experienced psychological abuse had a greater risk of developing dementia in model 1 (HR, 1.97; 95% CI, 1.35-2.88). The association between psychological abuse and dementia remained in the final model (HR, 1.66; 95% CI, 1.12-2.44).

Discussion

To our knowledge, this is the first study to examine the association between adverse childhood experiences and dementia incidence using a large-scale cohort study of older Japanese people. The cumulative number of adverse childhood experiences was associated with increased risk of developing dementia.

Table 2. Hazard Ratios for Association of Dementia With Adverse Childhood Experiences in Older Japanese Men and Women

| Adverse Childhood Experiences, No. | Participants With Dementia, No. (%) | Incidence Rate/100 000 Person-Years (95% CI) | HR (95% CI) | | | |
|------------------------------------|-------------------------------------|--|----------------------|----------------------|----------------------|----------------------|
| | | | Model 1 ^a | Model 2 ^b | Model 3 ^c | Model 4 ^d |
| All (N = 17 412) | | | | | | |
| 0 | 414 (3.8) | 3.4 (3.1-3.7) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 1 | 220 (4.3) | 3.9 (3.4-4.4) | 1.08 (0.92-1.28) | 1.08 (0.92-1.27) | 1.04 (0.89-1.23) | 1.02 (0.87-1.21) |
| 2 | 46 (4.8) | 4.4 (3.3-5.8) | 1.29 (0.94-1.76) | 1.26 (0.92-1.72) | 1.15 (0.84-1.57) | 1.06 (0.78-1.46) |
| ≥3 | 23 (6.6) | 6.0 (4.0-9.1) | 2.18 (1.42-3.35) | 2.13 (1.38-3.27) | 1.93 (1.26-2.97) | 1.78 (1.15-2.75) |
| Men (n = 8131) | | | | | | |
| 0 | 173 (3.6) | 3.2 (2.8-3.7) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 1 | 108 (4.3) | 3.9 (3.2-4.7) | 1.14 (0.89-1.45) | 1.14 (0.89-1.45) | 1.08 (0.85-1.38) | 1.06 (0.83-1.35) |
| 2 | 18 (3.4) | 3.1 (2.0-4.9) | 0.95 (0.58-1.55) | 0.93 (0.57-1.53) | 0.81 (0.50-1.33) | 0.76 (0.46-1.25) |
| ≥3 | 13 (6.3) | 5.9 (3.4-10.1) | 2.20 (1.24-3.90) | 2.13 (1.20-3.80) | 2.03 (1.14-3.62) | 1.81 (1.01-3.24) |
| Women (n = 9281) | | | | | | |
| 0 | 241 (4.0) | 3.5 (3.1-4.0) | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| 1 | 112 (4.3) | 3.9 (3.2-4.6) | 1.04 (0.83-1.31) | 1.04 (0.83-1.30) | 1.01 (0.81-1.27) | 1.00 (0.79-1.25) |
| 2 | 28 (6.4) | 5.9 (4.1-8.5) | 1.66 (1.12-2.48) | 1.63 (1.10-2.44) | 1.51 (1.01-2.25) | 1.36 (0.91-2.04) |
| ≥3 | 10 (6.9) | 6.2 (3.4-11.6) | 2.17 (1.13-4.15) | 2.12 (1.11-4.05) | 1.76 (0.92-3.39) | 1.67 (0.86-3.23) |

Abbreviation: HR, hazard ratio.

^a Model 1 is adjusted for age, sex, other childhood environmental factors (economic hardship and height), and education.

^b Model 2 includes model 1 and is adjusted for adult health status associated with cardiovascular risk (hypertension, diabetes, stroke, and heart disease).

^c Model 3 includes model 2 and is adjusted adult sociodemographic characteristics (annual income and longest occupation), social relationships (marital status, frequency

of meeting friends, social participation, and employment status), and health behavior (smoking).

^d Model 4 includes model 3 and is adjusted for current health status (body mass index [calculated as the weight in kilograms divided by height in meters squared], depressive symptoms, and hearing loss).

The current findings are consistent with those of previous studies¹²⁻¹⁴ that examined the association between childhood parental death and dementia. In the present study, among older people who experienced 3 or more adverse childhood experiences, 55% of them experienced parental death, which was associated with a higher risk of developing dementia. However, having only 1 adverse childhood experience (61% of which were parental deaths) was not associated with dementia incidence, suggesting that the cumulative theory on the association between adverse childhood experience and adult disease⁴¹ may support the current findings. A prospective study in Sweden¹⁴ showed a dose-response association between dementia and psychosocial risk factors, such as parental death and arduous manual work, during the life course. In the present study, most participants with 3 or more adverse childhood experiences had experienced parental death, psychological neglect, and abuse (eTable 2 in the Supplement). Although it is unclear which adverse childhood experience happened first, parental death alone was not associated with the risk of dementia in old age, but it was associated with increased risk if psychological neglect and abuse were added.

Table 3. Hazard Ratios for Association of Dementia With Adverse Childhood Experiences in Older Japanese Men and Women

| Adverse Childhood Experiences | HR (95% CI) | | | |
|-------------------------------|----------------------|----------------------|----------------------|----------------------|
| | Model 1 ^a | Model 2 ^b | Model 3 ^c | Model 4 ^d |
| All (N = 17 412) | | | | |
| Interpersonal loss | | | | |
| Parental death | 0.99 (0.83-1.18) | 0.99 (0.83-1.18) | 0.97 (0.82-1.16) | 0.96 (0.81-1.14) |
| Parental divorce | 1.29 (0.76-2.20) | 1.27 (0.75-2.17) | 1.22 (0.72-2.08) | 1.20 (0.70-2.05) |
| Family psychopathology | | | | |
| Parental mental illness | 1.76 (0.87-3.53) | 1.74 (0.87-3.51) | 1.66 (0.82-3.34) | 1.60 (0.79-3.24) |
| Family violence | 1.41 (0.94-2.09) | 1.40 (0.94-2.08) | 1.39 (0.93-2.07) | 1.33 (0.89-1.98) |
| Abuse and neglect | | | | |
| Physical abuse | 2.61 (1.65-4.14) | 2.60 (1.64-4.12) | 2.48 (1.56-3.94) | 2.42 (1.52-3.86) |
| Psychological neglect | 1.26 (1.02-1.55) | 1.25 (1.01-1.54) | 1.16 (0.94-1.43) | 1.09 (0.88-1.35) |
| Psychological abuse | 1.65 (1.23-2.20) | 1.58 (1.18-2.11) | 1.44 (1.08-1.93) | 1.35 (1.01-1.81) |
| Men (n = 8131) | | | | |
| Interpersonal loss | | | | |
| Parental death | 1.05 (0.81-1.35) | 1.05 (0.82-1.36) | 1.03 (0.79-1.33) | 1.01 (0.78-1.30) |
| Parental divorce | 1.50 (0.77-2.93) | 1.48 (0.76-2.89) | 1.41 (0.72-2.76) | 1.43 (0.73-2.81) |
| Family psychopathology | | | | |
| Parental mental illness | 2.31 (0.95-5.59) | 2.32 (0.96-5.62) | 2.08 (0.85-5.05) | 2.10 (0.86-5.12) |
| Family violence | 1.42 (0.84-2.41) | 1.42 (0.84-2.40) | 1.53 (0.90-2.60) | 1.49 (0.88-2.53) |
| Abuse and neglect | | | | |
| Physical abuse | 2.82 (1.64-4.85) | 2.79 (1.62-4.80) | 2.73 (1.58-4.73) | 2.70 (1.56-4.70) |
| Psychological neglect | 1.04 (0.76-1.43) | 1.03 (0.75-1.41) | 0.92 (0.67-1.26) | 0.87 (0.63-1.20) |
| Psychological abuse | 1.30 (0.83-2.04) | 1.26 (0.81-1.97) | 1.15 (0.73-1.80) | 1.03 (0.65-1.64) |
| Women (n = 9281) | | | | |
| Interpersonal loss | | | | |
| Parental death | 0.95 (0.75-1.20) | 0.94 (0.74-1.20) | 0.93 (0.73-1.18) | 0.92 (0.72-1.16) |
| Parental divorce | 1.03 (0.42-2.50) | 1.01 (0.41-2.44) | 1.01 (0.41-2.45) | 0.96 (0.39-2.34) |
| Family psychopathology | | | | |
| Parental mental illness | 1.29 (0.41-4.04) | 1.27 (0.40-3.98) | 1.23 (0.39-3.87) | 1.07 (0.33-3.43) |
| Family violence | 1.39 (0.76-2.55) | 1.39 (0.76-2.56) | 1.26 (0.69-2.32) | 1.18 (0.64-2.19) |
| Abuse and neglect | | | | |
| Physical abuse | 2.05 (0.85-4.99) | 2.08 (0.86-5.05) | 1.76 (0.72-4.31) | 1.74 (0.71-4.29) |
| Psychological neglect | 1.51 (1.14-2.00) | 1.51 (1.14-2.00) | 1.40 (1.06-1.85) | 1.31 (0.99-1.74) |
| Psychological abuse | 1.97 (1.35-2.88) | 1.97 (1.30-2.78) | 1.72 (1.17-2.52) | 1.66 (1.12-2.44) |

Abbreviation: HR, hazard ratio.

^a Model 1 is adjusted for age, sex, other childhood environmental factors (economic hardship and height), and education.

^b Model 2 includes model 1 and is adjusted for adult health status associated with cardiovascular risk (hypertension, diabetes, stroke, and heart disease).

^c Model 3 includes model 2 and is adjusted for adult sociodemographic characteristics (annual income and longest occupation), social relationships (marital status, frequency of meeting friends, social participation, and employment status), and health behavior (smoking).

^d Model 4 includes model 3 and is adjusted for current health status (body mass index [calculated as the weight in kilograms divided by height in meters squared], depressive symptoms, and hearing loss).

The association between adverse childhood experiences and dementia incidence decreased after adjusting for social relationships, health behavior, and health status, suggesting that these factors may mediate the association between adverse childhood experiences and dementia. When we performed a mediation analysis, adult sociodemographic characteristics, social relationships, health behavior, and health status mediated 67% of the association between the adverse childhood experiences and dementia. Adverse childhood experiences can hinder opportunities in terms of receiving education, building social relationships, and developing healthy behaviors, thus increasing the risk of diseases associated with the onset of dementia. We found that participants who experienced adverse childhood experiences had a lower education level, were more likely to be unmarried, had less social participation, were more likely to have a history of smoking, and were more likely to have depression (all $P < .001$) (eTable 3 in the [Supplement](#)). Adjusting for cardiovascular risk factors (hypertension, diabetes, stroke, and heart disease) reduced the association between adverse childhood experiences and dementia incidence. This may be partially explained by genetic factors—that is, it is possible that a certain portion of parental death may be attributed to fatal cardiovascular conditions, which are partly inheritable. In this case, cardiovascular diseases can be potential confounders. However, even after adjusting for cardiovascular risk factors, an association between adverse childhood experiences and dementia incidence remained.

A dose-response association between adverse childhood experiences and dementia incidence was found for women but not for men. Sex differences have also been identified for adverse childhood experiences and other subsequent adulthood outcomes, such as physical health problems and well-being,¹⁹⁻²² possibly because the sensitivity to adverse childhood experiences may differ between men and women. A previous study¹⁰ investigating the association between adverse childhood experiences and cognitive function reported that parental death during childhood was associated with poor verbal retrieval only among women but not men. In the current study, more than 60% of women were housewives before 1980, and women were mainly in charge of childcare.⁴² Thus, it is also possible that performing childcare may remind women of being abused or neglected more often than men. This may be supported by the fact that psychological neglect and abuse were associated with dementia only in women. Duration, starting age, and types of adverse childhood experiences may differ between men and women. The belief that men are superior to women still exists in Japanese culture.⁴³ Therefore, women may have experienced more-severe adverse childhood experiences from a very young age. On the other hand, only physical abuse was associated with dementia among men (Table 3). The proportion of physical abuse was less than 8% for men with fewer than 2 adverse childhood experiences, but 45% for men with 3 or more adverse childhood experiences (eTable 2 in the [Supplement](#)). This may explain why having fewer than 2 adverse childhood experiences was not associated with dementia in men. Another explanation of sex difference is survival effect—that is, people who survive adverse circumstances earlier in life are a select group of hardy individuals. In a previous study of older people in Japan,³⁸ we found that men with deprived childhood socioeconomic circumstances had a lower risk of death, but this was not true among women. It is possible that men with deprived childhood socioeconomic circumstances were less likely than women to be resistant to adversities such as wartime food shortages and infectious diseases and, hence, more likely to have died at younger ages. Therefore, in the context of this study, men who experienced several adverse childhood experiences died prematurely, and the association between adverse childhood experiences and dementia may have been underestimated among men. Further study is needed to elucidate the differential outcomes of adverse childhood experiences on dementia by sex.

When analyzing each adverse childhood experience item separately, we found that physical abuse was significantly associated with dementia. Physical abuse could damage the brain,⁴⁴ which could increase the risk of dementia. Although the association between parental mental illness and dementia was not significant, perhaps because of the small number of participants, the point estimates were high. Given that parental mental health disorders may be inheritable, this association is important and further research is needed.

Limitations

Several limitations to this study should be mentioned. First, because a cutoff point of the dementia scale in this study corresponded to a 16-point rating on the Mini-Mental State Examination,³³ the onset of dementia may be underestimated. In a nationwide study⁴⁵ estimating the prevalence of dementia in Japan, this cutoff point of the dementia scale did not cover 34% of dementia cases; however, most of these were mild cases of dementia. Second, we assessed adverse childhood experiences via retrospective assessment, which may induce recall biases. Previous meta-analyses⁴⁶⁻⁴⁸ reported that retrospective assessment of adverse childhood experiences overestimated actual adverse childhood experiences. However, we confirmed that the prevalence of psychological neglect was similar across each age cohort, and the prevalence of parental death was higher among the older age cohort.²⁴ This is plausible because the older the participants were, the more likely their parents would have been involved in World War II. Thus, recall bias is not likely to affect accuracy of reporting. Third, we did not directly assess the experience of World War II. People who have severe war experiences may also have multiple adverse childhood experiences. Therefore, interpretation of the results should be done with caution, because the association between adverse childhood experiences and dementia may be altered by a severe war experience.

Fourth, in addition to the 71% response rate, we were able to link to dementia data for 92% of participants, and 2276 people did not answer questions regarding adverse childhood experiences, so the generalizability of this study is somewhat weak. The characteristics of the nonparticipants in this survey were unavailable. However, comparisons of characteristics for whether they answered the questions regarding adverse childhood experiences revealed that the nonrespondents tended to be older and shorter, have lower socioeconomic status, and be unmarried compared with the respondents (eTable 4 in the [Supplement](#)). This suggests that our study sample lacked people who were vulnerable to dementia, which may have been linked to an underestimation of the association between adverse childhood experiences and dementia. Fifth, although the participants were older people without functional disabilities, which was defined as not being certified as eligible for benefits from the long-term care insurance, it may not rule out potential prevalent dementia cases at baseline. When assessed using the subjective cognitive function score,⁴⁹ 1% of participants had 3 cognitive complaints at baseline. Therefore, our study may include some people with dementia at baseline. Sixth, because the sample was limited to people aged 65 years and older who had not received a diagnosis of dementia, the association between adverse childhood experiences and early-onset dementia cannot be analyzed. It is possible that only healthier participants were included in this study, and the association of adverse childhood experiences with dementia may be underestimated.

Conclusions

This study found an association between adverse childhood experiences and late-life dementia onset longitudinally among older adults, using a large-scale population-based sample in Japan. These findings may not be generalizable to other generations and cultures. Further study is warranted to replicate the association of cumulative adverse childhood experiences and dementia in other settings, taking into consideration the mechanisms of sex difference.

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SUPPLEMENT.

eTable 1. Characteristics of Adverse Childhood Experiences in Older Japanese Men and Women

eTable 2. Relationships Between Categories of Adverse Childhood Experiences

eTable 3. Baseline Characteristics of Older Japanese Men and Women

eTable 4. Characteristics of Participants Nonresponse to Adverse Childhood Experiences and Study Samples in Older Japanese Adults