Title:

Widened Pulse Pressure is a Potential Risk Factor for Significant Cognitive Impairment among Community-Dwelling Chinese Younger Old People

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Abstract

Hypertension is a risk factor for dementia, but its exact role in contributing to dementia remains unknown. We conducted a community-based retrospective cohort study to examine the association of hypertension and widened pulse pressure (PP) with incident significant cognitive impairment (SCI) in the Chinese older people in Hong Kong. A total of 1925 subjects who were 65 years and older, ethnic Chinese, and community-living, with no history of cerebrovascular accidents or dementia, were recruited. Demographics, medical history, and physical parameters recorded at baseline were retrieved for analysis. Primary outcome was SCI developed in 6 years, which was defined by the presence of clinical dementia, scoring below the cutoff point on the Cantonese version of the Mini-Mental State Examination, and/or a global Clinical Dementia Rating of 1 to 3. Our data showed no difference in the point prevalence of pre-existing hypertension between subjects who remained cognitively stable and those who developed SCI (64.2% versus 65.8%; χ^2 test, p=0.68). However, subjects with incident SCI had a higher baseline PP (70mmHg versus 66mmHg; Mann-Whitney U-test, p=0.03) and a decreasing trend in PP with time. Multiple logistic regression analysis showed that PP had a small but significant effect on the risk of SCI among the younger old subjects (OR=1.02, p=0.03). Our findings suggested that widened PP might be a risk factor for SCI among the younger old

people. Further studies are needed to ascertain the association between hypertension and SCI in the Chinese older population and how widened PP contributes to SCI.

Keywords: hypertension, pulse pressure, cognitive impairment, older people

Introduction

Dementia is a syndrome characterized by progressive global cognitive decline, resulting in an appreciable deterioration in intellectual functioning and interference with personal activities of daily living [1]. In view of the limitations in modifying the disease burden, current research focuses on the identification of risk factors to prevent or delay the onset of cognitive decline. Age, genetic predispositions, and cerebrovascular diseases are recognized risk factors for Alzheimer's disease and vascular dementia [2, 3]. Vascular risk factors, in particular hypertension, however, have a less straightforward association with cognitive impairment. Longitudinal population-based studies suggested that mid-life hypertension increased the risk of late-life cognitive impairment [4, 5], whereas hypertension and hypotension at late life were associated with cognitive impairment [6, 7]. Nevertheless, the underlying mechanism of how hypertension at different stages of life affects cognition is not well understood [8], and it remains controversial whether systolic or diastolic hypertension plays a more important role in the development of cognitive impairment [9]. Furthermore, the target blood pressure (BP) for a cognitively beneficial effect has yet to be determined [10]. Convincing evidence supporting that anti-hypertensive treatment can lower the risk of dementia and cognitive impairment in patients with no known cerebrovascular disease is still lacking [11]. Hence, further studies examining

the relationship between hypertension and dementia are much needed.

Apart from systolic blood pressure (SBP) and diastolic blood pressure (DBP), a major component of BP is the pulse pressure (PP), which is the difference between SBP and DBP. PP is a surrogate measure of the arterial stiffness. Prospective population-based studies of heart diseases suggested that the higher the PP a person had, the greater the chance of developing cardiovascular events [12, 13]. However, there has been no consensus as to the normal range of PP for different age groups despite PP is known to change with age. In early mid-life, SBP and DBP increase in parallel, so PP remains relatively stable. In late mid-life, SBP continues to increase while DBP starts to level off or even decline because of arterial stiffness, causing PP to increase progressively with time [14]. Several recent studies have suggested that a higher PP is associated with late-life cognitive impairment [15–17], and arterial stiffness is believed to play an important role in the development of cognitive impairment and dementia [18, 19]. However, the longitudinal trend of PP in older people with dementia, which is likely to be different from that in people with normal cognition because both SBP and DBP are noted to decrease a few years prior to the onset and during the course of dementia [20, 21], is not well studied. Hence, additional studies are needed to determine if PP may be used as a predictor for dementia among the older people.

In Hong Kong, majority of the population is ethnic Chinese, and the proportion of older people suffering from cognitive impairments is similar to that of the mainland counterparts [22–25]. Although the prevalence of mid-life hypertension is comparable with that of developed countries, the prevalence of late-life hypertension is much higher, with 66.3% of people aged 65 to 74 years in Hong Kong having hypertension [26] comparing to 53% in the North American countries [27]. Given the differences in the prevalence of hypertension and the population demographics between the Chinese and the Caucasian communities, it would be of interest to find out whether hypertension is also an independent risk factor for cognitive impairment among the Hong Kong Chinese older people and whether PP can be predictive of cognitive impairment in the Chinese older population.

In this retrospective cohort study, we aimed to examine if hypertension and PP were associated with development of significant cognitive impairment (SCI) in community-living Chinese older people over a 6-year period. The findings may provide some additional insight into how PP, a potential proxy marker for arterial health, contributes to the development of cognitive impairment in later life.

Methods

Participants:

Participants in this community-based retrospective cohort study were drawn from all the people who attended the Elderly Health Centre (EHC) in Nam Shan district (one of the 18 EHCs in Hong Kong) in 2005. The EHCs were set up by the Elderly Health Services (EHS) of the Department of Health of the Government of Hong Kong Special Administrative Region (HKSAR) in 1998. With one EHC established in every district of Hong Kong, these public walk-in clinics provide annual primary health care for the interested local residents aged 65 years and above. In 2005, 37620 older people aged 65 years and above attended EHCs in Hong Kong for clinical and cognitive assessment.

Eligibility requirements for this study included subjects who were 65 years and older, ethnic Chinese, and community dwelling, with no known history of cerebrovascular accidents or dementia when they attended the Nam Shan EHC in 2005. Subjects who were living in old-aged homes, had history of cerebrovascular accidents, and/or had SCI as defined by presence of clinical dementia or scoring below the cutoff point on the Cantonese version of the Mini-Mental State Examination (C-MMSE) – 18 or below for illiterate subjects, 20 or below for those having 1 to 2 years of education, and 22 or below for those with more than 2 years of education [28] – were excluded.

Clinical assessment:

At baseline and in the annual re-assessments, subjects were interviewed at EHC by trained nurses and doctors using questionnaires covering demographics and medical history including hypertension, diabetes mellitus (DM), hypercholesterolemia, heart disease, cerebrovascular disease, dementia, smoking and drinking pattern, and depression. In addition, physical parameters such as body weight, body height and body mass index (BMI), BP, and fasting total cholesterol level were measured. Glycated hemoglobin (HbA1c) was also measured for subjects who had DM.

BP measurement:

Brachial BP was measured with an electronic sphygmomanometer using an appropriately sized cuff after the subject sat at rest for at least 5 minutes. Subjects with SBP ≥140mmHg and/or DBP ≥90mmHg would have their BP rechecked again after resting for another 5 minutes, and the average of the two BP readings would be used for analysis. Subjects with average SBP ≥140mmHg or average DBP ≥90mmHg were defined as having hypertension. PP was measured by subtracting DBP from SBP.

Cognitive assessment:

Cognitive status was examined by the EHC staff at baseline and in the annual re-assessments. The Simplified Memory Test (SMT), which was equivalent to the 3-object delayed recall test, was used to screen for any significant memory problem among subjects who had no known history of dementia or no report of memory impairment. C-MMSE was performed on subjects who failed to score full marks in SMT, had history of dementia, complained of memory decline, or were noticed by others to have memory problem. Subjects who did not attend EHC for re-assessment were traced by the research assistants, and C-MMSE and Clinical Dementia Rating (CDR) were used to evaluate their cognitive function. CDR is a semi-structured interview and evaluates six domains of cognitive and functional performance, namely memory, orientation, judgment, community affairs, home and hobbies, and personal care. The scoring is based on the information collected from the subjects and their informants and the clinical judgment of the rater [29]. A global CDR of 0, 0.5, 1, 2, and 3 is given to subjects who have no dementia, very mild dementia, mild dementia, moderate dementia, and severe dementia, respectively. CDR has been widely used as a clinical staging tool for dementia, including in the Asian populations where its validity and reliability had been published elsewhere [30]. In this study, the inter-rater reliability of CDR among the research team members, measured by the intraclass correlation, was 0.86.

Data collection for follow-up assessments:

For participants who attended at least two follow-up assessments at any EHC between 2006 and 2011, with at least one assessment since 2008, anonymized data were retrieved from the database of EHS for group analyses. For participants who had less than two assessments at EHCs since 2006 or had no follow-up since 2008, active tracing was performed. EHS would first crosscheck the subjects' names with the Deaths Registries of the Government of HKSAR. For subjects not identified in the Deaths Registries, postal and/or phone contacts were made for invitation of follow-up. Subjects who agreed for assessment were interviewed at EHC or at home by trained research assistants and geriatric psychiatrists. Informed consent was obtained from each subject before the assessment was started. In the occasional situation when the subjects were mentally incapable in giving consent for assessment, consent from their relatives was sought. In this study, tracing and assessment of the defaulted subjects was conducted from October 2011 to February 2012. Clinical interview, measurement of physical parameters, and cognitive assessment were performed by the research team in the same way as done by the EHC staff, with the exception of using CDR as an additional tool of outcome measurement. In some occasions when the defaulted subjects agreed for phone interview only, assessment of cognition using CDR and

enquiry of medical history were conducted over the phone.

Primary outcome:

The primary outcome in this study was incident SCI, which was defined by the presence of dementia in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [31], scoring below the cutoff point on C-MMSE, and a global CDR of 1–3.

Sample size estimation:

The sample size estimation was performed using the Power and Precision software version 3.0 (Biostat, Englewood, New Jersey, USA). Sample size was obtained from estimates of conversion rate of SCI and previous estimate of major risks for dementia in Hong Kong. Given that the participants at EHC were community-dwelling older people with no clinical dementia at baseline, an estimate of 6% incidence for SCI over a 6-year period was adopted [32]. For sample size estimates from computation of significant predictors, 48% of the variance for dementia diagnosis could be explained by gender, age, education, exercise participation and significant cerebrovascular risks [22]. With covariates of age and education estimated as significant variables, for 100 cases of SCI identified, the power for estimation of

risk factors would be 80% power (α=0.05). A baseline sample of 2,000 participants would yield adequate power for detection of cognitive outcomes at follow-up.

Statistical analyses:

All other analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 17.0 (SPSS, Chicago, Illinois, USA). Normality of the data distribution, which was found to be positively skewed in this study, was assessed with the Kolmogorov-Smirnov test. The prevalence of hypertension of our sample was compared with that of the general older population using the one-sample *t*-test. Comparison of baseline continuous and categorical variables between the two groups (subjects who remained cognitively stable and those who developed SCI in 6 years) was analyzed with the Mann-Whitney U-test and the Chi-squared (χ^2) test, respectively. To examine if late-onset vascular risk factors (hypertension, DM, hypercholesterolemia, heart disease, and CVA) were associated with incident SCI, subjects who had no vascular risk factors at baseline but were diagnosed with vascular risk factors during the follow-up period prior to the development of SCI were selected, and χ^2 test was used for analysis. The level of statistical significance was set at $p<0.05$. To determine if widened PP and other factors at baseline were risk factors for SCI, variables with statistical significance of $p<0.1$ were selected as potential confounders

and entered into the multiple logistic regression model. The odds ratios (ORs) were computed to yield point estimates with a 95% confidence interval (CI). To look for any changes in PP with time, subjects who had re-assessment in both 2008 and 2011 were selected, and the median PP in 2005, 2008, and 2011 were compared with one another in pairs using the Wilcoxon test. Using the Bonferroni correction, the cutoff for statistical significance for the longitudinal changes in median PP was set at $p<0.01$.

Results

Baseline characteristics:

A total of 2071 subjects attended EHC in 2005. The prevalence of hypertension of these subjects (65.2%) was lower than that of the general older population in Hong Kong (68.8%) [26] (p<0.001). 146 (7.0%) subjects were excluded from this study because they were living in old-aged homes, were not ethnic Chinese, had history of cerebrovascular accidents, and/or had already had SCI (Figure 1). Therefore, 1925 (93.0%) subjects were recruited into our study.

Among the recruited subjects, 1453 (75.5%) attended at least two annual assessments at EHCs since 2006, with at least one assessment since 2008. On average, they visited EHCs 3.4 times for re-assessment in the 6-year study period. The remaining 472 (24.5%) subjects had less than two assessments at EHCs since 2006 or defaulted follow-up since 2008. They were older (p<0.001), had a higher prevalence of hypertension and heart diseases (p<0.001), had a lower prevalence of hypercholesterolemia (p<0.001), and had a lower BMI (p=0.01) at baseline comparing with those who had regular follow-up (Table 1).

Among the defaulted subjects, 143 were dead, leaving 329 for active tracing: 159 subjects were interviewed by the research team; 2 subjects attended EHC by themselves after they were traced by the research team; 5 were confirmed to be dead;

and the rest declined for interview or could not be traced. This made up a total of 1614 (83.8%) subjects having at least one assessment since 2008.

Incident SCI:

A total of 161 (8.4%) subjects developed SCI in the 6-year study period. The proportion of subjects developing SCI increased with advancing age (Table 2). Table 3 showed the differences in demographic characteristics and baseline cardiovascular risk factors between subjects who remained cognitively stable and those who developed SCI. Subjects with incident SCI were older (p<0.001) and had lower education attainment (p=0.06). No significant difference in the point prevalence of DM, hypercholesterolemia, heart disease, obesity, smoking, alcohol use, and depression at baseline was noted between the two groups.

Association between hypertension and SCI

1239 (64.4%) subjects had history of hypertension at baseline. However, there was no statistically significant difference in the point prevalence of pre-existing hypertension between subjects who remained cognitively stable and those who developed SCI (64.2% versus 65.8%; χ^2 test, p=0.68; Table 3).

Baseline SBP appeared to be slightly higher among subjects who developed SCI

compared to those who did not, but the difference was not statistically significant (140mmHg versus 138mmHg; Mann-Whitney U-test, p=0.10; Table 3). There was no difference in baseline DBP between the two groups.

Association between PP and SCI

Baseline PP was higher among subjects who developed SCI compared to those who remained cognitively stable (70mmHg versus 66mmHg; Mann-Whitney U-test, p=0.03; Table 3). Although PP was the only vascular risk factor at baseline that was associated with incident SCI, it might be related to an underlying cardiovascular or cerebrovascular disease which predisposed to SCI. Therefore, the association between late-life vascular risk factors and incident SCI was examined by excluding subjects with known vascular risks at baseline and those who developed SCI before vascular risk factors emerged during the follow-up period. Hypertension, hypercholesterolemia, heart disease, and CVA that were newly developed during the follow-up period all had no association with incident SCI. The association between late-onset DM and incident SCI could not be ascertained in this study due to the limited number of subjects suffering from late-life DM and SCI.

Since a higher baseline PP was found to be associated with incident SCI, multiple logistic regression analysis was performed to assess the association between PP and

other potential confounders, including age, literacy, and SBP. As shown in Table 4, age was the only variable remained to be statistically significant in the regression model (OR = 1.07, 95% CI: 1.04–1.11, $p<0.001$).

To study the effect of age on the association between PP and SCI, multiple logistic regression was repeated with the exception of using age as a categorical variable with cutoff at 70, 75, and 80 years old. As illustrated in Table 5, PP had a small but significant effect on the risk of SCI in the younger old subjects (OR = 1.02, 95% CI: 1.00–1.05, $p=0.03$). The effect of age on the risk of SCI was not statistically significant until age reached 75 and above (OR = 1.89–2.19, $p<0.001$).

To determine if PP changed with time, Wilcoxon test was used to look for any difference in the median PP between 2005 and 2008, 2008 and 2011, and 2005 and 2011. A total of 627 subjects who remained cognitively stable and 53 subjects who had incident SCI had re-assessment in 2008 and 2011. As shown in Table 6, PP increased with time among subjects who remained cognitively stable (64.5mmHg in 2005, 68.0mmHg in 2008, and 70.0mmHg in 2011; Bonferroni correction, $p<0.01$), but not among subjects with incident SCI (74.0mmHg in 2005, 70.0mmHg in 2008, and 69.0mmHg in 2011; Bonferroni correction, $p>0.01$).

Discussion

Our present study did not find an association between pre-existing hypertension and incident SCI in the Chinese older people. This is apparently inconsistent with the results of the western epidemiologic studies which highlighted an association between hypertension and cognitive impairment. There are several possible explanations for the difference in findings. First, hypertension is highly prevalent among the Hong Kong Chinese, so it may be difficult to find a statistically significant difference in the point prevalence of hypertension between the two groups. Second, the association between hypertension and cognitive impairment is dependent on the age of onset of hypertension. In this study, we could not examine whether hypertension at mid-life or late-life, or both, was associated with incident SCI because all our subjects were at least 65 years old at baseline and we did not have information on their age of onset of hypertension. Third, our sample might represent only the mild to moderate cases of hypertension, as older people with moderate to severe hypertension were likely receiving treatment in the medical specialist out-patient clinics instead. Last, subjects with hypertension might have already received anti-hypertensive treatment. Indeed, both groups of subjects had relatively normal SBP and normal DBP at baseline despite having high point prevalence of pre-existing hypertension. The treatment effect would bias towards the null hypothesis and thus underestimate the power of hypertension in

predicting the risk of SCI as suggested by a previous study [4]. Further studies are needed to ascertain whether the degree of BP control influences the association between hypertension and SCI in the local older population.

Another interesting finding of this study is that widened PP is associated with the development of SCI in the Chinese older people. Since age influences both BP and cognition, it might be a confounding factor in the association between PP and SCI. Our results showed that after controlling for factors including age, PP still had a small but significant effect on the risk of SCI among the younger old Chinese. Hence, younger old people with widened PP may be at risk of developing cognitive impairment in their later life. Since PP is a surrogate measure of the arterial compliance, several mechanisms might explain how widened PP is involved in the development of SCI. First, increased stiffness of the arterial wall might lead to narrowing of vessel lumen, reduction of cerebral perfusion, and greater susceptibility of hypoxia and ischemia [21]. Second, the resultant hypoxia might induce upregulation of the β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) gene and increase the production of amyloid-β plaques [33, 34]. Third, the loss of damping due to increased arterial stiffness might increase the transmission of pulse wave towards the distal blood vessels, making the brain tissues more susceptible to direct injury [16]. Last, diminished arterial compliance might reflect diffuse atherosclerosis, which was

implicated in the development of dementia [35, 36]. Further studies are required to ascertain the underlying pathogenic mechanisms of widened PP in cognitive impairment in the older population.

We found that PP continued to increase with time in subjects who remained cognitively stable, whereas a decreasing trend in PP was observed among those with incident SCI. This observation is consistent with the current understanding that PP increases progressively with time among older people with no dementia, whereas both SBP and DBP decrease in the years prior to the onset and during the course of dementia [14, 20, 21]. The difference in the trajectories of PP between subjects who remained cognitively stable and those who developed SCI is of potential clinical significance. Since widened PP is suggestive of arterial stiffness, we speculate that older people with a high PP but not yet cognitively impaired may be at the stage when compensatory mechanisms are still functioning, so the cerebral autoregulation remains relatively effective in keeping an optimal blood flow in the brain [37]. This may help explain why higher PP has been observed to be associated with better cognition in some older people [38]. However, once the compensatory mechanisms are lost, the older people may become predisposed to cerebral arterial insufficiency, which leads to ischemia, hypoxia, and direct injury of the brain tissues as described above and thereby results in SCI. The loss of baroreflex function observed in patients with

Alzheimer's disease may further aggravate the cognitive decline [39]. Hence, a widened PP may be a useful clinical marker for late-life SCI.

Although our study showed that PP might be a risk factor for SCI among the younger old Chinese, there were a few potential limitations and precautions in using PP as a predictor of SCI. First, because of the dynamic and age-dependent changes of BP, measuring BP (and thereby calculating PP) on a single occasion might not accurately reflect the BP profile of an individual. Ambulatory BP monitoring is an alternative method which allows BP to be recorded over a longer period of time, but it is impractical for population-based studies. Hence, taking the average of several BP readings that are measured in different occasions remains to be a reasonably good option in measuring PP. Second, instead of measuring the central PP, the use of sphygmomanometer at brachial artery allows measurement of the peripheral PP only. Because of the amplification of PP between central and peripheral arteries, there is a high peripheral-to-central PP gradient in healthy adults [40]. Nevertheless, since the compliance of arteries decreases with age, such gradient is often lost in the older people, thus making the peripheral and central PP being similar. Therefore, the peripheral PP measured at the brachial artery using the cuff technique can still provide a fairly good estimation of the central PP among the older people. Third, although pulse wave velocity (PWV) measured by transcutaneous Doppler has been proposed to

be a better alternative to PP in assessing the arterial stiffness, similar outcomes have been reported when studying the association between cognitive decline and arterial stiffness with either method [16]. Therefore, PP appears to be reliable in estimating the degree of arterial compliance. Last, PP can be affected by various factors such as aortic regurgitation and congestive heart failure [41]. The reason is that apart from being a function of the arterial compliance, PP is partly dependent on the stroke volume. Therefore, subjects with aortic regurgitation might have a higher PP, whereas those suffering from congestive heart failure might have a lower PP. Certain types of anti-hypertensive medication might also influence PP [42]. In this study, we did not have detailed information about the type of heart problems or the class of anti-hypertensive medications our subjects had been having at baseline. Nevertheless, there was no significant difference in the proportion of subjects who suffered from pre-existing heart diseases between the two groups. It would be of interest to study if different types of heart diseases or anti-hypertensive medications would influence the association between PP and SCI in the Chinese older people.

There are a number of methodological limitations to the current study. First, although follow-up data were available for 83.8% subjects, the remaining ones who could not be interviewed might be cognitively impaired as the defaulted subjects had more co-morbidities comparing to those who had regular follow-up. Therefore, the

number of subjects with incident SCI might be underestimated. Second, as mentioned above, it is best to measure BP by taking the average of several BP readings that are measured in different occasions. In our study, subjects with normal BP were not required to have a second reading due to logistic reason at EHC. Only subjects with SBP ≥140mmHg and/or DBP ≥90mmHg had their BP rechecked. Third, due to the restraint in time and resources, comprehensive cognitive assessments were not feasible in the daily clinical practice at EHC. The use of SMT as a screening tool for cognitive impairment might not be sensitive enough to identify subjects who had mild dementia. Also, C-MMSE could not substitute a formal cognitive assessment in diagnosing dementia. To improve detection rate and diagnostic certainty of SCI, we adopted CDR to help identify defaulted subjects who had cognitive impairment at follow-up. Last, collection of medical history was based on the subjects' or their informants' self-reporting information, which would have introduced recall bias.

In spite of the limitations, our study had several strengths. The demographic characteristics and the point prevalence of the baseline cardiovascular risk factors of our sample were representative of the community-living Chinese older people in Hong Kong [26]. Our present findings may therefore be more robust among the general healthy older population. Also, our study included a relatively long follow-up period and a sufficiently large sample size. In addition, we managed to identify the latest

cognitive status of the majority of the sample, and we took into consideration of various potential confounders when studying the association between hypertension and SCI.

With widened PP being a potential risk factor for SCI and not simply being a function of age, it adds to the predictive value of the currently known risk factors for cognitive impairment among the younger old people. Since measuring PP is simple, inexpensive, and easily accessible without any risk involved, it brings great clinical and public health implication. First, measuring PP can be included as part of the assessment in the population screening for dementia as it can help identify people that are at risk of cognitive impairment. Second, widened PP can help predict the progression of SCI. Third, since widened PP is suggestive of diffuse atherosclerosis, therapeutic options aimed at reducing PP and limiting the progression of atherosclerosis would be important in attenuating the risk of SCI in addition to lowering the risk of cardiovascular diseases.

Although it is still too early to call for modification to the current treatment recommendations for hypertension based on our single study, and further studies are obviously needed to determine the optimal range of PP for people of different age groups, our study might be helpful in developing new directions for the prevention of dementia. In addition, our results suggest that the potential confounding effect of PP

should be taken into account when examining the role of vascular risk factors in cognitive impairment in future studies.

In conclusion, although our present study did not find any evidence to show that hypertension was associated with development of SCI in the Chinese older people, further studies may help ascertain if there is indeed no association between hypertension and SCI in the local older population. In addition, our study showed that widened PP might be a risk factor for SCI among the younger old people, whereas age remained to be a major predictor of SCI among the older old people. More studies are needed to determine the role of PP in contributing to late-life cognitive impairment and the target BP for a cognitively beneficial effect in the older population.

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Conflict of Interest

None declared.

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Figures and Tables

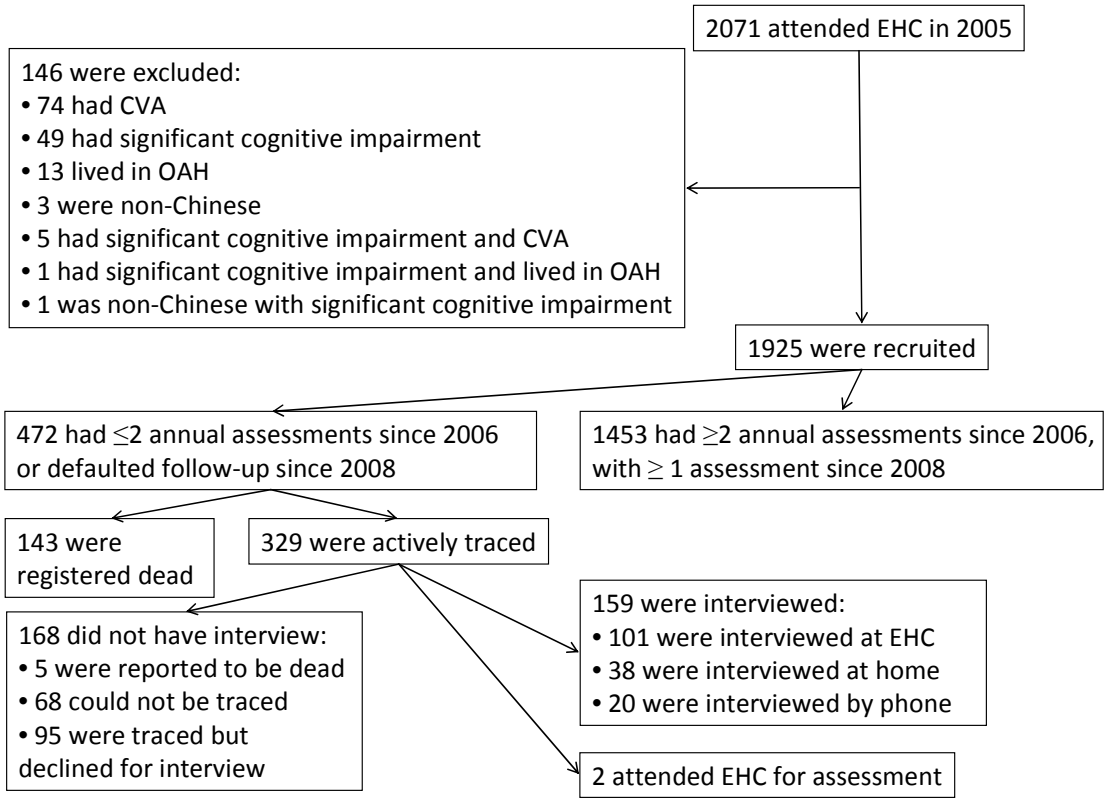

Figure 1. Flowchart showing how the subjects were included in this study.

EHC, Elderly Health Centre; CVA, Cerebrovascular Accidents; OAH, Old-aged Homes.

Table 1. Comparison of baseline characteristics between subjects who had regular follow-up in Elderly Health Centres (EHCs) and those who defaulted follow-up in the 6-year study period.

	Subjects with regular follow-up (n=1453)	Subjects who defaulted follow-up (n=472)	Statistics (*p*-value)
Median age, years	73	75	<0.001[b]
Female, n (%)	913 (62.8)	292 (61.9)	0.71[a]
Illiterate, n (%)	347 (23.9)	123 (26.1)	0.34[a]
Hypertension, n (%)	903 (62.1)	336 (71.2)	<0.001[a]
Median SBP, mmHg	138	140	0.06[b]
Median DBP, mmHg	72	73	0.85[b]
Median PP, mmHg	66	68	0.06[b]
DM, n (%)	156 (10.7)	61 (12.9)	0.19[a]
Median HbA1c	7.0	7.0	0.72[b]
Hypercholesterolemia, n (%)	630 (43.4)	147 (31.1)	<0.001[a]
Median fasting total cholesterol level, mmol/L	5.4	5.3	0.01[b]
Heart disease, n (%)	116 (8.0)	69 (14.6)	<0.001[a]
Median BMI, kg/m^2	23.6	23.3	0.01[b]
Daily smoking, n (%)	70 (4.8)	30 (6.4)	0.19[a]
Weekly alcohol use, n (%)	61 (4.2)	13 (2.8)	0.16[a]
Depression, n (%)	53 (3.6)	25 (5.3)	0.11[a]

[a]χ^2 test; [b]Mann-Whitney U-test

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PP, Pulse Pressure; DM, Diabetes Mellitus; BMI, Body Mass Index

Table 2. Age distribution among subjects who developed significant cognitive impairment in the 6-year study period.

		Number of subjects with incident significant cognitive impairment		Percentage of subjects with incident significant cognitive impairment in each age group
		Male	Female	
Age group	65-69	7	10	5.1
	70-74	17	34	6.5
	75-79	14	37	9.5
	80-84	12	17	14.4
	≥85	4	9	20.6
Total		54	107	

Table 3. Comparison of baseline characteristics between subjects who remained cognitively stable and those who developed significant cognitive impairment in 6 years.

	Cognitively stable (n=1764)	Significant cognitive impairment (n=161)	Statistics (*p*-value)
Median age, years	73	75	<0.001[b]
Female, n (%)	1098 (62.2)	107 (66.5)	0.29[a]
Illiterate, n (%)	421 (23.9)	49 (30.4)	0.06[a]
Hypertension, n (%)	1133 (64.2)	106 (65.8)	0.68[a]
Median SBP, mmHg	138	140	0.10[b]
Median DBP, mmHg	72	72	0.50[b]
Median PP, mmHg	66	70	0.03[b]
DM, n (%)	194 (11.0)	23 (14.3)	0.21[a]
Median HbA1c	7.0	7.2	0.53[b]
Hypercholesterolemia, n (%)	706 (40.0)	71 (44.1)	0.31[a]
Median fasting total cholesterol level, mmol/L	5.4	5.5	0.79[b]
Heart disease, n (%)	168 (9.5)	17 (10.6)	0.67[a]
Median BMI, kg/m^2	23.5	23.1	0.14[b]
Daily smoking, n (%)	92 (5.2)	8 (5.0)	0.89[a]
Weekly alcohol use, n (%)	67 (3.8)	7 (4.3)	0.73[a]
Depression, n (%)	69 (3.9)	9 (5.6)	0.30[a]

[a] χ^2 test; [b]Mann-Whitney U-test

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PP, Pulse Pressure; DM, Diabetes Mellitus; BMI, Body Mass Index

Table 4. Effect of pulse pressure on significant cognitive impairment of all ages using multiple logistic regression analysis.

	Odds Ratio (95% confidence interval)	*p*-value
Age	1.07 (1.04–1.11)	<0.001
Illiteracy	0.82 (0.57–1.17)	0.27
SBP	0.99 (0.98–1.01)	0.36
PP	1.02 (0.99–1.04)	0.12

SBP, Systolic Blood Pressure; PP, Pulse Pressure

Table 5. Effect of pulse pressure on significant cognitive impairment in different age groups using multiple logistic regression analysis.

	Odds Ratio (95% confidence interval)	*p*-value
(A) Age ≥70 years old		
Age	1.47 (0.91–2.37)	0.12
Illiteracy	0.78 (0.54–1.11)	0.17
SBP	0.99 (0.97–1.01)	0.22
PP	1.02 (1.00–1.05)	0.03
(B) Age ≥75 years old		
Age	1.89 (1.35–2.65)	<0.001
Illiteracy	0.80 (0.56–1.14)	0.22
SBP	0.99 (0.98–1.01)	0.33
PP	1.02 (0.99–1.04)	0.08
(C) Age ≥80 years old		
Age	2.19 (1.48–3.23)	<0.001
Illiteracy	0.77 (0.54–1.10)	0.15
SBP	0.99 (0.97–1.01)	0.29
PP	1.02 (0.99–1.04)	0.07

SBP, Systolic Blood Pressure; PP, Pulse Pressure

Table 6. Comparison of the longitudinal readings of pulse pressure over the 6-year study period between subjects who remained cognitively stable and those who developed significant cognitive impairment.

Year	Median PP, mmHg	*p*-value[a] 2005 versus 2008	2008 versus 2011	2005 versus 2011
Subjects who remained cognitively stable:				
2005	64.5	<0.001		
2008	68.0		0.03	<0.001
2011	70.0			
Subjects who developed significant cognitive impairment:				
2005	74.0	0.48		
2008	70.0		0.92	0.39
2011	69.0			

[a]Wilcoxon test

PP, Pulse Pressure