Education Level may Modify the Association Between Cardiac Index and Cognitive Function Among Elders with Normal Ejection Function

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Abstract

Background Lower cardiac index (CI) in elders has been associated with incident dementia, and higher CI has protectively effect with brain aging. In the present study, we investigated the modulating effects of education level and arterial stiffness on the association between CI and cognitive function among older adults.

Methods A total of 723 elders($\geq$ 60 years, 50.1% female) with normal left ventricular ejection-fraction ($\geq$50%) were identified from the Cardiovascular Diseases Risk Factor Two-Township Study. CI was calculated from the Doppler-derived stroke volume. We evaluated arterial stiffness by measuring carotid-femoral pulse wave velocity(CFPWV) and global cognitive function by using the Mini-Mental Short Examination(MMSE). Education level was determined by years of formal education.

Results In linear regression analysis adjusting for age, sex, formal years of education and CFPWV, CI was significantly positively associated with MMSE (BETA = 0.344±0.130,P = 0.0082). In logistic regression analysis adjusting for age, sex, formal years of education and CFPWV, subjects with a CI$\geq$75 percentile had a significantly lower risk of low MMSE (< 26)(OR = 0.495,95%CI = 0.274–0.896,P = 0.02). In subgroup analysis, higher CI was significantly associated with higher MMSE and lower risk of low MMSE only in elders with $\leq$9 years of formal education. Causal mediation analysis suggests that higher CI maintains higher MMSE in elders with lower education levels whereas higher CFPWV causes lower MMSE in all elders.

Conclusion In elders with normal ejection fraction, a higher CI was associated with a lower risk of cognitive function impairment, independent of arterial stiffness, mainly in subjects with a lower education level and possibly a smaller cognitive reserve.

Background

Reduced systemic blood flow may reduce cerebral perfusion and cause subclinical brain injury, and thereby compromise cognitive function.[1, 2] In the extreme, patients with systolic heart failure have a higher prevalence of cognitive impairment than those with normal cardiac function.[3–5] In the community-based participants free from clinical stroke, transient ischemic attack, dementia, or heart disease, a subtle reduction in cardiac index (CI) may be associated with reduced brain volumes,[1, 6] furthermore, the higher CI (top tertile) had a higher mean total brain volume equivalent to nearly brain aging compared with those participants in either the middle or bottom teriles of CI. Therefore, a higher CI, implying better systemic blood flow, may help ensure adequate cerebral blood flow to prevent cognitive function decline due to aging.

Most age related cardiac changes, including impaired heart rate acceleration and impaired augmentation of blood ejection from the left ventricle, are considered adaptive in response to age related arterial changes.[8] In the healthy community-dwelling elders, CI at rest usually does not change with aging but may decline by 25% during exercise due to chronotropic insufficiency.[8, 9] Arterial aging assessed by carotid-femoral pulse wave velocity (CFPWV) is a major independent determinant of cerebral microvascular damage and cognitive function impairment.[10–12] Therefore, the benefit of normal CI in preserving cognitive function may be compromised by advanced arterial aging characterized by enhanced pulsatile hemodynamics and increased left ventricular afterload, even in subjects with apparently normal cardiac function.

In addition to aging, low education is a recognized risk factor for dementia.[13] A higher level education in early life is usually associated with a significant reduction in prevalence and incidence of dementia.[13] Education may influence the course and outcome of cognitive decline and protect against the onset of dementia, the so-called cognitive reserve hypothesis.[13–16] The interaction between the effect of education on cognitive reserve and the joint effect of cardiac and arterial aging on cognitive decline remains poorly understood.[17] We hypothesized that the potential protective effect of relatively higher CI and the well-documented detrimental effect from arterial aging on cognitive decline may differ in elders with different education levels, because of the difference in cognitive reserve. Therefore, the present study aimed to elucidate the interrelationship of CI, arterial aging and education level with cognitive function among the elders with normal left ventricular ejection fraction in the community. Specifically, we investigated the modulating effects of education level and arterial stiffness on the association between CI and cognitive function among older adults.

Methods

Study population

The Cardiovascular Disease Risk Factors Two-Township Study (CVDFACTS) is an ongoing longitudinal study of the risk factors for and pathogenesis of cardiovascular disease in two Taiwanese townships, Chu-Dung (a Hakka community) and Pu-Tzu (a Fukienese community).[18] The CVDFACTS study was instituted in 1989–1991 (baseline) and had had 4 waves of surveys (1991–1993, 1993–1997, 1997–1999 and 1999–2002). Subjects who were aged 60 years or more and who had had participated in one or more CVDFACTS surveys (n = 2,014) were invited either by letter or by telephone to attend the present study project entitled “The Impact of Pulsatile Hemodynamics on Elderly Cognitive Function: the Cardio-cerebral Interactions” conducted between 2014 and 2016. The study protocol was approved by the Institutional Review Board of National Yang-Ming University. Each participant was well informed, and a written consent was obtained before entering the study.

Two visits of data collection within three months were arranged for each participant. In the first visit, personal characteristics, anthropometric measurements, cognitive function assessment, and fasting blood samples were collected. The histories of stroke and heart disease were collected by the structured questionnaires such as: “Did you have heart disease diagnosed by a physician at a clinic or hospital?”. The second visit involved the measurements of cardiovascular hemodynamics.

A total of 819 elders aged 60 years or more participated in the project and completed the cognitive function assessment. For the purpose of the present analysis, we excluded 89 subjects with a left ventricular ejection fraction less than 50% or missing ejection fraction data, and 7 additional subjects with missing CI data. Finally, 723 subjects aged ≥ 60 years and with normal left ventricular ejection fraction (> 50%) were eligible and included in the present analysis (Supplemental Figure).

Measurements

Cognitive function

The global cognitive function was assessed using the Mini-Mental Short Examination (MMSE),[19] Chinese version for Taiwan, via face-to-face interview with the well-trained study nurses at the study sites. The MMSE consists of 20 items clustered into 11 subscores to assess different aspects of cognitive function, including orientation, memory, attention, calculation and following a three-stage command, and has a total score of 30 points.[19] A cut-off point of 26 was used to define cognitive impairment.

Education level

The usual formal education in Taiwan is elementary school (6 years), junior high school (3 years), senior high school (3 years), college (4 years), and graduate school (2–4 years). Total years of formal education were registered for each participant and a cut-off point 9 years was used to define lower education level (≤9 years), since 9-year education was compulsory education in the period of these elders.

Cardiac index

All subjects received a transthoracic echocardiography performed by the same experienced sonographer using a commercially available machine (HD11 XE Ultrasound system, Koninklijke Philips N.V.). All images were digitized for off-line analysis by the sonographer, using the TomTec Image-Arena™ Software 4.0 (TomTec Imaging Systems GmbH, Munich, Germany). Left ventricular volume was measured from the summation of a stack of elliptical disks by tracing the endocardial border of the left ventricle at end-diastole and end-systole in apical 4 chamber view. Left ventricular ejection fraction was calculated from the M-mode measurements. Doppler derived stroke volume was the product of the cross-sectional area of the left ventricular outflow tract and the flow across the left ventricular outflow tract, which is determined by the velocity time integral of the Doppler signal during systole.[20] Doppler-derived cardiac output was calculated as stroke volume times heart rate and CI was cardiac output divided by body surface area.[20]

Arterial stiffness

Applanation tonometry was performed with a pencil-type tonometer incorporating a high-fidelity strain-gauge transducer in a 7-mm-diameter flat tip (SPC-350, Millar Instruments Inc, Texas) to record the pulse waveforms at the right common carotid artery and right femoral artery sequentially.[21] CFPWV was estimated by the distance between the right carotid and right femoral artery measured by a measuring tape divided by the pulse transit time. The pulse transit time between the right carotid artery and the right femoral artery was calculated by a simultaneously recorded ECG signal using a custom-designed software on a commercial software package (Matlab, version 4.2, The MathWorks, Inc.).[21]

Others

Supine brachial systolic and diastolic blood pressure were measured at the right arm using automated analyzer, VP-1000 (Colin Co., Komaki, Japan) with an appropriate-sized cuff at heart level. Body surface area was calculated by the product of body height (cm) and body weight (kg) divided by 3600. Body mass index was estimated by the body weight in kg divided by body height in meter.

Statistical analysis

Characteristics of study population and subgroups of higher and lower education levels > and ≤9 years of formal education) were presented as mean and standard deviation for interval variables, and number with proportion for categorical variables. Association of MMSE with CI and CFPWV was evaluated by univariable and multivariable linear regression analyses for the total study population and subgroups of education levels. Association between low MMSE (total score < 26) and quartile analyses of CI and CFPWV was evaluated by multivariable logistic regression analyses for the total population and subgroups of education levels. We further constructed causal models to elucidate the significance of CI and CFPWV as mediators on the causal pathway between advancing age and declining MMSE, with years of formal education as a confounder. The direct effect of each pathway in the causal models was estimated by a Path coefficient and its P value and the goodness of fitness index of each model was presented. The CALIS procedure in SAS 9.4 was used to perform the Path analysis. Significance level was set at 0.05.

Results

Characteristics of study population

Among the 723 eligible elders with normal left ventricular ejection fraction (mean age 69.2 ± 7.2 years, 49.93% female, average left ventricular ejection fraction 71.3 ± 6.7%), the average MMSE score was 27.9 ± 2.7 (28.3 ± 2.07 for men, 27.6 ± 3.08 for women, $P = 0.0008$), and 97 subjects had a MMSE < 26 (13.4%; 10.8% for men vs. 16.0% for women, $P = 0.0395$) (Table 1).

Table 1
Characteristics of the study population with lower and higher levels of education (n = 723)

Variable	Total (n = 723)	Lower education level (≤9 years) (n = 231)	Higher education level (> 9 years) (n = 492)	P value
Age, years	69.2 ± 7.2	**72.3 ± 7.6**	**67.8 ± 6.5**	**< 0.0001**
Male gender, n (%)	361 (49.9%)	**86 (36.9)**	**275 (55.9)**	**< 0.0001**
Formal education, years	10.3 ± 4.2	**5.2 ± 1.9**	**12.6 ± 2.7**	**< 0.0001**
Body mass index, kg/m^2	24.7 ± 3.4	**25.3 ± 3.3**	**24.4 ± 3.4**	**0.0013**
Brachial systolic BP	133.4 ± 17.7	**136.3 ± 17.3**	**132.0 ± 17.8**	**0.0024**
Brachial diastolic BP	77.1 ± 10.3	77.2 ± 9.3	77.0 ± 10.7	0.8188
Triglycerides, mg/dL	127.4 ± 77.5	134.1 ± 77.1	124.1 ± 77.4	0.1066
HDL-cholesterol, mg/dL	54.3 ± 15.6	53.3 ± 14.1	54.8 ± 16.3	0.2293
LDL-cholesterol, mg/dL	116.3 ± 34.6	116.7 ± 34.2	116.4 ± 35.0	0.9114
Total cholesterol, mg/dL	195.8 ± 39.5	196.5 ± 38.5	195.6 ± 40.0	0.7766
Fasting glucose, mg/dL	104.3 ± 26.3	**107.6 ± 31.3**	**102.7 ± 23.4**	**0.0192**
Cardiac index, $L/min/m^2$	2.8 ± 0.7	**2.92 ± 0.75**	**2.75 ± 0.65**	**0.0022**
CFPWV, m/sec	13.7 ± 4.6	**14.6 ± 5.2**	**13.3 ± 4.3**	**0.0007**
Ejection fraction, %	71.3 ± 6.7	71.3 ± 6.8	71.3 ± 6.7	0.9677
MMSE	27.9 ± 2.7	**26.3 ± 4.3**	**28.6 ± 1.8**	**< 0.0001**
MMSE < 26, n (%)	97 (13.42)	**68 (29.19)**	**31 (6.30)**	**< 0.0001**
Heart disease, n (%)	151 (20.89)	**59 (25.32)**	**92 (18.70)**	**0.0403**
Stroke history, n (%)	24 (3.32)	12 (5.15)	12 (2.44)	0.0567

BP = blood pressure; CFPWV = carotid-femoral pulse wave velocity; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MMSE = Mini-Mental State Examination.

Subjects with a lower education level (≤9 years of formal education, average 5.2 years) were significantly older, had a significantly lower MMSE score and higher prevalence of cognitive impairment (MMSE < 26), and had a significantly higher CI and CFPWV than those with a higher education level (> 9 years of formal education, average 12.6 years) (Table 1).

Subjects with a lower education level had a higher proportion of female sex, greater body mass index, higher brachial systolic blood pressure and fasting glucose, and a higher prevalence of heart disease, compared to those elders with a higher education level (Table 1).

Association Of MMSE With CI And CFPWV

In univariate analysis for the study population, age and CFPWV were negatively, and male sex and years of formal education were positively associated with MMSE (all $P < 0.0001$) (Table 2). CI was not significantly associated with MMSE in the univariable analysis. In subjects with a lower education level, age, years of formal education, and CFPWV were significantly associated with MMSE. In subjects with a higher education level, only age and CFPWV remained significantly associated with MMSE.

Table 2
Association of MMSE with CI and CFPWV, univariable and multivariable linear regression analyses stratified by levels of education

Variable	**Total (n = 723)**		**Lower education level (≤9 years) (n = 231)**		**Higher education level (> 9 years) (n = 492)**	
Univariable analysis	**BETA (SE)**	**P value**	**BETA (SE)**	**P value**	**BETA (SE)**	**P value**
Age, years	**-0.119 (0.013)**	**< .0001**	**-0.104 (0.030)**	**0.0006**	**-0.076 (0.012)**	**< .0001**
Gender, Male vs. Female	**0.661 (0.195)**	**0.0008**	0.717 (0.474)	0.1319	0.165 (0.162)	0.3115
Formal education, years	**0.248 (0.021)**	**< .0001**	**0.798 (0.108)**	**< .0001**	0.036 (0.030)	0.2275
CFPWV, m/sec	**-0.131 (0.021)**	**< .0001**	**-0.141 (0.044)**	**0.0015**	**-0.082 (0.019)**	**< .0001**
CI, L/min/m^2	-0.013 (0.142)	0.9278	0.423 (0.304)	0.1654	-0.022 (0.123)	0.8602
Multivariable analysis						
Age, years	**-0.071 (0.014)**	**< .0001**	-0.052 (0.030)	0.089	-0.068 (0.013)	< .0001
Gender, Male vs. Female	**0.490 (0.186)**	**0.0086**	0.737 (0.436)	0.0928	0.346 (0.165)	0.0362
Formal education, years	**0.197 (0.023)**	**< .0001**	0.701 (0.110)	< .0001	0.013 (0.030)	0.6507
CFPWV, m/sec	**-0.070 (0.021)**	**0.0008**	**-0.090 (0.042)**	**0.0341**	**-0.045 (0.020)**	**0.0250**
CI, L/min/m^2	**0.344 (0.130)**	**0.0082**	**0.649 (0.274)**	**0.0187**	0.093 (0.112)	0.4467

BETA = standardized regression coefficient; CFPWV = carotid-femoral pulse wave velocity; CI = cardiac index; SE = standard error of BETA.

In the multivariable analysis for the study population, CFPWV was significantly negatively, and CI was significantly positively associated with MMSE, when age, gender, and years of formal education were included in the model (Table 2). In subjects with a lower education level, CFPWV was significantly negatively, and CI was significantly positively associated with MMSE (Table 2). In contract, in subjects with a higher education level, CFPWV remained significantly negatively associated with MMSE, but CI was no longer associated with MMSE (Table 2).

Association between cognitive impairment and quartile analyses of CI and CFPWV

For the study population, subjects in the upper quartile of CI ($\geq 75^{th}$ percentile, sex-specific) were significantly associated with a lower risk, and subjects in the upper quartile (sex-specific) of CFPWV were associated with a higher risk of cognitive impairment when age, sex, and years of formal education were accounted for (Table 3, separate upper quartile analysis). In subjects with a lower education level, subjects in the upper quartile of CI were significantly associated with a lower risk, whereas subjects in the upper quartile of CFPWV were not significantly associated with a higher risk for cognitive impairment ($P = 0.0592$). In contrast, in subjects with a higher education level, subjects in the upper quartile of CFPWV were significantly associated with a higher risk, whereas subjects in the upper quartile of CI were not associated with a lower risk of cognitive impairment (Table 3, separate upper quartile analysis).

Table 3

Association between low MMSE and cardiac index, carotid-femoral pulse wave velocity and education years, multivariable logistic analyses stratified by levels of education

Variable	**Total (n = 723)**		**Lower education level (< 9 years) (n = 231)**		**Higher education level (≥9 years) (n = 492)**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Separate upper quartile analysis						
Cardiac index, ≥ vs. <75th percentile	**0.484 (0.268–0.872)**	**0.0158**	**0.350 (0.155–0.790)**	**0.0115**	0.765 (0.306–1.913)	0.5664
CFPWV, ≥ vs. <75th percentile	**2.218 (1.313–3.748)**	**0.0029**	1.986 (0.974–4.051)	0.0592	**2.565 (1.108–5.941)**	**0.0279**
Bivariate upper quartile analysis						
Cardiac index, ≥ vs. <75th percentile	**0.495 (0.274–0.896)**	**0.0202**	**0.357 (0.158–0.808)**	**0.0134**	0.788 (0.314–1.977)	0.6116
CFPWV, ≥ vs. <75th percentile	**2.187 (1.287–3.716)**	**0.0038**	1.947 (0.939–4.037)	0.0732	**2.553 (1.100-5.925)**	**0.0292**
Combined upper quartile analysis						
Higher CI (≥75th percentile) and lower CFPWV(< 75th percentile) (N = 133)	**0.246 (0.112–0.542)**	**0.0005**	**0.211 (0.073–0.609)**	**0.0040**	0.297 (0.077–1.149)	0.0786
Lower CI (< 75th percentile) and lower CFPWV(< 75th percentile) (N = 409)	**0.403 (0.221–0.737)**	**0.0031**	**0.385 (0.167–0.889)**	**0.0040**	0.406 (0.156–1.057)	0.0649
Higher CI (≥75th percentile) and higher CFPWV(≥75th percentile) (N = 49)	**0.364 (0.143–0.929)**	**0.0345**	**0.171 (0.043–0.671)**	**0.0254**	0.845 (0.238–3.001)	0.7940
Lower CI (< 75th percentile) and higher CFPWV (≥75th percentile) (N = 132)	1.0 (referent)		1.0 (referent)		1.0 (referent)	

All models were adjusted for age, sex, and years of formal education.

CI = cardiac index;

CFPWV = carotid-femoral pulse wave velocity.

When upper quartiles of CI and CFPWV were included in the same logistic model, upper quartile CI was significantly associated with a lower risk, and upper quartile CFPWV was significantly associated with a higher risk for cognitive impairment for the study population when age, sex, and years of formal education were accounted for (Table 3, bivariate upper quartile analysis). In subjects with a lower education level, upper quartile CI was significantly associated with a lower risk, and upper quartile CFPWV was not significantly associated with a higher risk for cognitive impairment ($P = 0.0732$). In contrast, in subjects with a higher education level, upper quartile CFPWV was significantly associated with a higher risk, whereas upper quartile CI was not associated with a lower risk for cognitive impairment (Table 3, bivariate upper quartile analysis).

All subjects were then divided into 4 subgroups according to higher and lower CI and CFPWV using the sex-specific 75th percentile as the cut-points. For the study population, subjects in the subgroups of higher CI and lower CFPWV, higher CI and higher CFPWV, and lower CI and lower CFPWV had significantly lower risks of cognitive impairment as compared with the referent subgroup of lower CI and higher CFPWV when age, sex, and years of formal education were accounted for (Table 3, combined upper quartile analysis). Similar significant results were observed in subjects with a lower education level but not in those with a higher education level.

Modulating effects of CI and CFPWV on the causal relationship between age and MMSE

According to the Path analysis with years of formal education as a confounder, advancing age might directly decrease MMSE, and indirectly affect MMSE favorably and unfavorable by increasing CI and CFPWV for the total study population (Fig. 1, A), and in subjects with a lower education level (Fig. 1, B). In contrast, in subjects with a higher education level, advancing age might directly decrease MMSE and indirectly decrease MMSE through increased CFPWV. However, the favorable effect of increased CI on MMSE was no longer observed (Fig. 1, C).

Discussion

Main Findings

Our study found that education level could modify the association between CI and cognitive function among elders with normal left ventricular ejection. In the whole study population, a higher CI was associated with a higher MMSE score and a lower risk for cognitive impairment independent of CFPWV. However, the association was significant only in elders with a lower education level but was not significant in those with a higher education level. In contrast, a higher CFPWV was associated with a lower MMSE score and a higher risk of cognitive impairment; the association was independent of CI in all elders and regardless of the education level. In elders with a lower education, subjects with higher CI and/or lower CFPWV were significantly associated with a lower risk for cognitive impairment when compared with those with lower CI and higher CFPWV. Causal inference by the Path analysis supports that higher CI maintains higher MMSE in elders with lower education levels whereas higher CFPWV causes lower MMSE in all elders. Thus, elders with a lower education level may have a lower cognitive reserve and may be more vulnerable to the adverse effect of a subtle reduction of systemic blood flow on cognitive function. Since CI and CFPWV simultaneously and independently contribute to the pathogenesis of cognitive function decline in the elders, especially in those with a lower education level, strategies to preserve systemic blood flow and prevent arterial stiffening may be considered for maintaining or restoring brain health. Enrichment of cognitive reserve through early life education and life-time learning may help preserve cognitive function during late life.

Cardiac Index And Cognitive Function In Other Studies

CI has been viewed as more accurate for assessing the systemic perfusion than other cardiac function indices, such as left ventricular ejection fraction.[1, 22, 23] Cerebral hypoperfusion resulting from the reduced systemic perfusion has been considered as the major cause of cognitive function impairment in heart failure patients.[3–5] Cerebral blood flow is substantially reduced in patients with severe heart failure and it may be reversible after heart transplantation.[5] Moreover, it has been shown that decreased CI was associated with smaller subcortical gray matter volume in patients with heart failure, and hypertension was associated with reduced total gray matter volume.[3] The two factors could interact to exacerbate white matter hyperintensities.[3] Furthermore, cardiac resynchronization therapy in the moderate to severe heart failure patients may improve left ventricular ejection fraction and enhance cognitive outcome, including global cognition, executive function and visuospatial function.[24]

In elders without heart failure, lower Doppler-echocardiography derived CI was associated with lower resting cerebral blood flow in the left and right temporal lobes quantified from pseudo-continuous arterial spin-labeling magnetic resonance imaging.[23] Decreasing cardiac function, even at normal CI levels may be associated with accelerated brain aging.[1] However, CI was not associated with cognition (a memory domain and three executive function measures) in an older (≥ 70 years) heterogeneous group of 117 community dwelling cardiac patients (prevalence of heart failure was 9.9% in subjects with normal CI and was 29.5% in those with low CI).[22]

On the other hand, in the Framingham Offspring Cohort participants free of clinical stroke, transient ischemic attack, dementia and clinically prevalent cardiovascular disease, CI was significantly positively related to total brain volume, and low CI was related to poorer performances on information processing/executive function with borderline significance.[1] Follow-up of the same cohort excluding clinically prevalent cardiovascular disease and atrial fibrillation revealed that individuals with clinically low CI (< 2.5 L/min/m^2) had a higher relative risk of both dementia and Alzheimer disease compared with individuals with normal CI.[7] However, the underlying mechanisms of the association between cardiac function and cognitive function among subjects with normal cardiac function were unclear, and the mechanisms underlying clinically low CI in about one third of the ambulatory older adults were unknown.[7] In fact, few studies investigated the relationship between cardiac function and cognitive function among general population with normal cardiac function.[1, 25, 26] Moreover, the impact of arterial aging and stiffening on the association between CI and cognitive function was also unexplored in the Framingham Offspring Cohort study.[7]

Our study results may compliment the Framingham Offspring Cohort study, which showed the harmful effect of a clinically significant low CI, by clearly demonstrating the protective effect of a higher CI (upper quartile) in preventing the age-related cognitive function decline, independent of age-related arterial stiffening. Overall, our results may suggest that a normal systemic blood flow is important in maintaining adequate cerebral blood flow and normal cognitive function, especially in elders with a lower cognitive reserve.

Modulating Effect Of Cognitive Reserve On Cognitive Function Decline

Cognitive reserve refers to the ability of the brain to optimize or maximize performance through differential recruitment of brain networks or use of alternative strategies against brain damage.[16] Subjects with a higher education level usually experience less cognitive changes in the presence of age-related or Alzheimer's disease, probably due to a higher cognitive reserve.[27] High education in early life may help to postpone cognitive and brain reserve decline in normal aging.[28] Cognitive reserve can be measured by proxy indicators, such as years of full-time education and occupational complexity.[29] In 2,315 cognitively healthy participants aged 65 years and over in the Cognitive Function and Ageing Study Wales cohort, cognitive reserve was an important mediator of the association between lifestyle factors and cognitive function, with indirect effects via cognitive reserve contributing 21% of the overall effect on cognition.[29] In our study, education level measured by years of formal education was significantly associated with MMSE in both univariable and multivariable linear regression analyses (Table 2). In Path analysis, a formal education years was significantly associated with a higher MMSE score in subjects with a lower education level, but not in those with a higher education level (Fig. 1B and 1C). Moreover, the protective effect of higher CI on preserving MMSE was also significant only in subjects with a lower education level. These results may support that cognitive reserve plays an important role in the development of cognitive dysfunction in later life. Elders with a higher education level, implying the presence of a higher cognitive reserve, may rely less on the protective effect from a higher CI.

It has been shown that marked stiffening of the aorta may augment the transmission of excessive flow pulsatility into the brain, causing microvascular structural brain damage and various cognitive function impairments.[10] Our study also found that a higher CFPWV was significantly associated with a lower MMSE and a higher risk of low MMSE, independently of CI and education levels. Moreover, we found that the effects of CFPWV and CI on MMSE were additive in elders with a lower education level but not in those with a higher education level. In Path analysis, age had a significant direct effect and two separate and independent significant indirect effects via CI and CFPWV respectively, on MMSE. The indirect effect via CFPWV was significant in elders regardless of their education levels. In contrast, the indirect effect via CI was significant only in elders with a lower education level. These results may suggest that higher cognitive reserve does not prevent the age-related arterial stiffness, or arterial aging, from damaging the brain. [3] Strategies to slow down or reverse arterial aging may be needed to maintain brain health.

Limitations And Strength

Several limitations in this study are addressed as follows. First, this study was a cross-sectional design and therefore the results do not prove the causal inference. Second, the modulating effect of education levels on the association between CI and cognitive function observed in our study may not be extrapolated to other populations that have a higher homogeneity in education levels.

Conclusion/Implication

In elders with normal ejection fraction, a higher CI was associated with a lower risk of cognitive function impairment, independent of arterial stiffness, mainly in subjects with a lower education level and possibly a smaller cognitive reserve. A higher education level may imply a higher cognitive reserve that may not require the protective effect of high CI on cognitive function.

Abbreviations

CI
Cardiac Index
CFPWV
Carotid-Femoral Pulse Wave Velocity
MMSE
Mini-Mental Short Examination
CVDFACTS
The Cardiovascular Disease Risk Factors Two-Township Study

Declarations

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Ethics approval and consent to participate:

The study protocol was approved by the Institutional Review Board of National Yang-Ming University. Each participant was well informed, and a written consent was obtained before entering the study.

Availability of data and materials:

The datasets generated during and/or analysed during the current study are not publicly available due to rules of Institutional Review Board but are available from the corresponding author on reasonable request.

Consent for publication:

Not applicable

Competing interests:

The authors declare that they have no competing interests

Authors' contributions:

Manuscript draft and Study Design (HM-CHENG, SY-CHUANG, CH-CHEN, WH-PAN)
Data-Analysis (SY-CHUANG, WL-Liu)
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Figures

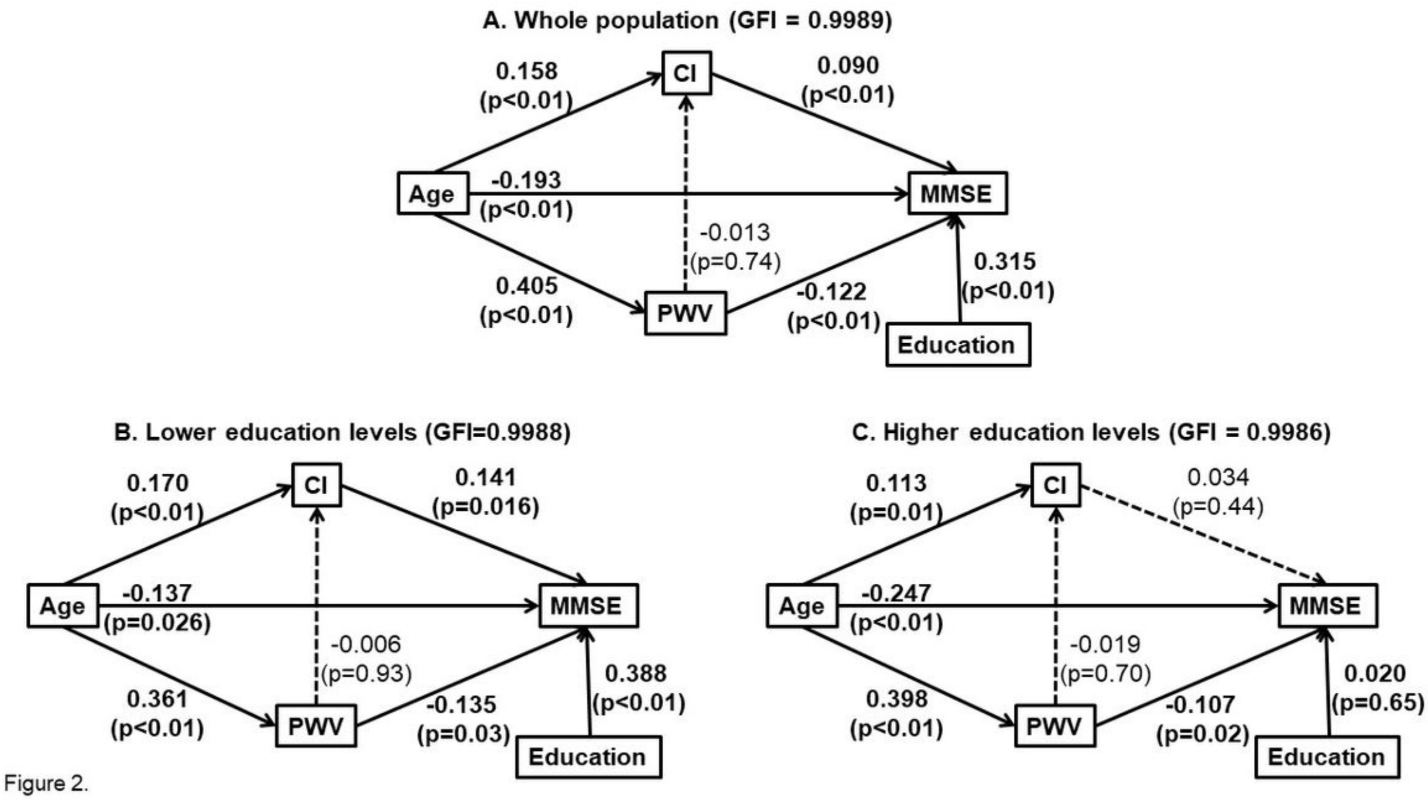

Figure 1

Path analysis diagrams for the whole study population (A), subjects with lower education levels (≤9 years of formal education, B) and those with higher education levels (>9 years of formal education, C). Solid line indicates significant association. Dotted line indicates none-significant association. Path coefficient and its P value are presented for the evaluation of direct effect between two adjacent variables. Figure 1A was for whole population and Figure 1B and 1C were for those elders with and without lower education, respectively. CI = cardiac index; education = years of formal education; GFI = the goodness of fitness index; MMSE = Mini-Mental State Examination; PWV = carotid-femoral pulse wave velocity; The interrelationship of cardiac index (CI), carotid-formal pulse wave velocity (PWV), education and cognitive function (Mini-Mental State Examination).

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