The KCL was proposed by the MHLW as a valid and low-cost assessment tool (Sewo Sampaio, Sampaio, Yamada, Ogita, & Arai, 2014; Fried et al., 2001; Ogawa et al., 2011; Umegaki et al., 2013). The KCL has shown good concurrent validity against Fried's criteria for evaluating frailty (Ogawa et al., 2011). To develop an effective preventive intervention strategy, it is important to determine the characteristics of those who are at high risk for assisted living in one entire city. In recent decades, studies have reported various factors that have contributed to the occurrence of disability, mortality and frailty (Crimmins & Sànchez, 2011; Crimmins & Saito, 2001; Mattos, Carmo, Santiago, & Luz, 2014); however, few studies have investigated them in a whole city setting. It is important for a prevention study to select participants from the whole community's healthy population for the further application of community intervention, instead of gathering participants from limited settings. Many researchers assume that the prevalence of frailty is associated with older age, sex (women), the existence of chronic disease, nutritional status, muscle strength, balance function, educational background, and social interaction; yet, they have not reached a consensus, especially on social factors, because of the complex background and elusive definition of frail older persons (Avila-Funes et al., 2008; Collard, Boter, Schoevers, & Oude Voshaar, 2012; Moriya, Murata, Kimura, Inoue, & Miura, 2013; Nishi et al., 2012; Stuck et al., 1999). To improve the quality and efficiency of preventive intervention in the community, it is critical to clarify the factors associated with risk for assisted living, especially paying attention to both individual biological factors and social factors. Therefore, we conducted a large-scale survey targeting the entire population of older people in one urban city to investigate the factors associated with high-risk status for assisted living.

2. Design and methods

2.1. Participants and procedure

This was a population-based cross-sectional large-scale mail survey conducted between 2012 and 2013. A local government (H-City) in Osaka Prefecture, which is a mid-sized urban city in western Japan with a population of approximately 410,000,

Basic Health Checklist ("Kihon Check List") for people aged 65 years and older

Number		Questionnaire	Circle either one.			
1. Daily life	1	Do you go out by bus or train by yourself?	0	Yes	1	No
	2	Do you go shopping to buy daily necessities by yourself?	0	Yes	1	No
	3	Do you manage your own deposits and savings at the bank?	0	Yes	1	No
	4	Do you sometimes visit your friends?	0	Yes	1	No
	5	Do you turn to your family or friends for advice?	0	Yes	1	No
2. Physical strength	6	Do you normally climb stairs without using handrail or wall for support?	0	Yes	1	No
	7	Do you normally stand up from a chair without any aids?	0	Yes	1	No
	8	Do you normally walk continuously for 15 minutes?	0	Yes	1	No
	9	Have you experienced a fall in the past year?	1	Yes	0	No
	10	Do you have a fear of falling while walking?	1	Yes	0	No
3. Nutritional status	11	Have you lost 2kg or more in the past 6 months?	1	Yes	0	No
	12	Height _____ cm; Weight _____ kg (BMI ____) If BMI is less than 18.5, this item is scored.				
4. Oral function	13	Do you have any difficulties eating tough foods compared to 6 months ago?	1	Yes	0	No
	14	Have you choked on your tea or soup recently?	1	Yes	0	No
	15	Do you often experience having a dry mouth?	1	Yes	0	No
5. Houseboundness	16	Do you go out at least once a week?	0	Yes	1	No
	17	Do you go out less frequently compared to last year?	1	Yes	0	No
6. Cognitive function	18	Do your family or your friends point out your memory loss?	1	Yes	0	No
	19	Do you make a call by looking up phone numbers?	1	Yes	0	No
	20	Do you find yourself not knowing today's date?	1	Yes	0	No

Physical strength ≥3

Nutritional status =2

Oral function ≥2

Overall high - risk score on questions 1–20 ≥10

Fig. 1. Basic health checklist for screening older people at high risk for assisted living.

administered a mail survey to nondisabled and nondemented community-dwelling older persons aged ≥65 years. About 18.0% of the older persons in H-City were excluded from the mail survey because they were approved as having a disability or dementia by the city government; i.e. certified for LTCI benefits by the nationally standardized needs certification system, and their information is in the city government's database. The certification is due to the initial recorded assessment questionnaire (an 85-item questionnaire) and decision by the municipal board; the Certification Committee for Long-term Care Need, consisting of about five health and welfare professionals, considering the applicant's primary care physician's statement (Tsutsui & Muramatsu, 2005).

When the survey was administered by the H-City government, participants were informed about the study purpose, and that Osaka University Graduate School of Medicine would analyze the data. Before releasing the data to researchers, personal identifiers were deleted from the dataset. Ethical approval for the study was obtained from the Ethics Committee in the Division of Health Sciences, Osaka University Graduate School of Medicine (approval number 230-1). The study design was based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (Vandenvbroucke et al., 2007).

2.2. Measurement

High-risk status for assisted living was measured by a basic health checklist ("KCL") (Arai & Satake, 2015; Sewo Sampaio et al., 2014) (Fig. 1). The KCL was developed by the MHLW in Japan for the screening of community-dwelling older people to detect those who are at high risk for assisted living. The basic health checklist we used was a 20-item, self-rated questionnaire and consisted of the following categories: physical strength, nutritional status, oral function, overall high-risk score on questions 1–20, housebound-ness, and cognitive function (Fukutomi et al., 2013; Ministry of Health, Labour and Welfare, 2015). A participant was identified as having "low physical strength" if he/she scored three or more points out of five. Nutritional status had two questions; if he/she scored two, it indicated "low nutritional status". Scoring two points or more in the oral function domain suggested "low oral function" (Fukutomi et al., 2013; Ministry of Health, Labour and Welfare, 2015). People who were considered of "high-risk status for assisted living" had either low physical strength, low nutritional status, low oral function, or an overall high-risk score on questions 1–20 (≥10), which were based on the criteria of MHLW's standard (Fukutomi et al., 2013; Ministry of Health, Labour and Welfare, 2015).

In addition to the basic health checklist, demographic information (age, sex) and sociodemographic information, including family structure (living alone or not), duration of residence within H-City (<20 years or≥20 years), employment status (yes or no), and community participation (yes or no), were collected. We also asked about present illness (yes or no) and illness type.

2.3. Statistical analysis

After computation of the summary statistics, differences among means were tested for statistical significance using an independent *t*-test; a chi-square test was used for differences among frequencies. In order to examine the associations of age, present illness, living alone, years of residence, community participation, and employment status with risk, multiple logistic regression analysis was performed. We used odds ratio to measure the effective size. These statistical analyses were conducted using SPSS (Version 21.0; IBM Japan, Tokyo, Japan). The significance level was set at 0.05.

3. Results

Out of 56,608 questionnaires that we mailed out, participants who were left out from the local residential registration (i.e., moved or deceased) (n = 13) and participants who were certified as having a disability or dementia (n = 101) were excluded from the participant population. The overall response rate to the mailing was 73.8% (41,796 questionnaires), and there were 41,115 valid questionnaires.

The characteristics of the study participants are shown in the first data column in Table 1. The average age of all participants was 72.0 (±5.8) years. In all, 68.9% participants had some illness, 14.0% were living alone, 13.0% had been living in H-City <20 years, 57.1% participated in community activities, and 22.5% were employed. The percentage of participants at high risk for assisted living was 25.2%, with the percentage of women being higher than that of men in every age group (Fig. 2). Participants of high-risk status were more likely to be older, be women, have some illness, live

Table 1
Characteristics of the participants.

		All (n = 41,115)	Risk status for assisted living		
			Without risk (n = 30,767)	With risk (n = 10,348)	OR[b] (95%CI[c])
Men	Number (%)	19,455 (47.3)	15,148 (77.9)	4307 (22.1)	
	Age, mean (SD)[a]	72.0 (5.8)	71.5 (5.5)	74.1 (6.5)	
	Present illness; yes, n (%)	13,122 (69.4)	9713 (65.9)	3409 (82.1)	2.38***(2.18–2.59)
	Living alone; yes, n (%)	1669 (8.6)	1203 (8.0)	466 (10.9)	1.41***(1.26–1.58)
	Years of residence in H-City (≥20years), n (%)	16,926 (87.4)	13,245 (87.9)	3681 (85.9)	0.85***(0.77–0.93)
	Community participation; yes, n (%)	9878 (52.2)	8118 (54.8)	1760 (42.6)	0.61***(0.57–0.66)
	Employment; yes, n (%)	5786 (30.6)	4860 (32.8)	926 (22.4)	0.59***(0.55–0.64)
Women	Number (%)	21,660 (52.7)	15,619 (72.1)	6041 (27.9)	
	Age, mean (SD)	72.0 (6.0)	71.1 (5.5)	74.5 (6.7)	
	Present illness; yes, n (%)	14,162 (68.4)	9299 (62.2)	4863 (84.4)	3.29***(3.04–3.56)
	Living alone; yes, n (%)	4205 (18.9)	2758 (17.9)	1267 (21.4)	1.25***(1.16–1.35)
	Years of residence in H-City (≥20years), n (%)	18,617 (86.6)	13,568 (87.4)	5049 (84.5)	0.79***(0.72–0.86)
	Community participation; yes, n (%)	12,776 (61.6)	9832 (65.3)	2944 (51.8)	0.57***(0.54–0.61)
	Employment; yes, n (%)	3121 (15.0)	2512 (16.7)	609 (10.7)	0.60***(0.55–0.66)

[a] SD = Standard deviation.
[b] OR = Odds ratio.
[c] CI = Confidence interval.
*** $p < .001$.

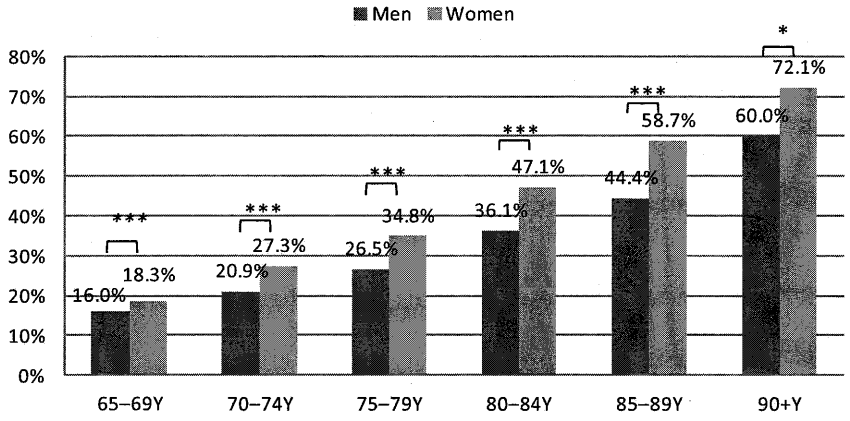

Fig. 2. The percentage of men and women at risk for assisted living by age group.
$P < ^{***}.001, ^{*}.05$.
Y = years old.

alone, have been living in H-City <20 years, have a lack of community participation, and be unemployed than non-risk participants (Table 1).

Multiple logistic regression analysis stratified for sex revealed the following to be independent factors associated with high-risk status for assisted living among men and women: higher age, present illness, <20 years of residence, lack of community participation, and unemployment (Table 2). Living alone was independently associated with risk among men, whereas this association was insignificant among women.

The strongest adjusted OR value was that for present illness both in men and women, and the adjusted OR among men was 2.10 (1.92–2.30) and 2.83 (2.60–3.07) among women. People at risk were more likely to have some illness regardless of the illness type (Fig. 3). The type of illness among people at risk was different between men and women (Fig. 4). Men were more likely to have strokes, diabetes, chronic respiratory disease, and cancer, whereas women were more likely to have falls and bone fractures, joint diseases, osteoporosis, rheumatism, and depression.

4. Discussion

Participants at high risk for assisted living were more likely to be older in age in the present study. In every age group, a higher percentage of women were at risk than men. The pattern was the same as in previous frailty studies, which showed that frailty increased with age and was more prevalent in women (Collard et al., 2012; Fried et al., 2001; Nishi et al., 2012; Mitnitski, Graham, Mogilner, & Rockwood, 2002). We investigated the nondisabled and nondemented older people in one entire city, and the results showed the same pattern for sex differences that the previous frailty studies had established (Collard et al., 2012; Fried et al., 2001; Mitnitski et al., 2002; Nishi et al., 2012). In the present study, the association between any illness and high-risk status had the strongest OR, and was stronger among women (OR = 2.83) than men (OR = 2.10). These results suggest that illnesses, such as joint diseases, osteoporosis, and bone fractures, which were more frequent among women in the present study, are the most influential factors for high-risk status for assisted living. As a potential explanation, men may not linger at the stage of being at risk, such as functional decline or frailty, because of the nature of their typical illnesses, like stroke, diabetes, hypertension, and cancer. Subjects with these illnesses tend to suffer from disability and subsequently require care or support (Manton, 1988); in the present study, the percentage of these illnesses was higher among men as shown in Fig. 4. In previous studies, results have indicated that men have a higher likelihood of dying suddenly than women, and that women show a steadier, more progressive decline (Collard et al., 2012; Puts, Lips, & Deeg, 2005). This decline could lead to infirmity, causing women to be of high-risk status for assisted living (Collard et al., 2012). Another possible explanation concerning sex differences for risk is the longer life expectancy of women and the lower average amount of lean body mass and muscle strength in women, which has been discussed in the same way in previous studies (Collard et al., 2012; Fried et al., 2001; Morley, 2008). Though the cross-sectional nature of the present study does not allow inference of a causal relationship, our results may suggest at least that preventive care should be differentiated according to sex; it might be important to promote preventive intervention for lifestyle-related disease in men at a younger age,

Table 2
Results of logistic regression coefficients predicting high-risk status for assisted living.

Characteristics	Men		Women	
	OR[a] (95%CI[b])	*P*-value	OR (95%CI)	*P*-value
Age	1.06 (1.06–1.07)	<0.001	1.09 (1.08–1.09)	<0.001
Present illness (yes = 1)	2.10 (1.92–2.30)	<0.001	2.82 (2.60–3.07)	<0.001
Living alone (yes = 1)[c]	1.35 (1.19–1.52)	<0.001	–	–
Years of residence in H-City (≥ 20 years = 1)	0.88 (0.79–0.98)	.021	0.87 (0.79–0.95)	0.003
Community participation (yes = 1)	0.53 (0.49–0.57)	<0.001	0.56 (0.53–0.60)	<0.001
Employment (yes = 1)	0.66 (0.60–0.72)	<0.001	0.77 (0.70–0.86)	<0.001

The risk status for assisted living: without risk = 0, with risk = 1.
[a] OR = Odds ratio.
[b] CI = Confidence interval.
[c] Variable not included in the model for women.

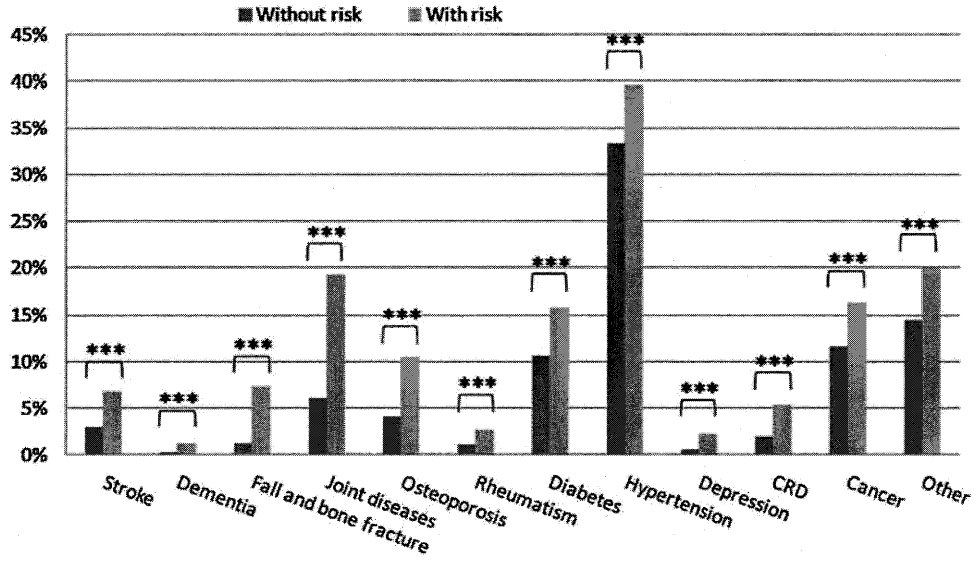

Fig. 3. The percentage of people with present illness among those with and without risk for assisted living.
CRD = Chronic respiratory disease.
$P < ^{***}.001$.
Odds Ratios (95%CI) were as follows: Stroke = 2.38 (2.15–2.64); Dementia = 5.22 (3.90–6.99); Fall and bone fracture = 6.03 (5.32–6.84); Joint diseases = 3.70 (3.45–3.96); Osteoporosis = 2.75 (2.53–3.00); Rheumatism = 2.61 (2.21–3.07); Diabetes = 1.56 (1.46–1.67); Hypertension = 1.31 (1.25–1.37); Depression = 4.19 (3.41–5.14); CRD = 2.89 (2.56–3.25); Cancer = 1.50 (1.40–1.59); Other = 1.49 (1.40–1.58).

whereas it might be critical to prevent musculoskeletal disease in women.

As for social factors, a statistically independent association was found between high-risk status and the lack of community participation. This finding is similar to a previous study that investigated the association between various health outcomes and participation in social activities (Takeuchi, Aida, Kondo, & Osaka, 2013). Researchers in Sweden found that social participation was the strongest predictor of decreased physical activity (Lindström, Hanson, & Östergren, 2001). A study in Japan also reported that people who do not participate in social activities are at higher risk of becoming disabled (Hirai, Kondo, Ojima, & Murata, 2009). Our

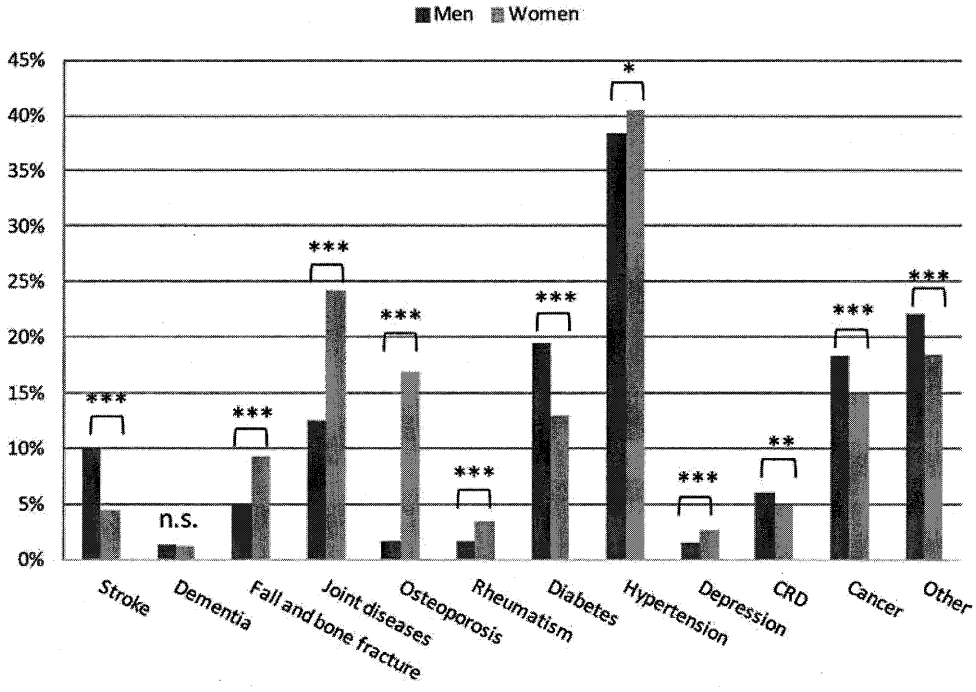

Fig. 4. The percentage of illness among men and women at risk for assisted living.
CRD = Chronic respiratory disease.
$P < ^{***}.001$, $^{**}.01$, $^{*}.05$.
n. s. = not significant.
Odds Ratios (95%CI) were as follows: Stroke = 0.39 (0.33–0.46); Dementia = 0.77 (0.54–1.10); Fall and bone fracture = 1.95 (1.65–2.31); Joint diseases = 2.22 (1.99–2.49); Osteoporosis = 12.41 (9.65–15.97); Rheumatism = 1.95 (1.48–2.55); Diabetes = 0.59 (0.52–0.66); Hypertension = 1.05 (0.96–1.14); Depression = 1.71 (1.27–2.29); CRD = 0.76 (0.64–0.91); Cancer = 0.74 (0.66–0.83); Other = 0.76 (0.69–0.84).

study confirmed the same association not only among the disabled people but also among the nondisabled, nondemented population. In addition, unemployment was also associated with the risk. Studies that have investigated the relationship between unemployment and health focusing on the general older population are scarce. Our finding was consistent with previous studies among the productive-age population (age between 15 and 64), which have discussed many mediating and confounding factors, such as those that are social, economic or clinical (Jin, Shah, & Svoboda, 1995). Though the effect size was small, we found that unemployment was independently associated with high-risk status for assisted living even among an older population, whose average age was 72.

We found a weak but independent association between high-risk status and less than 20 years of residence in H-City. We assume that high-risk older people who worried about becoming disabled may have relocated into H-City in order to receive support from their children; thus, this caused an association with short duration of living in H-City. As for the association between duration of residence and health, earlier results have demonstrated that people residing in the same neighborhood between 7 and 22 years have a stronger association between health and neighborhood social capital than people who have lived in the area for a shorter or longer period of time (Mohnen, Völker, Flap, Subramanian, & Groenewegen, 2013). Based on these findings, there may be some connecting factors, such as social capital, that link short duration of living and high-risk status, which should be clarified in further studies.

We also found that a significant association between high-risk status and living alone only existed in men. Previous studies have shown that living alone can predict the incidence of disability in older people (Lund, Nilsson, & Avlund, 2010; Escobar-Viera, Jones, Schumacher, & Hall, 2014). However, we found no significant association between living alone and high-risk status in women. No study has specifically examined the differences between men and women in terms of the association between living alone and high-risk status. From our results in men, living alone may lead to some maladaptive health behaviors, thereby leading to the onset of risk status; however, this mechanism remains unclear after this cross-sectional study, and requires further investigation.

Since the present study was cross-sectional, it was not possible to infer a causal relationship between these factors and risk status. However, the strength of the present study is that it was a large-scale survey with a high response rate, which ensured the participation of diverse subjects from one entire city. We found that older age, present illness, short duration of residence, lack of community participation, unemployment, and living alone were associated with high-risk status, and the associations between these factors and the prevalence of high risk status for assisted living were different between men and women.

Our findings showed an association between various factors and risk status for assisted living through a large-scale survey with a high percentage of participants in the community. This may provide basic information for the further application of effective preventive intervention; strategies should be differentiated according to subjects' characteristics, such as sex, present illness, and social factors. Further studies will be needed to evaluate the causal relationship between factors that might lead to high-risk health status for assisted living, such as functional decline and frailty, to understand the earlier phases of the disablement process. Obtaining basic information for effective community intervention for the prevention or moderation of further risk, such as functional decline, frailty and disability, in older people will be necessary to realize a society with healthier longevity.

Conflict of interest

None.

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ORIGINAL ARTICLE

Differences in the association between high blood pressure and cognitive functioning among the general Japanese population aged 70 and 80 years: The SONIC study

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High blood pressure in middle age (up to 64 years) has been proposed as a predictive indicator of dementia. However, the association between hypertension and the cognitive functioning is controversial in older age groups. The aim of this study was to investigate this association in 70–80-year-old participants in the Japanese study of Septuagenarians, Octogenarians and Nonagenarians Investigation with Centenarians (SONIC). Participants aged 70 (±1) and 80 (±1) years (n = 1000 and 973, respectively) were randomly recruited from the general population in Japan. Cognitive functioning was measured by the Montreal Cognitive Assessment. Blood pressure and other medical and social variables were analyzed by multiple regression analyses. High systolic blood pressure (SBP) was significantly correlated with a reduced cognitive functioning only in participants aged 70 years. Additionally, this correlation became more marked in participants with uncontrolled blood pressure at age 70 years. In contrast, SBP was not significantly correlated with the cognitive functioning at age 80 years. Nutritional status indicators such as serum albumin and frequency of going outdoors were significantly associated with cognitive functioning at age 80 years. Our findings indicate that high SBP has a significant role in cognitive functioning at age 70 years; however, blood pressure is less important as a risk factor for cognitive decline at age 80 years.
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Keywords: cognitive functioning; high blood pressure; older population

INTRODUCTION

The number of elderly people with dementia is increasing, especially in developed countries.[1] Many studies have considered the association between hypertension and cognitive impairment, including mild cognitive impairment and dementia, in various generations.[2–4] According to several longitudinal studies, high blood pressure (BP) in midlife significantly increases the risk of cognitive impairment and dementia in later life.[5–8] Several previous studies have also noted that in later life, around age 70 years, hypertension and/or elevated BP may be significant predictors of a progressive decline in cognitive performance. However, the influence of BP on the progression of cognitive impairment has not been aggressively investigated in the general population, including those over age 80 years.

The association between later-life BP and cognitive impairment may be because of the very strong effect of aging on cognitive functioning, hypertensive treatment status and the emergence of comorbidities, such as cardiovascular diseases.[3,10–12] Additionally, hypertension is associated with body mass index (BMI), smoking, alcohol consumption and salt intake.[13–17] Furthermore, cognitive functioning in later life is associated with social factors, especially the level of activity, including the frequency of going outdoors.[18,19] In most cross-sectional studies, there are inconclusive data regarding the association between hypertension and cognitive functioning in later life.[20,21]

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Our primary objective was to investigate differences in the influence of aging on the association between cognitive functioning and BP in later life in a narrow age range cohort study. This is known as the SONIC (Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians) study, a longitudinal cohort study targeting individuals of older ages (70, 80, 90 and over 100 years) of the general Japanese population and including medical and social variables.

METHODS

Study population

This study was a cross-sectional examination conducted as a baseline assessment of a prospective study called SONIC, which investigated health and longevity. The participants were all volunteers living independently, and included 1000 individuals (excluding institutionalized individuals) aged 69–71 years (479 men, 521 women) and 973 individuals aged 79–81 years (456 men, 517 women) from four areas of both western and eastern, as well as urban and rural parts of Japan: Itami City, Hyogo (Western urban); Asago City, Hyogo (Western rural); Itabashi ward, Tokyo (Eastern urban); and Nishitama County, Tokyo (Eastern rural). Participants were randomly selected from the local resident registry and enrolled between 2010 and 2011.[22] We used the alternative narrow age range cohort approach to a cross-sectional design, in which covariances among age-related variables in cross-sectional studies are highly confounded with regard to inferences of association among rates of change within individuals. This is because covariances can result from a number of sources, including average population age-related differences (fixed age effects) and initial individual differences and effects of aging (random age effects).[23]

The study protocol was approved by the Institutional Review Board of Osaka University Graduate School of Medicine, Dentistry and Human Sciences and the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology (approval number 266, H22-E9, 22 018 and 38, respectively). All participants provided written informed consent to participate.

Measurements

BP measurement and classification. BP of the left and right arm was measured two times by a physician or trained nurse using a mercury sphygmomanometer or electronic monitor while the participant was seated after at least 1 min of rest. The mean of the two measurements of both arms was used in the analysis. BP measurements were classified into two categories according to the criteria of the Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009) (Supplementary Figure S1).[24] Based on these guidelines, the uncontrolled BP group was defined as those with a systolic blood pressure (SBP) of 140 mm Hg or greater and a diastolic BP (DBP) of 90 mm Hg or greater, and the controlled BP group was defined as those with an SBP lower than 140 mm Hg and a DBP lower than 90 mm Hg. Diagnosis of hypertension was based on BP values greater than 140/90 mm Hg and/or receiving antihypertensive treatment at the first contact.

Other factor measurements. Participants were interviewed at enrollment using questionnaires covering demographics, clinical information and psychosocial characteristics. Blood samples were drawn after overnight fasting. Levels of total cholesterol, high-density lipoprotein cholesterol, triglycerides, serum albumin and fasting/casual blood glucose were determined by biochemical examinations. Diabetes mellitus (DM) was defined by fasting blood glucose concentrations $\geqslant 7.0\ \mathrm{mmol\,l^{-1}}$ ($126\ \mathrm{mg\,dl^{-1}}$), casual blood glucose concentrations $\geqslant 11.1\ \mathrm{mmol\,l^{-1}}$ ($200\ \mathrm{mg\,dl^{-1}}$), HbA1c (National Glycohemoglobin Standardization Program) $\geqslant 6.5\%$ or taking medications for diabetes according to the World Health Organization criteria for epidemiologic studies of DM. Dyslipidemia was defined as a low-density lipoprotein cholesterol $\geqslant 3.62\ \mathrm{mmol\,l^{-1}}$ ($140\ \mathrm{mg\,dl^{-1}}$), high-density lipoprotein cholesterol $<1.03\ \mathrm{mmol\,l^{-1}}$ ($40\ \mathrm{mg\,dl^{-1}}$), triglyceride $\geqslant 1.69\ \mathrm{mmol\,l^{-1}}$ ($150\ \mathrm{mg\,dl^{-1}}$) and/or medications for dyslipidemia. Smoking behavior was based on a questionnaire that classified subjects into three categories: never, past and current. Alcohol consumption was also classified into three categories by ethanol units: never, current (1–3 days and <3 units per week) and excessive current (≥3 days and ≥3 units per week). Salt and fat intake was assessed with a Brief-Type Self-Administered Diet History Questionnaire, which was completed by each participant at home and checked by a trained research staff member during the medical examination.

Assessment of cognitive functioning

We used the Japanese version of the Montreal Cognitive Assessment (MoCA-J) as a general index of the cognitive status.[25] MoCA is a brief cognitive screening tool for detecting mild cognitive impairment in elderly people.[26] MoCA consists of a one-page, 30-point test administered by trained geriatricians and psychologists, with higher scores reflecting more favorable cognitive functioning, and assesses the following domains of cognition: visuospatial ability (3 points), naming task (3 points), attention task (6 points), language (3 points), abstraction task (2 points), delayed recall (5 points) and orientation (6 points). The MoCA-J showed favorable reliability and better validity for predicting mild cognitive impairment than conventional cognitive tests.[25] We used the MoCA-J total score as a predictor of cognitive functioning.

Statistical analyses

In this cross-sectional examination, descriptive data were summarized using the mean ± s.d. and proportions. Student's *t*-test for independent groups was used, and the comparison of proportions among groups was performed using a χ^2 test. Multiple linear regression models were produced for each group to calculate the standardized regression coefficients (β) expressing independent statistical associations between variables. In these analyses, data were stratified by age, BP category and antihypertensive treatment. All statistical analyses were performed with SPSS Statistics 21 (IBM Japan, Tokyo, Japan). All reported *P*-values are two-tailed, and $P<0.05$ was considered significant.

RESULTS

Clinical and social characteristics between participants aged 70 and 80 years

The characteristics of the participants aged 70 and 80 years are shown in Table 1. A total of 1973 participants answered the questionnaire and underwent the examinations and were analyzed after we excluded missing BP data (Supplementary Figure S1).

SBP and PP at age 80 years were higher compared with that at age 70 years. In contrast, DBP at 80 years was significantly lower compared with that at age 70 years. The proportions of those with hypertension and taking medication for hypertension were also higher at age 80 years. Specifically, the proportions of major antihypertensive drugs, including calcium channel blockers (CCB), angiotensin receptor blockers (ARB) and diuretics, were higher at age 80 years compared with that at age 70 years. The proportions of those with DM and dyslipidemia at age 70 years exhibited no significant differences between the age groups. Serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, serum albumin and BMI at age 70 years were also higher compared with that at age 80 years. Salt and fat intake evaluated by brief-type self-administered diet history questionnaire showed no significant differences between the age groups. Smoking habits, alcohol consumption and frequency of going outdoors were significantly different between the age groups. The MoCA-J total score at age 70 years was higher compared with that at age 80 years. A similar trend was observed in subscale scores, except for delayed recall (Supplementary Table S1).

Participant characteristics by sex are shown in Supplementary Table S2. At age 70 years, SBP, DBP, the proportion with hypertension and those taking medication for hypertension were higher in men compared with that in women, whereas at age 80 years, SBP and PP were higher in women compared with that in men. The proportion with DM was higher in men compared with that in women at both age 70 and 80 years. The proportion with dyslipidemia

Table 1 Characteristics of study population aged between 70 and 80 years

Characteristics	*All participants*	*70 years*	*80 years*	P-*value**
No. of participants	1922	957	965	
Men (%)	47.4	47.2	46.9	0.645
SBP (mm Hg)	143.4±18.5	140.1±18.2	146.6±18.2	<0.001
DBP (mm Hg)	78.6±10.6	79.4±10.7	77.9±10.4	0.002
PP (mm Hg)	64.7±15.6	60.8±14.5	68.7±15.6	<0.001
HTN (%)	73.3	65.8	81.8	<0.001
Taking medication for HTN (%)[a]	46.0	38.8	52.7	<0.001
CCB (%)	30.8	24.4	37.4	<0.001
ARB (%)	17.0	15.3	18.8	<0.05
ACEI (%)	2.8	3.0	2.7	0.656
Diuretics (%)	4.5	3.0	6.1	<0.01
Diabetes mellitus (%)	16.5	18.8	16.6	0.790
Dyslipidemia (%)	60.0	64.1	60.2	0.114
Serum total cholesterol (mmol l^{-1})	5.35±0.90	5.50±0.92	5.21±0.86	<0.001
LDL-C (mmol l^{-1})	3.08±0.76	3.19±0.79	2.99±0.72	<0.001
HDL-C (mmol l^{-1})	1.57±0.42	1.62±0.42	1.52±0.41	<0.001
TG (mmol l^{-1})	1.49±0.85	1.49±0.89	1.48±0.81	0.703
BMI (kg m^{-2})	22.7±3.0	22.8±2.9	22.4±3.0	0.001
Serum albumin (g dl^{-1})	4.4±0.3	4.4±0.3	4.3±0.3	<0.001
Salt intake (g per day)	12.4±4.3	12.3±4.1	12.5±4.5	0.370
Fat intake (g per day)	55.6±22.3	54.9±20.9	56.1±23.4	0.302
MoCA-J total score (0–30)	22.6±3.7	23.5±3.2	21.8±3.8	<0.001
Smoking (%)				0.001
Never	60.3	60.2	60.5	
Current	7.6	9.7	5.4	
Past	32.1	30.1	34.1	
Alcohol consumption (%)				<0.001
Never	65.8	62.4	69.2	
Current	30.8	32.2	29.3	
Current excessive	3.4	5.3	1.5	
Frequency of going outdoors (%)				<0.001
Once a day	38.1	45.0	31.0	
Five or six times per week	19.2	20.7	17.7	
Three or four times per week	20.8	17.7	24.0	
At least once a week	14.8	11.3	18.5	
Seldom (housebound)	7.0	5.3	8.7	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MoCA-J, Japanese version of the Montreal Cognitive Assessment; PP, pulse pressure; SBP, systolic blood pressure; TG, triglycerides..
**P*-values are between ages of 70 and 80 years.
[a]CCB, ARB, ACEI, diuretics, β-blocker, renin inhibitor, aldosterone antagonist, and compounding agent. A total of 1973 participants answered the questionnaire and underwent the examinations, and they were analyzed after excluding those with missing data.

was lower in men compared with that in women at both 70 and 80 years. The MoCA-J total score was lower in men compared with that in women at age 70 years but not at age 80 years. Smoking habits and alcohol consumption were significantly different between men and women. The frequency of going outdoors was significantly higher in women compared with that in men at both age 70 and 80 years.

Comparison of participant characteristics divided by BP category

Table 2 displays the clinical characteristics according to BP categories within each age group. In participants at both age 70 and 80 years, significant differences between BP categories can be observed. SBP, DBP, and PP in the uncontrolled BP group were higher than those in the controlled BP group. The proportion with hypertension in the uncontrolled BP group was also higher than that in the controlled BP group. The proportion with DM in the uncontrolled BP group was higher than that in the controlled BP group at age 70 years but not at 80 years. Dyslipidemia and low-density lipoprotein cholesterol showed no significant differences at either 70 or 80 years. On the other hand, high-density lipoprotein cholesterol in the controlled BP group was higher compared with that in the uncontrolled BP group at age 70 years, whereas at age 80 years, the uncontrolled BP group showed higher values compared with the controlled BP group. BMI was higher in the uncontrolled BP group compared with that in the controlled BP group at both 70 and 80 years. Salt and fat intake showed no significant differences between BP categories. Smoking and alcohol consumption were significantly different between BP categories at age 70 years but not at age 80 years.

Table 2 Characteristics of study population according to BP categories within each age group

	70 years			*80 years*		
Characteristics	*Uncontrolled BP*	*Controlled BP*	P-*value*	*Uncontrolled BP*	*Controlled BP*	P-*value*
No. of participants	481	476		616	349	
Men (%)	51.1	43.3	0.015	44.5	51.3	0.042
SBP (mm Hg)	154.2±12.5	125.9±10.4	<0.001	156.9±13.2	128.3±9.1	<0.001
DBP (mm Hg)	84.7±9.9	74.0±8.4	<0.001	81.4±9.9	71.7±8.2	<0.001
PP (mm Hg)	69.5±13.1	51.9±9.7	<0.001	75.5±14.1	56.6±9.7	<0.001
HTN (%)	100	31.3	<0.001	100	49.6	<0.001
Taking medication for HTN (%)[a]	46.3	31.3	<0.001	54.5	49.6	0.137
Diabetes mellitus (%)	22.6	14.9	0.004	16.4	17.0	0.819
Dyslipidemia (%)	66.0	62.1	0.221	61.8	57.5	0.185
Serum total cholesterol (mmol l^{-1})	5.55±0.91	5.44±0.94	0.071	5.25±0.85	5.13±0.87	0.049
LDL-C (mmol l^{-1})	3.20±0.79	3.18±0.79	0.632	3.00±0.72	2.97±0.72	0.498
HDL-C (mmol l^{-1})	1.59±0.41	1.65±0.42	0.032	1.55±0.43	1.48±0.38	0.018
TG (mmol l^{-1})	1.65±1.00	1.33±0.72	<0.001	1.52±0.84	1.41±0.76	0.054
BMI (kg m^{-2})	23.3±3.0	22.4±2.8	<0.001	22.6±3.0	22.1±3.0	0.010
Serum albumin (g dl^{-1})	4.4±0.3	4.4±0.3	0.453	4.3±0.3	4.3±0.3	0.023
Salt intake (g per day)	12.3±4.1	12.3±4.1	0.786	12.6±4.6	12.4±4.3	0.555
Fat intake (g per day)	54.7±20.6	55.2±21.2	0.725	56.4±23.2	55.4±23.9	0.519
MoCA-J total score (0–30)	23.2±3.3	23.8±3.1	0.007	21.7±3.9	21.9±3.8	0.411
Visuospatial/executive (0–5)	4.4±0.9	4.3±0.8	0.641	2.8±1.3	3.0±1.4	0.004
Naming task (0–3)	2.9±0.4	2.9±0.4	0.723	1.5±1.2	1.7±1.2	0.008
Attention (0–6)	4.9±1.2	5.0±1.0	0.012	4.6±1.2	4.6±1.2	0.552
Language (0–3)	1.4±0.9	1.6±0.9	0.001	1.1±0.8	1.1±0.9	0.769
Abstraction (0–2)	1.3±0.8	1.4±0.7	0.075	1.2±0.7	1.2±0.8	0.526
Delayed recall (0–5)	1.8±1.6	1.9±1.6	0.135	1.9±1.6	1.9±1.6	0.978
Orientation (0–6)	5.9±0.4	5.9±0.4	0.816	5.7±0.7	5.8±0.6	0.163
Smoking (%)			0.031			0.462
Never	59.0	62.7		60.9	59.4	
Current	11.7	7.6		5.8	4.7	
Past	29.3	29.7		33.3	35.9	
Alcohol consumption (%)			0.007			0.203
Never	57.8	67.5		68.8	69.8	
Current	36.0	28.5		30.2	27.8	
Current excessive	6.2	4.0		1.0	2.4	
Frequency of going outdoors (%)			0.587			0.384
Once a day	45.0	46.5		32.8	28.1	
Five or six times per week	19.9	22.5		17.4	18.6	
Three or four times per week	17.8	17.1		22.1	26.6	
At least once a week	11.7	9.5		19.2	17.5	
Seldom (housebound)	5.6	4.4		8.6	9.2	

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MoCA-J, Japanese version of the Montreal Cognitive Assessment; PP, pulse pressure; SBP, systolic blood pressure; TG, triglycerides.
[a]Calcium channel blocker, angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, diuretics, β-blocker, renin inhibitor, aldosterone antagonist, and compounding agent.

The MoCA-J total score and subscales were significantly different between BP categories within each age group. More specifically, at age 70 years, the MoCA-J total score and two subscales, attention and language tasks, in the uncontrolled BP group were lower compared with those in the controlled BP group, whereas the MoCA-J total score showed no significant difference at age 80 years, except in the two subscales of visuospatial/executive functioning and naming tasks (Supplementary Table S1).

Supplementary Table S3 shows BP and cognitive functioning according to the treatment status within each age group. At age 70 years, SBP, DBP and PP in the treated group were significantly higher compared with that in the untreated group. In contrast, SBP, DBP and PP showed no significant differences at age 80 years. The MoCA-J total score was significantly different at age 80 years; in other words, the score in the treated group was significantly higher compared with that in the untreated group, although there was no significant difference in SBP between the treated and untreated groups at age 80 years (Supplementary Table S3). Similar trends were observed among subjects who were or were not taking ARB or CCB in both age groups (Supplementary Figure S3).

Table 3 Standardized multiregression coefficients (β) of age and BP category as predictors of MoCA-J total score

	70 years			*80 years*		
		Uncontrolled BP	*Controlled BP*		*Uncontrolled BP*	*Controlled BP*
SBP	−0.08*	−0.10*	−0.05	−0.03	−0.05	0.04
Taking medication for HTN	−0.05	−0.07	−0.04	0.04	0.03	0.05
Diabetes mellitus	−0.05	0.01	−0.11*	−0.04	−0.04	−0.03
Dyslipidemia	0.04	0.01	0.08	0.03	0.02	0.04
BMI	−0.07	−0.12*	−0.01	0.00	0.00	−0.02
Smoking	−0.08*	−0.08	−0.06	−0.02	0.01	−0.08
Excessive alcohol intake	0.01	0.02	−0.00	0.01	0.05	−0.04
Serum albumin	−0.05	−0.06	−0.04	0.08*	0.04	0.14†
Frequency of going outdoors	0.17‡	0.17†	0.17†	0.09†	0.14†	0.03
Sex	0.08*	0.11*	0.05	−0.02	0.01	−0.07
Adjusted R^2	0.074	0.094	0.058	0.023	0.030	0.042

Abbreviations: BMI, body mass index; BP, blood pressure; HTN, hypertension; MoCA-J, Japanese version of the Montreal Cognitive Assessment; SBP, systolic blood pressure.
Parameter estimates (β) can be interpreted as differences in cognitive function score for each 10 mm Hg increase in SBP.
*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

Effects of BP on cognitive functioning

The regression coefficients are shown in Table 3 and Supplementary Table S4. To examine the main effect of SBP on the cognitive functioning, we stratified the BP control status and antihypertensive treatment for each age group and used the same model in the stratified analysis. Because this study used a narrow age range design, there was no SBP × age interaction for cognitive functioning within each age group.

At age 70 years, SBP, BMI, smoking, sex and frequency of going outdoors were correlated with cognitive functioning. In the case of uncontrolled or treated BP, a negative association between SBP and cognitive functioning was found. However, in the controlled BP or untreated BP cases, there was no significant correlation between SBP and cognitive functioning; in contrast, DM was independently correlated with cognitive functioning in controlled BP cases at age 70 years. At age 80 years, on the other hand, SBP and other clinical factors were not significantly correlated with cognitive functioning. Serum albumin and frequency of going outdoors were significantly correlated with cognitive functioning. Additionally, in the case of controlled or treated BP, clinical factors were not correlated with cognitive functioning, except for the no-hypertensive treatment model.

DBP and PP were also examined in each age group, and we used the same model for ease of comparison with the subsequent BP analysis (Supplementary Table S5). Although DBP was not a significant predictor of cognitive functioning, the pattern of association between PP and cognitive functioning was similar to that observed with SBP.

DISCUSSION

A high BP in middle age has been suggested to be a predictive indicator of cognitive functioning and dementia.[5–7] We aimed to clarify the association between high BP and cognitive functioning in a general Japanese elderly population using the SONIC study, a large-scale longitudinal cohort study of elderly Japanese individuals in the general population.[22] In general, age is one of the crucial predictors of an elevated SBP and of cognitive functioning. Therefore, we investigated a cohort study involving participants within a narrow age range (the SONIC study) to specify predictors under conditions that minimize the influence of age.[23] This narrow age approach in the cross-sectional study may clarify differences in the influence of aging on the association between cognitive functioning and BP among those aged 70 and 80 years, accounting for important potential confounders of not only age but also medication for hypertension and dyslipidemia, BMI, smoking, excessive alcohol consumption, serum albumin as a predictor of the nutritional status and frequency of going outdoors as a predictor of activities.[23]

The most important finding of this study was a high SBP at age 70 years, especially in the case of uncontrolled BP (SBP ⩾ 140 mm Hg or DBP ⩾ 90 mm Hg), but not in the case of controlled BP, and this result may be independently associated with reduced cognitive functioning. This association indicates that high BP in later life is a risk factor for cognitive decline at age 70 years. Several cross-sectional studies suggested that uncontrolled BP was associated with reduced cognitive functioning compared with normal BP around the age of 70 years.[17,27] Our study supported these findings of an apparent age-related distinction. This is consistent with our primary hypothesis, which is attributed to the effect of aging on the association between BP and cognitive functioning. When we stratified the effect of antihypertensive treatment (Supplementary Table S4), a higher SBP was associated with reduced cognitive functioning in the treated BP group at age 70 years compared with the untreated group. In the previous randomized controlled trial, patients who had previously been treated with antihypertensive medication had lower mini-mental state examination scores compared with their untreated counterparts; however, they had a higher baseline SBP.[28] Our findings suggest similar results, whereby the level of control of SBP may be more important than taking a class on antihypertensive medication for the prevention of cognitive decline.

In contrast, no such associations were observed in participants aged 80 years. Although previous cross-sectional studies indicated a conflicting association between high BP and cognitive functioning, with positive and negative associations, most studies varied in terms of the ages and ranges of BP values of the participants; therefore, age may strongly influence the association between BP and cognitive functioning.[3,8,21,28] Several prospective studies demonstrated that middle-aged participants with hypertension still had a higher risk of cognitive decline and dementia in later life.[5–7] Additionally, one of the previous randomized controlled trials, which assessed the effects of antihypertensive intervention on cognition in patients aged 80 years or older, did not reveal a significant influence of BP on cognition.[29] Our study clearly demonstrated a positive association between high SBP and reduced cognitive functioning at age 70 years, but not at age 80 years, in a general Japanese population. However, when an individual

reaches his or her 80s, BP is controlled for many reasons other than to prevent cognitive decline. Also noteworthy is that our study does not suggest that BP control is unimportant after age 80 years because the beneficial effect of taking medication for hypertension (i.e., CCB and ARB) on cognitive functioning has been found only at age 80 years; nevertheless, the cognitive functioning of SONIC participants appeared less likely to be associated with BP at age 80 years. Recently, another Japanese study that included middle-aged participants reported the positive association of home BP with cognitive decline, but only in participants who were not prospectively treated with antihypertensive medication.[9] The age range of this study was relatively younger than that of the SONIC participants; therefore, medication adherence in this study may be better than in the SONIC study population (which recruited late-life volunteers). Because this Japanese study longitudinally investigated the relationship between home BP and cognitive decline,[9] the evidence level in this study was very high. Our present study confirmed the aforementioned study results in an elderly population. The SONIC study will also provide causal information about the association in those over 70 years of age based on future follow-up data collected every 3 years.

This study also demonstrated that DBP was not associated with cognitive functioning, whereas PP may have an important role in the progression of functional disability at age 70 years. Previous studies suggested that DBP and PP were also associated with a higher risk of cognitive decline; however, no such associations were observed at age 80 years.[10,30] These findings may suggest that SBP control at 70 years is more important in predicting cognitive functioning than DBP levels.

Frequency of going outdoors was the only variable to exhibit a unique association with cognitive functioning at both 70 and 80 years. Several previous studies suggested that a high frequency of going outdoors was directly linked to the levels of physical and cognitive functioning among community-dwelling older Japanese; therefore, high activity levels, such as going outdoors, may actually help preserve cognitive functioning in later life.[18,19] Our study may provide support for the suggestion that a high frequency of going outdoors exerts a protective effect against cognitive functioning decline by way of increased physical activity and social engagement.[18,19] Furthermore, serum albumin was significantly correlated with cognitive functioning at age 80 years. In previous case–control studies, serum albumin was reported to be decreased in patients with Alzheimer's disease,[31] and several cross-sectional studies showed that higher serum albumin was associated with higher cognitive performance.[32,33] Our study may indicate that a sufficient nutritional status and level of activity, such as the frequency of going outdoors, may prevent cognitive decline in both age groups.

The strength of our SONIC study was that the MoCA-J score, exhibiting a comparatively normal distribution, was sensitive compared with the mini-mental state examination (Supplementary Figure S2).[25] Only a few previous studies used the MoCA score, so we provided additional outcomes to examine the association between BP and cognitive functioning.[2]

On the other hand, there are several limitations of this study. First, most of our study participants voluntarily participated in the SONIC study. Thus, it is also probable that the study participants are relatively healthy and show lower rates of mild cognitive impairment and dementia than the normal population, including nonparticipants. Therefore, there is potential inconsistency between these results and previous studies at age 80 years, in that previous studies did not generally include this age group.[8,34] Study subjects at age 80 years did not demonstrate a positive association between SBP and cognitive decline in the present study. We speculate that the reason for this inconsistency with previous studies is mainly due to the age ranges of the study subjects. HYVET-COG (Hypertension in the Very Elderly Trial cognitive function assessmen)[29] indicates the negative association between high BP and cognitive function in study subjects over age 80 years. The result of HYVET-COG is consistent with our study results, although HYVET-COG is an randomized controlled trial design. However, the mean SBP, mean DBP and prevalence of hypertension observed in our SONIC study were similar compared with both Japanese national survey data from the Ministry of Health, Labor and Welfare, and with data from previous studies.[5,10,35,36] In fact, similar regression coefficients were observed compared with the previous studies.[28] Second, because of the study's cross-sectional design, our findings do not clarify whether high BP directly reduces cognitive functioning. Although we confirmed the absence of a correlation with cognitive functioning in the case of controlled BP, prospective findings are essential to clarify this issue. Third, the differences in the MoCA-J did not exceed the clinical cutoff point. Although this difference would not emerge in a clinical setting, the significance of the difference is noteworthy and contribute to important evidence of the association between SBP and cognitive functioning at age 70 years. Our study did not clarify the period of hypertension, considering midlife BP in relation to late-life cognitive decline, as assessed prospectively in the previous studies. Consequently, our study helps to clarify the association between late-life onset of hypertension and cognitive decline over the age of 70 years. Fourth, we could not clarify the influence of medication adherence in the present study, although SBP was strongly associated with cognitive functioning in participants treated with antihypertensive medication. Poor medication adherence caused by impaired cognitive functioning may affect these results. We have now begun examining medication adherence and will therefore be able to adjust for confounders, including medication adherence, in the follow-up analysis. Finally, we used self-reported questionnaires about the frequency of going outdoors as the indicator of activity. This may be a crude measure compared with energy expenditure; therefore, we need to use objective measures, such as digital devices that automatically measure activity level, walking speed and periods of activity.

In conclusion, our study clarified the difference in the influence of aging on the association between cognitive functioning and BP in the elderly. Because uncontrolled, high BP at 70 years is significantly correlated with cognitive decline, strict BP management from midlife according to high BP guidelines may protect against cognitive decline. Furthermore, an adequate nutritional status and daily activities, such as the frequency of going outdoors, are very important for preventing cognitive decline in old age, especially over the age of 80 years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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STUDY PROTOCOL Open Access

ICC-dementia (International Centenarian Consortium - dementia): an international consortium to determine the prevalence and incidence of dementia in centenarians across diverse ethnoracial and sociocultural groups

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Abstract

Background: Considerable variability exists in international prevalence and incidence estimates of dementia. The accuracy of estimates of dementia in the oldest-old and the controversial question of whether dementia incidence and prevalence decline at very old age will be crucial for better understanding the dynamics between survival to extreme old age and the occurrence and risk for various types of dementia and comorbidities. International Centenarian Consortium – Dementia (ICC-Dementia) seeks to harmonise centenarian and near-centenarian studies internationally to describe the cognitive and functional profiles of exceptionally old individuals, and ascertain the trajectories of decline and thereby the age-standardised prevalence and incidence of dementia in this population. The primary goal of the ICC-Dementia is to establish a large and thorough heterogeneous sample that has the power to answer epidemiological questions that small, separate studies cannot. A secondary aim is to examine cohort-specific effects and differential survivorship into very old age. We hope to lay the foundation for further investigation into risk and protective factors for dementia and healthy exceptional brain ageing in centenarians across diverse ethnoracial and sociocultural groups.

Methods: Studies focusing on individuals aged ≥95 years (approximately the oldest 1 percentile for men, oldest 5th percentile for women), with a minimum sample of 80 individuals, including assessment of cognition and functional status, are invited to participate. There are currently seventeen member or potential member studies from Asia, Europe, the Americas, and Oceania. Initial attempts at harmonising key variables are in progress.

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Discussion: General challenges facing large, international consortia like ICC-Dementia include timely and effective communication among member studies, ethical and practical issues relating to human subject studies and data sharing, and the challenges related to data harmonisation. A specific challenge for ICC-Dementia relates to the concept and definition of'abnormal' in this exceptional group of individuals who are rarely free of physical, sensory and/or cognitive impairments.

Keywords: Centenarians, Dementia, International, Prevalence, Incidence, Risk factors

Background

The prevalence of dementia in centenarian studies varies widely from 27 % (or 42 % once drop-outs were accounted for [1]) to 76 % [2] and even 85 % (albeit in a small sample [3]). Reasons for this variability include small sample sizes, non-ascertainment of all centenarians within a selected region, the healthy volunteer effect, non-inclusion of residents in skilled nursing facilities, refusal of proxy-consent by 'protective' family members, frequent shift in residence owing to care needs, and other potential biases. Longitudinal studies suffer the limitation of selective attrition, particularly due to high mortality in such an elderly sample. Additionally, not all studies demand adequate proof of age, a problem particularly relevant when the claimed age is greater than 110 years old ([4, 5]).

In the context of dementia diagnosis, accurate cognitive assessments of centenarians can be challenging due to decreased stamina and difficulty with hearing and/or vision, and most studies, at least to date, have not used an adequately sensitive battery of tests to rule out false negative results. Differences in cognitive assessment tools, variability in diagnostic criteria, and difficulty in selecting an appropriate comparison group are further challenges in comparing and/or merging results from different studies. Birth year cohort-specific influences are likely to also explain differences between studies, with accumulating evidence that the age-specific incidence of dementia may be decreasing in high income countries [6]. Cho et al. [7] found that a later cohort of centenarians was significantly better off in mental, physical, social and economic domains. A recent UK study found later-born individuals to have a lower risk of dementia [8]. Steen [9] found similar cohort effects in five different cohorts of 70 year olds, with later cohorts performing significantly better than their earlier counterparts, although a Swedish study [10] found no differences in cognitive function between two cohorts. Influences of environment, such as climate [11] and geography, including rural versus urban [12], may need to be taken into consideration when examining dementia prevalence and its determinants in different populations. Dietary factors may also play a role, however data remain insufficient to date.

Given the limitations of prevalence data, it can be argued that incidence data on dementia might offer a better metric to examine the cognitive profile of this age group. However, only a handful of studies have provided incidence data on dementia in the oldest-old [13], most of which have few participants at the oldest ages and sometimes all participants aged over 90 years are combined into a single age category. A review, with sufficient age-specific data, contends that dementia incidence increases in the age range of 95–115 years [13]. A North American study, with baseline ages of 90–103, also observed an increase in dementia incidence with age [14]. Other studies that include participants aged 95 or over, observed a *slowing* of the age-related increase in incidence of dementia [15, 16], and a decline in rates for men [17, 18]. Finally, a study that included the oldest 0.01 percentile (e.g. currently 110+ years old) has demonstrated the progressive compression of both disability and morbidity (in 6 diseases including dementia) with older ages of survival beyond 100 years [19]. Given these different results further examination of the incidence of dementia for males and females for different age groups among the oldest ages is warranted.

Another approach taken by investigators is to examine specific cognitive functions in this group. Although relatively unexplored in the oldest old, it appears that episodic memory continues to decline through the 10th and 11th decades of life [20] with processing speed [21] and attention [22] being particularly susceptible to ageing. By contrast, many aspects of language [23] as well as executive functions [24] may remain intact with increasing age, although the data are limited by small sample sizes. The domains of cognitive function most susceptible to advanced ageing, and their magnitude of decline, have important bearing on the differentiation of the transition from normal cognition to mild cognitive impairment and dementia. In general, the patterns appear similar to cognitive changes observed in younger cohorts [25], although much more extensive evaluation of this dynamic is needed.

Some research has been conducted on risk and protective factors of dementia onset in centenarians, but little is known about the course and rate of this decline [26]. The limited data available suggest that some exceptionally long-lived individuals share risk factors for

dementia with their younger counterparts [26], such as African American race [27], low education [27], smoking [28], and poor physical health as evidenced by strength, balance and gait measures [29]. Conversely, a well-known genetic risk factor for Alzheimer's disease, the apolipoprotein E ε-4 allele, is rare amongst centenarians [30, 31]. Similarly, a number of risk factors for cardiovascular disease, although consistent in predicting cognitive impairment in younger cohorts [32], have different effects on cognition in older populations [33]. Interestingly, a number of studies recently demonstrated that centenarians have frequencies of disease-associated genetic variants that are similar to the general population [34, 35]. Yet, as noted above, people achieving ages over 105 years tend to avoid or delay such age-related diseases [19]. Bergman and colleagues [36] noted this "buffering effect" of certain genes previously, however limited research exists on the relation of this effect to dementia.

Most existing studies of the oldest old are necessarily small, limiting the power to appropriately examine prevalence and incidence data, cognition and risk factors. Data harmonisation across numerous studies is a cost-effective approach with increased statistical power that offers the potential to explore both existing and novel research questions. Harmonising data across studies to create a single, large database permits evaluation of both study-level and individual-level effects, and the direct comparison of results across studies with opportunity for immediate evaluation of differences, when found, and additional analyses to reconcile such differences [13, 27]. It is important to note that the provenance and contextual information of each study must be taken into account in any such analysis. Other benefits of collaboration include accelerated accumulation of scientific knowledge and enhanced generalisability associated with using a larger heterogeneous sample [13].

In the proposed consortium of centenarian and near-centenarian studies, comprising at least fifteen datasets from Asia, Europe, the Americas, and Oceania, The Dementia Harmonisation Project of the International Centenarian Consortium (ICC-Dementia https://cheba.unsw.edu.au/group/icc-dementia) plans to address the epidemiological challenges confronting the study of this exceptional group of individuals. The Consortium's objectives are to: (i) determine the sex specific and percentile of survival-standardised prevalence and incidence of dementia and likely dementia type at the extreme tail of survival; (ii) delineate subgroups of cognitive function and their specific patterns of cognitive decline; (iii) identify associated risk and protective factors for dementia and healthy brain ageing that cross or do not cross ethnic and cultural lines; and (iv) examine the influence of contextual factors such as population ageing, survival rates and differential causes of death in different countries on the cognitive health of the oldest old.

Methods

Membership

Studies are eligible to participate in ICC-Dementia if they meet the following criteria: (i) the focus is on individuals aged ≥95 years; (ii) have a minimum sample of 80 individuals; (iii) assessment includes measures of cognitive function; and (iv) informed consent allows for de-identified data sharing with academic partners. Official enrolment in ICC-Dementia involves a lead investigator's signed memorandum of understating (MOU) to share de-identified raw and/or processed data for mega-analyses as well as comparative analyses. All participating studies have the opportunity to participate in the analyses and to propose specific projects and papers. ICC-Dementia was established in 2012, as part of the long established International Consortium of Centenarian Studies (ICC), and has stated interest in participating from the 17 studies listed in Table 1. At the time of writing this report, data had been received from eight of these studies and others were in the process of submitting institutional review board protocols.

Structure of the consortium

Each study is invited to provide one member for the Steering Committee, which leads the scientific agenda of the consortium and provides governance. Rules of participation approved by the Steering Committee include regulations about approval of projects, timelines for analyses, presentations and publications. New member studies are invited by the Steering Committee by consensus. Periodic teleconferences are planned to discuss scientific and administrative issues of the consortium, with some special teleconferences and/or videoconferences to deliberate case vignettes and agree upon common criteria. Consortium members plan to meet face-to-face once a year at the annual meeting of the International Centenarian Consortium, or another suitable international meeting, and most recently met in June 2015 in Sardinia, Italy.

Website

A website has been constructed and is an information resource for potential members and the general public, https://cheba.unsw.edu.au/group/icc-dementia. A secure section of the website will be used for data queries.

Ethics

The ICC-Dementia project has been approved by the Human Research Ethics Committee of The University of New South Wales, Sydney. Member studies are responsible for obtaining approval, when considered necessary, from their local institutional review board for the sharing of data.

Table 1 Contributing Centenarian Studies

Study	Setting	Sample of centenarians	Age range	Females (%)	Race/Ethnicity	Start/end date	Reference	Centenarians per 100,000 people (year of estimate)
Sydney Centenarian Study (SCS)[a]	Sydney, Australia	345+	95–106	72	Caucasian	2008-ongoing	[48]	18.75 (2010) [55]
New England Centenarian Study (NECS)	Boston, USA	1500+	100–119	76	Caucasian	1994-ongoing	[56, 57]	22.6 (2014) [58]
Georgia Centenarian Study (GCS)	Georgia, USA	381	98–110	82	Caucasian African American	1988–2009	[59]	22.6 (2014) [58]
Tokyo Centenarian Study (TCS)[a]	Tokyo, Japan	304	100–108	79	Japanese	2000–2002	[20, 45, 60]	42.76 (2013) [61]
Swedish Centenarian Study (SwCS)[a]	Southern Sweden	100	100–101	82	Caucasian	1987–1992	[39]	20.1 (2014/15) [62]
Gothenburg 95+ Study (Go95+)[a]	Gothenburg, Sweden	1020	95–109	82	Caucasian	1996–2015	[63]	20.1 (2014/15) [62]
90+ Study (90+)[a]	California, USA	960	95–107	79	Caucasian	2003–2007	[64]	22.6 (2014) [58]
Cognitive Function and Aging Study (CFAS)	England and Wales, UK	700	95–100+	NA	Caucasian	1991–1994	[65]	21.49 (2013) [66]
Longevity Gene Project (LGP)[a]	New York, USA	462+	95–110	75	Caucasian	1998-ongoing	[67]	22.6 (2014) [58]
Five Country Oldest Old Project (5COOP)	Montpellier, France	1241	100	80	Danish (251), French (211), Japanese (337), Swedish (274), Swiss (168)	2011–2014	Personal correspondence	NA
Polish Centenarian Study (PCS)[a]	Katowice, Poland	86+	99–105	81	Caucasian	2007-ongoing	[68, 69]	8.015 (2010) [70]
Spanish Centenarian Study (SpCS)	Valencia, Spain	47+	98–107	74	Caucasian	2010-ongoing	[71]	26.44 (2013) [72]
Oregon Brain Aging Study (OBAS)	Oregon, USA	156+	55–111	60	299 Caucasian, 2 Native American, 3 Asian	1989-ongoing	[73]	22.6 (2014) [58]
Monzino 80+ Study (M80+)	Varese Province, Italy	542+	95–107	71	Caucasian	2002-ongoing	[74]	29.42 (2014) [75]
Hong Kong Centenarian Study (HKCS)	Hong Kong	153	95–108	78	Chinese	2009–2011	[76–78]	26.73 (2011) [79]
Centenarians at Trieste (CaT)	Trieste, Italy	100+	100+	90	Caucasian	2014-ongoing	[80]	29.42 (2014) [75]
The 100+ Study (100+)	Amsterdam, The Netherlands	133+	100–115	75	Caucasian	2013-ongoing	Personal correspondence	12.4 (2014) [81]

[a]data received

Data harmonisation

ICC-Dementia faces numerous challenges associated with data harmonisation, many of which have been previously described [27, 37]. The major challenge stems from differences between studies in design, language used for assessment, the measurement instruments used and/or differences in how questions from similar instruments are worded and responses are categorised. Cultural factors influence many of the measures and the response bias of participants. Attempts to maximise the number of studies contributing to a final dataset can require that complex information be simplified, e.g., converted from a continuous measure to a categorical scale. Although there is a possible reduction in validity involved in simplifying data, there are mechanisms by which this can be tested (see below) [27].

ICC-Dementia will harmonise demographic data, scores on screening measures of cognitive function (e.g. Mini-mental State Examination, MMSE [38]), neuropsychological test data and measures of functional status. Data received will be handled according to the following protocol:

Demographic data

All studies provide age in years, birth year and sex; these variables will require minimal recoding to common scales. Education is categorised into a four-level scale of the highest level of education achieved (less than high school completion, high school completion, technical or college diploma, university degree).

Measures of cognitive status

Table 2 shows the cognitive and functional measures available from each of the participating studies. Score ranges and means will be reported for all measures, with appropriate cut-offs derived using all available data from each contributing study. Where there is no overlap in specific measures between studies, when possible, published data on equivalence of scores and thresholds for different measures are used. For example, the MMSE was not administered in the Swedish Centenarian Study [39], so equivalence of scores on the Berger Scale [40, 41] are used.

Harmonisation plan for neuropsychological test performance

Different studies' test batteries differ in the tests included, versions of the same test, and methods of administration and/or scoring. Inspection of the range of tests available from each study led to the decision to obtain scores from as many studies as possible for the following five domains: memory, attention/processing speed, language, executive function and visuospatial/constructional function. Tests are allocated to domains consistent with common practice [42, 43]. To harmonise neuropsychological test scores across studies, raw scores are converted to Z-scores, adjusted for age, sex and education, using the means and

Table 2 Mental status and dementia scales used by contributing studies

Study	SCS	NECS	GCS	TCS	SwCS	Go95+	90+	CFAS	LGP	5COOP	PCS	SpCS	OBAS	M80+	HKCS	CaT	100+
Mental status or cognitive scales																	
MMSE	✓	✓[a]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ACE-R	✓																
CPRS						✓											
CAMCOG								✓									
CASI-S							✓										
ADL scale	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Neuropsychological data	✓	✓[a]	✓	✓[a]	✓	✓	✓	✓		✓			✓	✓		✓	✓
Dementia scales																	
CDR	✓	✓[a]	✓	✓		✓	✓			✓			✓			✓	
GDS			✓	✓								✓	✓				
BDS		✓												✓			
Berger					✓												
MDRS		✓[a]				✓											
AGECAT								✓									
CAMDEX								✓									

ACE-R Addenbrooke's Cognitive Examination, *AGECAT* Automated Geriatric Examination for Computer Assisted Taxonomy, *BDS* Blessed Dementia Scale, *CAMDEX* Cambridge Examination for Mental Disorders in the Elderly, *CAMCOG* the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly, *CASI-S* Cognitive Abilities Screening Instrument-Short, *CDR* Clinical Dementia Rating Scale, *CPRS* Cognitive Participation Rating Scale, *GDS* Global Deterioration Score, *MDRS* Mattis Dementia Rating Scale, *MMSE* Mini-Mental State Examination

[a]Data only available for a subset of the sample

standard deviations (SD) of an appropriate reference group. Most contributing studies that have neuropsychological data use a contemporaneous younger, culturally-equivalent cohort as the reference group to norm centenarian data; we will obtain these data from each contributing study. For studies that may not have these data available, we source a younger, culturally equivalent cohort as a reference group. This can be achieved using data from another consortium within our group, i.e. the Cohort Studies of Memory in an International Consortium (COSMIC) [44], where data have already been received from 11 different countries. Performance on a test or in a cognitive domain is regarded as impaired or exceptional if its Z-score, calculated using the mean and SDs of the reference group, is less or greater than 1.5 SD from the mean.

Functional data

Contributing studies differ in their assessment of functional ability both in instruments used and in areas of functional ability assessed, e.g. basic versus instrumental activities of daily living. In order to harmonise data, the most common and compatible items are chosen to form harmonised variables [45], although this requires judgement by an assessor which may be subjective.

Harmonisation of risk factor variables

We harmonise risk variables using standard definitions for hypertension, diabetes, high cholesterol, alcohol use, body mass index (BMI), etc. Some of the procedures, developed as part of our multiple longitudinal studies (Sydney Memory and Ageing Study (MAS) [46], Older Australian Twins Study [47] and Sydney Centenarian Study [48]) have been used previously in a project where MAS data were harmonised with data from the Australian Imaging Biomarker and Lifestyle (AIBL) Study [40].

Dementia diagnoses

Dementia, or Major Neurocognitive Disorder as designated in DSM-5, is diagnosed on the basis of DSM-IV [49] and DSM-5 [50] criteria within a subsample of the consortium studies. Diagnoses are made via an algorithmic approach supported by clinical consensus meetings for five of the consortium studies. Participants are categorized as having dementia if they exhibit significant cognitive impairment from a previously stable level and these cognitive deficits are interfering with independence in everyday living. Cases are brought to consensus meetings if the diagnoses differ from those given previously by the study investigators, or if other factors, e.g. sensory or motor problems impacting performance, are present and not easily incorporated into an algorithmic approach. Expert panels comprising physicians (minimum of two neurologists, neuropsychiatrists, psychogeriatricians or geriatricians) and one or more neuropsychologists make consensus diagnoses, using all available clinical, neuropsychological, laboratory and imaging data to do so. The panel takes into account cross-cultural issues, fatigue, multi-morbidity and sensory abnormalities. Inter-rater reliability between panels is established with a representative set of 20 cases being reviewed by all panels.

Statistical analyses

Prevalence and incidence data

Overall rates from the different studies will be age-standardised to allow direct comparisons to be made between studies with different age distributions and sampling methods. The age distribution of the sample formed by pooling all participating studies will be used as the standard distribution to which all studies will be adjusted. Participants will be divided into 5-year age categories and rates will be obtained for each of these age ranges. The standardized rate (SR) for each of the studies will be calculated using the following formula: SR = (SUM (ri x Pi))/SUM Pi, where ri is the rate in each of the 5-year age ranges, Pi is the proportion of the population in the standard distribution in each of the 5-year age ranges, and SUM is the sum of values over each of the age ranges, "i". Birth years of the various cohorts will be taken into account.

Cognitive data

For the analysis of patterns of change in cognition over time, as measured by continuous variables with distributions close to that of the normal distribution, Linear Mixed Modelling (LMM) will be employed. This procedure will minimise bias due to non-random attrition, and allow whole-of-sample analyses. For the analysis of non-normally distributed continuous variables, these can be transformed to approximate the normal distribution better using the Box-Cox procedure so that LMM procedures can be used. Alternatively, Generalized Linear Mixed Modelling (GLMM) can be used with an appropriate link function (e.g. loglinear, negative binomial) depending on the nature of the distribution. To allow for asynchronous measurement occasions across studies, time will be modelled as a continuous independent variable, with non-linear effects examined by the introduction of polynomial power terms into the equation. The compression of morbidity hypothesis will be investigated by examining the correlation between the age of onset of dementia (determined both historically and by examining incident cases) with the time interval between the onset and the time of death. A negative correlation would provide support for the hypothesis.

Risk factors

For the examination of risk factors for dementia, survival analysis using Cox regression, and also GLMM, will be used. For the GLMM analyses, the logit link function will be used to accommodate the binary outcome variable. Both procedures allow for whole of sample analyses to minimise bias due to selective attrition over time, and reduce the loss of power due to smaller samples if only cases with complete data were used. For both procedures, risk factors will be entered as independent variables, together with other appropriate control variables (sex, age and education). To examine whether the operation of risk factors vary across studies or different national-cultural groups, such factor(s) will be included in the equations, together with interactions between these factors and the risk-factor variables.

Discussion

Challenges

General challenges facing large international consortia have been described previously [51]. These include funding, timely and effective communication among member studies in different countries and, data harmonisation. Specific challenges for ICC-Dementia relate to the identification of cognitive and functional impairment and the diagnosis of dementia in this exceptional group of long-lived individuals where testing is subject to numerous constraints and normative data are lacking. Additionally, the included studies vary in their age ranges, with most including both nonagenarians and centenarians. Considering that nonagenarians (5th-15th percentile of survival for men and women born in 1900 and thereafter) are increasingly common and centenarians (<1 percentile of survival) are still relatively rare, they likely represent different phenotypes in terms of underlying environmental and genetic influences and therefore risks of age-related diseases and disability [52]. Thus, grouping nonagenarians with centenarians, or claiming that a study of primarily nonagenarians is a study of the oldest 1 percentile runs the risk of missing important differences. We recently reviewed the many challenges of diagnosing dementia in this group and proposed some solutions [53]. Although the approaches for diagnosing dementia in centenarians vary widely, the essential denotation of a dementia diagnosis is that the individual has experienced a decline in cognitive function from a previous level to the extent that their independence in everyday activities has been affected and this decline is not better explained by some other physical or mental disorder. Challenges for ICC-Dementia include operationalising cognitive decline, defining what is 'normative' [53], attributing functional impairment to cognitive decline in the presence of physical and sensory impairments [54], and doing this for populations that differ greatly in education, language and cultural expectations.

Future projects

Future ICC-Dementia projects are planned which endeavour to make comparisons between cohorts, countries and ethnic groups. These include: (i) the cognitive profile and trajectory of cognitive decline in centenarians and near centenarians; (ii) risk and protective factors for dementia and exceptional healthy brain ageing; and (iii) where possible, biomarkers (e.g. blood, genetic and MRI-derived) of dementia in the oldest old.

It is expected that future work will investigate more refined and specific topics addressing the overall objectives of ICC-Dementia. These could include systematic investigation of the 'compression of morbidity hypothesis' and the association between cognitive and physical frailty. These projects will be enabled and facilitated by increasing the number of ICC-Dementia member studies to ensure that there are sufficient data on variables not collected by all studies. The ICC-Dementia is open to membership to other studies that meet the eligibility criteria. We envision the ICC-Dementia setting the stage for an ambitious well-coordinated study of cognitive impairment and dementia in the oldest old.

Conclusions

The accuracy of estimates of the number of people with dementia and the unanswered question of whether dementia continues to rise with age are crucial for health planning and care of the very old. The identification of cohort-specific and non-specific influences on survival to very late life and risk factors for dementia will provide insights into underlying mechanisms of delaying or escaping common dementias. The dementia-free centenarians, and those who delay the onset of dementia until very late in life, can serve as models of healthy brain ageing, potentially providing insights for the entire population.

Declarations

Ethics approval

ICC Dementia was approved by the Human Research Ethics Committee at the University of New South Wales. https://research.unsw.edu.au/human-research-ethics-home.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Abbreviations

ADL: activities of daily living; AIBL Study: Australian Imaging Biomarker and Lifestyle Study; APOE: apolipoprotein E; BMI: body mass index; COSMIC: Cohort Studies of Memory in International Consortium; GLMM: Generalized Linear Mixed Modelling; ICC-Dementia: International Centenarian Consortium–Dementia; LMM: Linear Mixed Modelling;