Original Research

Predictive value of hypercholesterolemia, vegetarian diet, and hypertension for incident dementia among elderly Taiwanese individuals with low educational levels

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Abstract

Objective: Early management of modifiable dementia-related factors is seen as a novel approach to preventing dementia onset; however, these efforts are often hindered by the complexity of interactions among these factors. In addition, different modifiable dementia-related factors may contribute to different etiologies of dementia.

Design: The current study investigated the effects of common modifiable dementia-related factors on prediction of incident dementia, dementia of the Alzheimer's type (DAT), and vascular dementia (VaD).

Methods: Vascular- and lifestyle-related factors were used as predictors of incident dementia, DAT, and VaD among 1,285 elderly individuals without obvious signs of dementia or mild cognitive impairment. Cox proportional hazard models were used to evaluate the risks associated with each modifiable factor.

Results: After controlling for factors other than stroke-related factors, hypercholesterolemia was correlated with a relatively low risk of all-cause incident dementia and DAT, whereas a vegetarian diet was correlated with an elevated risk of all-cause incident dementia and VaD. Hypertension was correlated with incident VaD. After controlling for stroke-related factors, a vegetarian diet was correlated with an elevated risk of all-cause dementia. A history of myocardiac infarction and the use of anti-platelet medication were, respectively, associated with a reduced risk of DAT and elevated risk of VaD. The use of anti-hypertensives was associated with a reduced risk of all-cause dementia, whereas the use of anti-lipid agents was associated with slow progression DAT (i.e. exceeding the average conversion time). Hypercholesterolemia was associated with an elevated risk for slow progression DAT.

Conclusion: These findings could perhaps be used as clinical markers in predicting and preventing incident dementia, DAT, and VaD.

Keywords: dementia, hypercholesterolemia, hypertension, modifiable factors, vegetarian diet

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Introduction

The global burden of dementia is growing yearly and the progressive nature of most types of dementia hinders the prediction of dementia onset.[1] Thus, it is crucial that practitioners seeking to reduce the occurrence of the dementia have the ability to detect modifiable factors.[2]

Researchers have recently identified several modifiable factors that are correlated with incident dementia.[3,4] A recent Lancet Commission identified smoking, depression, social isolation, physical inactivity, air pollution, and diabetes onset later in life as factors correlated with incident dementia.[5] The American Heart Association has

proposed seven principles by which to lower the vascular risks related to incident dementia, include managing blood pressure, controlling cholesterol, reducing blood sugar levels, adopting a more active lifestyle, eating better, losing weight, and quitting smoking.[6] Nonetheless, the relationship between incident dementia and many risk factors is highly complex.[4] Among middle-aged individuals, hypercholesterolemia at baseline has been correlated with incident dementia; however, among the elderly, it has been identified as a protective factor against incident dementia in some studies.[7] The relationship between diet and Alzheimer's disease (AD) or vascular pathology is also highly complex.[8] Moreover, the relationship between hypertension and incident dementia appears to be affected by drugs for anti-hypertension.[9] Finally, researchers have yet to determine whether the general principles underlying efforts prevent incident dementia are applicable to populations with other clinical characteristics.[8]

The complex relationship between AD and vascular etiologies is another issue that could complicate the correlation between modifiable factors and incident dementia.[10] Researchers are currently debating whether the pathogenesis pathways are consistent or distinct.[11] This could perhaps be clarified by identifying the modifiable factors affecting dementia of AD type and VaD.

In this study conducted in Taiwan, we investigated the correlation between incident dementia and modifiable vascular factors (hypertension, diabetes, and hypercholesterolemia), drugs to treat these risk factors, and lifestyle-related factors (smoking, drinking, and vegetarian diets) among elderly individuals. We also compared the predictive value of these factors among patients with dementia of AD type *versus* patients with VaD.

Materials and methods

Participants

The participants were selected from a dataset created for the 'History-Based Artificial Intelligent Clinical Dementia Diagnostic System (HAICDDS) Project'.[12] The HAICDDS Project is a 2015 initiative to establish a dementia registry database at the Show Chwan Healthcare System (several locations across Taiwan) to facilitate the longitudinal analysis of cognitive and physiological functions among subjects visiting neurology
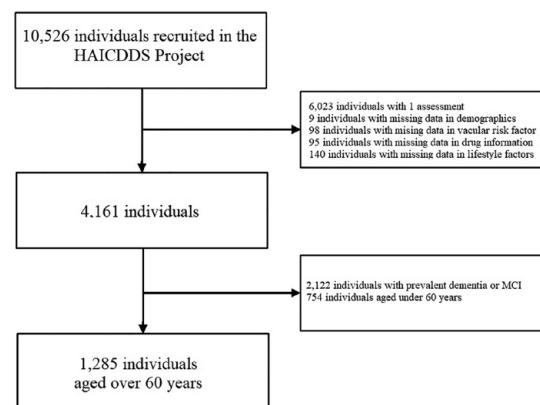
Figure 1. Selection of study participants.
HAICDDS, History-Based Artificial Intelligent Clinical Dementia Diagnostic System; MCI, mild cognitive impairment.

clinics. Participants undergo regular examinations, including fasting blood laboratory examination and cognitive assessments with the aim of facilitating the early detection of dementia and perhaps taking steps toward prevention. All participants and their families were interviewed by clinical neuropsychologists. The cognitive functions and daily functions of participants were assessed by the clinical neuropsychologists using standardized assessments. Laboratory blood studies were performed at the time of each assessment. Subjects with history of dementia were excluded. Computed tomography (CT) or magnetic resonance imaging (MRI) studies performed using a Siemens 3T scanner were used to exclude marked etiologies other than degenerative or cerebrovascular conditions and to identify evidence of stroke or silent stroke. At present, the database covers 10,526 participants with 20,018 data points. Among those individuals without missing data in terms of demographics, vascular risk, drugs to treat the vascular risk, or lifestyle factors, 4,161 were assessed at least two times (mean follow-up duration = 2.33 years, range = 0.5–6.1 years; mean times of assessment = 1.99, range = 1–9). From that group, we selected 1,285 participants aged over 60 years who did not present obvious signs of dementia or mild cognitive impairment (MCI) (Figure 1). Note that the subjects excluded from analysis tended to be older (75.62 ± 6.23 years), male (55.40%), and possessing a lower educational level (4.30 ± 4.12 years, ps < 0.05). The study was approved by the Institutional Review Board of the Show Chwan Memorial Hospital (SCMH_IRB1081006).

Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Assessments and diagnosis

Instances of incident dementia were identified through regular consensus meetings aimed at gathering the opinions of neurologists and clinical neuropsychologists. The cognitive function of participants was evaluated by clinical neuropsychologists in accordance with the Cognitive Assessment Screening Instrument,[13] Montreal Cognitive Assessment, and the Mini-Mental State Examination.[14] Daily function was assessed by neurologists or clinical neuropsychologists in accordance the Lawton's Instrumental Activities of Daily Living.[15] The criteria used to identify instances of incident dementia were those proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA).[16] Consensus meetings gathered the opinions from experienced neurologists and neuropsychologists were regularly held to identify instances of DAT or VaD were those proposed by the NIA-AA[16] and National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),[17,18] respectively. To facilitate inter-observer reliability, we based the diagnostic criteria for VaD on operational definitions related to topography and severity in the NINDS-AIREN imaging guidelines.[18] Structured interviews by neuropsychologists or a review of medical charts was used to determine whether the participants presented vascular modifiable factors (hypertension, diabetes, and hypercholesterolemia) and whether they received drug interventions related to the risk factors. The identification of vascular modifiable factors in the medical charts was based on the results of fasting blood examinations. A structured interview or review of medical charts was used to assess patients in terms of lifestyle-related factors, including smoking (current smoker, quit, or never), drinking (current drinker, quit, or never), and whether the participant followed a vegetarian diet. Individuals with a known family history of AD or VaD were excluded.

Data analysis

Demographic and clinical characteristics were compared among individuals with or without incident dementia at the time of follow-up examination using one-way analysis of variance (ANOVA) or chi-square tests. Survival analysis was performed using Cox proportional hazard regression models using the following predictors: Demographic details (i.e. age, gender, educational levels), vascular risk factors (i.e. hypertension, diabetes, coronary artery disease, hypercholesterolemia, myocardiac infarction), drugs for the control of vascular risk factors (i.e. taking anti-hypertensives, taking anti-diabetics, taking anti-lipid agents), and lifestyle-related factors (i.e. smoking, drinking, vegetarian diet). All risk models conformed to the proportional assumptions of risk determined by assessing the interaction between variables and survival time (all $p > 0.05$). Age and educational level were coded using the number of years in the models. Females were coded as 0 and males as 1 in the models. Smoking and drinking statuses were coded as never (0), quit (1), or current (2) in the models. Separate risk models were used to assess the effects of silent stroke and stroke-related medications (anti-platelet and anti-coagulant) on the predictions of dementia.

Receiver operating curve (ROC) analysis was used to assess the discriminative power of vascular- and lifestyle-related risk factors among individuals with or without all-cause incident dementia. Risk scores were summed using relative weights to represent regression results and variable distributions. Weights for the total sample were as follows: age over 73 years (1 point), educational level of 6 years or less (1 point), diagnosis of hypercholesterolemia (–4 points), and consuming a vegetarian diet (5 points). Weights for the DAT prediction model were as follows: consuming vegetarian diets (not included). Weights for the VaD prediction model were as follows: diagnosis of hypertension (3 points), consuming a vegetarian diet (3 points). In our sensitivity analysis, we repeated the main analyses after excluding 264 converters who displayed dementia prior to the completion of the mean follow-up (i.e. < 2.58 years). Post hoc power analysis of the risk models (performed using G*Power 3.1 software) revealed that all of the risk models possessed sufficient power (exceeding 0.99).

Results

Characteristics of participants

The mean age of participants was 72.36 years and 53% ($n = 681$) were female. A total of 445

participants (34.6%) displayed incident dementia at the time of follow-up (i.e. converters) with a mean follow-up duration of 428.07 days ($SD = 234.94$). The mean follow-up duration of participants without incident dementia (i.e. non-converters) was 1,264.80 days ($SD = 437.34$; $t = -9.72$; $p < 0.001$) (Table 1). A total of 238 participants displayed incident DAT (mean follow-up duration: 425 ± 209.31 days) and 74 displayed incident VaD (425 ± 259.19 days) (Table 2).

All-cause dementia
Among the 1,285 participants recruited in this study, age (hazard ratio [HR] = 1.05, 95% confidence interval [CI] = 1.04–1.07, $p < 0.001$) and a vegetarian diet (HR = 1.68, CI = 1.03–2.75, $p < 0.05$) were positively correlated with the incidence of incident dementia. Educational level (HR = 0.97, CI = 0.95–0.99, $p < 0.01$) and hypercholesterolemia (HR = 0.63, CI = 0.46–0.85, $p < 0.001$) were negatively correlated with the incidence of incident dementia. No other demographic and clinical characteristics were correlated with incident dementia ($p = 0.12$–0.96) (Figures 2(a) and 3). After considering the effects of silent stroke and the use of anti-platelet or anti-coagulant medication, only a vegetarian diet was associated with incident dementia (HR = 1.95, CI = 1.12–4.30, $p < 0.001$) (Supplementary Figure 1).

Incident DAT and VaD
Age was positively correlated with the incidence of incident DAT (HR = 1.07, CI = 1.05–1.09, $p < 0.001$). Educational level (HR = 0.96, CI = 0.93–0.99, $p < 0.05$) and hypercholesterolemia (HR = 0.62, CI = 0.40–0.97, $p < 0.05$) were negatively correlated with the incidence of incident DAT (Figure 2(b)). It appears that hypercholesterolemia is protective against incident VaD; however, the effect was not statistically significant, due perhaps to the small sizes of the VaD subgroup. Age was also positively correlated with incident VaD (HR = 1.05, CI = 1.01–1.08, $p < 0.01$). A vegetarian diet (HR = 3.15, CI = 1.10–9.00, $p < 0.05$) and hypertension (HR = 2.27, CI = 1.02–5.06, $p < 0.05$) were positively correlated with incident VaD (Figure 2(c) and Supplementary Figures 2 and 3). Note that only four patients with VaD followed a vegetarian diet. Other factors were not significantly correlated with the incidence of incident DAT ($p = 0.12$–0.98) or VaD ($p = 0.08$–0.97). After considering the effects of silent stroke and the use of anti-platelet or anti-coagulant medication, a history of myocardial infarction was associated with reduced risk of DAT (HR = 0.15, CI = 0.03–0.74, $p < 0.001$) and the use of anti-platelet medication was associated with an elevated risk of VaD (HR = 4.67, CI = 1.45–12.19, $p < 0.001$) (Supplementary Figures 4 and 5).

Sensitivity and discriminative analyses
Hypercholesterolemia became a risk factor (HR = 3.36, CI = 1.97–5.75, $p < 0.001$) and using anti-lipid agents become a protective factors (HR = 0.40, CI = 0.25–0.63, $p < 0.001$) among patients with DAT after excluding individuals with faster conversion and controlling all covariates. In addition, taking anti-hypertensive drugs (HR = 0.29, CI = 0.10–0.84, $p < 0.05$) and anti-platelet (HR = 6.44, CI = 1.75–13.74, $p < 0.01$) were associated with reduced risks of incident dementia and increased risks of VaD, respectively. Age and educational levels remained to be positively and negatively associated with risks of dementia (all-cause dementia: age: HR = 1.05, CI = 1.03–1.06, $p < 0.001$, educational level: HR = 0.95, 0.92–0.99, $p < 0.001$; DAT: age: HR = 1.04, CI = 1.02–1.07, $p < 0.001$; educational level: HR = 0.95, CI = 0.93–0.98, $p < 0.001$; VaD: HR = 1.04, CI = 1.01–1.09, $p < 0.05$). A risk score of higher than or equal to 1 could discriminate between individuals with incident all-cause dementia or not (AUC = 0.63, sensitivity: 0.48, specificity: 0.73, $p < 0.001$), with DAT or not (AUC = 0.64, sensitivity: 0.48, specificity: 0.74, $p < 0.001$), and VaD or not (AUC = 0.60, sensitivity: 0.67, specificity: 0.46, $p < 0.001$) (Figure 4).

Discussion
This study investigated the value of hypertension, diabetes, hypercholesterolemia, and drugs to treat these problems as well as smoking, drinking, and following a vegetarian diet in predicting the occurrence of incident all-cause dementia, DAT, and VaD. Hypercholesterolemia was identified as a protective factor against incident dementia, whereas a vegetarian diet was predictive of incident dementia. Hypertension was correlated with the occurrence of incident VaD. After controlling for stroke-related factors, we determined that a vegetarian diet was correlated with an elevated risk of all-cause dementia, a history of myocardial

Table 1. Demographics and clinical characteristics among converters and non-converters.

|	Non-converters (*N* = 840)	Converters (*N* = 445)	Statistical comparison
Age (year)	70.70 (8.52)	75.47 (8.08)	$t = -9.72$, $p < 0.001$
Educational level (year)	6.78 (4.65)	5.10 (4.33)	$t = 6.36$, $p < 0.001$
Gender (female)	430 (51.2)	251 (56.4)	$\chi^2 = 3.18$, $p = 0.08$
Follow-up duration (day)	936.57 (486.54)	960.32 (490.28)	$t = -0.83$, $p = 0.41$
Range (day)	113–2,227	146–2,117	
Conversion time (day)	–	593.19 (268.60)	–
Range (day)	–	146–1,898	–
CASI (max. score = 100)	78.49 (13.25)	67.50 (16.06)	$t = 12.37$, $p < 0.001$
MoCA (max. score = 30)	18.72 (6.47)	13.55 (6.30)	$t = 13.51$, < 0.001
MMSE (max. score = 30)	24.04 (4.51)	20.32 (5.41)	$t = 12.40$, $p < 0.001$
IADL (max. score = 8)	7.60 (0.76)	6.96 (2.36)	$t = 9.23$, $p < 0.001$
Hypertension	395 (47.0)	213 (47.9)	$\chi^2 = 0.08$, $p = 0.77$
Diabetes	201 (23.9)	117 (26.3)	$\chi^2 = 0.87$, $p = 0.35$
Hypercholesterolemia	236 (28.1)	84 (18.9)	$\chi^2 = 13.22$, $p < 0.001$
Coronary heart disease	74 (8.81)	35 (7.87)	$\chi^2 = 0.33$, $p = 0.56$.
Myocardial infarction	20 (2.38)	11 (2.47)	$\chi^2 = 0.01$, $p = 0.92$.
Silent stroke	50 (6.17)	40 (9.43)	$\chi^2 = 4.38$, $p < 0.05$.
Taking anti-hypertensives	432 (51.4)	221 (49.7)	$\chi^2 = 0.36$, $p = 0.55$
Taking anti-diabetics	175 (20.8)	108 (24.3)	$\chi^2 = 2.00$, $p = 0.16$
Taking anti-lipid agents	267 (31.8)	124 (27.9)	$\chi^2 = 2.11$, $p = 0.15$
Taking anti-platelet	220 (27.16)	107 (25.24)	$\chi^2 = 0.53$, $p = 0.47$
Taking anti-coagulant	14 (4.67)	15 (8.72)	$\chi^2 = 3.12$, $p = 0.08$.
Smoking			$\chi^2 = 6.49$, $p = 0.09$
Current	51 (6.1)	23 (5.2)	
Quit	147 (17.5)	67 (15.1)	
Never	490 (58.3)	249 (56.0)	
Drinking			$\chi^2 = 4.48$, $p = 0.21$
Current	42 (5.0)	19 (4.3)	
Quit	72 (8.6)	39 (8.8)	
Never	558 (66.4)	276 (62.0)	
Vegetarian diet	19 (2.3)	17 (3.8)	$\chi^2 = 2.59$, $p = 0.11$
Duration (year)	2.38 (1.15)	2.93 (1.75)	$t = 1.13$, $p = 0.27$

CASI, Cognitive Assessment Screening Instrument; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.
Numbers are denoted as mean (*SD*) or number (percentage).

Table 2. Demographics and clinical characteristics among patients with DAT or VaD.

	DAT (*N* = 238)	VaD (*N* = 74)	Statistical comparison
Age (year)	76.22 (7.89)	74.62 (8.45)	$t = 1.50$, $p = 0.14$
Educational level (year)	4.95 (4.46)	5.07 (3.88)	$t = -2.21$, $p = 0.84$
Gender (female)	145 (60.9)	36 (48.6)	$\chi^2 = 3.49$, $p = 0.06$
Follow-up duration (day)	943.02 (468.24)	990.43 (495.90)	$t = -0.75$, $p = 0.45$
Range	146–2,117	146–2,044	
Conversion time (day)	784.37 (423.41)	844.43 (434.58)	$t = -1.06$, $p = 0.29$
Range (day)	146–1,898	142–1,898	
CASI (max. score = 100)	66.81 (15.40)	66.93 (14.65)	$t = -0.06$, $p = 0.95$
MoCA (max. score = 30)	13.09 (6.04)	13.30 (5.79)	$t = -0.27$, $p = 0.79$
MMSE (max. score = 30)	20.36 (5.08)	19.65 (5.30)	$t = 1.04$, $p = 0.30$
IADL (max. score = 8)	6.97 (1.30)	6.88 (1.56)	$t = 0.53$, $p = 0.60$
Hypertension	94 (39.5)	52 (70.3)	$\chi^2 = 21.47$, $p < 0.001$
Diabetes	60 (25.2)	26 (35.1)	$\chi^2 = 2.79$, $p = 0.10$
Hypercholesterolemia	38 (16.0)	19 (25.7)	$\chi^2 = 3.56$, $p = 0.06$
Coronary heart disease	9 (3.78)	9 (12.16)	$\chi^2 = 7.29$, $p < 0.01$
Myocardial infarction	6 (2.52)	2 (2.70)	$\chi^2 = 0.01$, $p = 0.93$
Silent stroke	10 (4.20)	24 (32.43)	$\chi^2 = 44.18$, $p < 0.001$
Taking anti-hypertensives	98 (41.2)	52 (70.3)	$\chi^2 = 19.14$, $p < 0.001$
Taking anti-diabetics	54 (22.7)	24 (32.4)	$\chi^2 = 2.86$, $p = 0.09$
Taking anti-lipid agents	57 (23.9)	28 (37.8)	$\chi^2 = 5.49$, $p = 0.02$
Taking anti-platelet	38 (15.97)	27 (36.49)	$\chi^2 = 13.12$, $p < 0.001$
Taking anticoagulant	5 (2.10)	6 (8.11)	$\chi^2 = 1.24$, $p = 0.27$
Smoking			$\chi^2 = 13.09$, $p < 0.01$
Current	10 (4.2)	7 (9.5)	
Quit	24 (10.1)	17 (23.0)	
Never	128 (53.8)	35 (47.3)	
Drinking			$\chi^2 = 4.48$, $p = 0.21$
Current	10 (4.2)	5 (6.8)	
Quit	10 (4.2)	14 (18.9)	
Never	140 (58.8)	39 (52.7)	
Vegetarian diet	8 (3.4)	4 (5.4)	$\chi^2 = 0.64$, $p = 0.43$
Duration (year)	2.90 (1.21)	3.02 (2.23)	$t = -0.60$, $p = 0.55$

CASI, Cognitive Assessment Screening Instrument; DAT, dementia of the Alzheimer's type; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; VaD, Vascular dementia.
Numbers are denoted as mean (*SD*) or number (percentage).
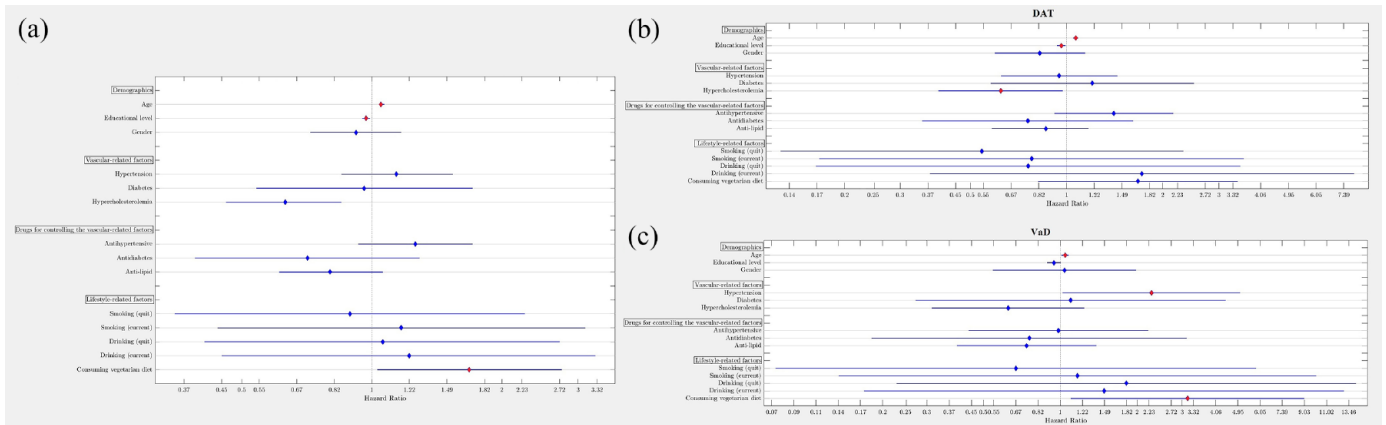
Figure 2. Hazard ratios of each factor for (a) all-cause dementia. (b) DAT. (c) VaD.
The red diamonds denote statistically significant effects.
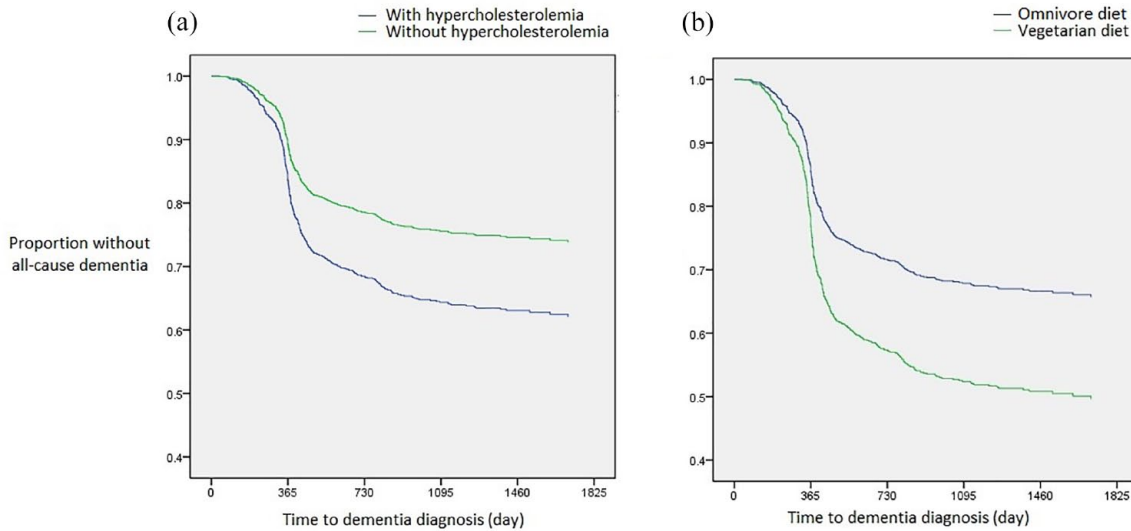
Figure 3. Survival curve of all-cause dementia between (a) individuals with or without hypercholesterolemia and (b) individuals following an omnivore or vegetarian diet.

infarction was associated with a reduced risk of DAT, and the use of anti-platelet medication was associated with a reduced risk of VaD. Taking anti-hypertensives was associated with a reduced risk for all-cause dementia, and taking anti-lipid agents was associated and slow progression DAT (exceeding the average conversion time). Hypercholesterolemia was associated with an increased risk of DAT and anti-platelet use was associated and slow progression VaD. Thus, it appears that a cumulated risk score based on the patterns of risk factors could be used to predict all-cause dementia, DAT, or VaD.

Myelin is composed primarily of lipids, and cholesterol plays a key role in maintaining the structural integrity in myelin and the transduction of neural impulses in the regulation of brain functions.[19] Researchers have previously recognized the importance of white matter integrity in the earliest stages of AD.[20] Although the mechanisms related to white matter lesions in the earliest of AD course remain a matter of debate,[20] it is likely that lipids play an important role.

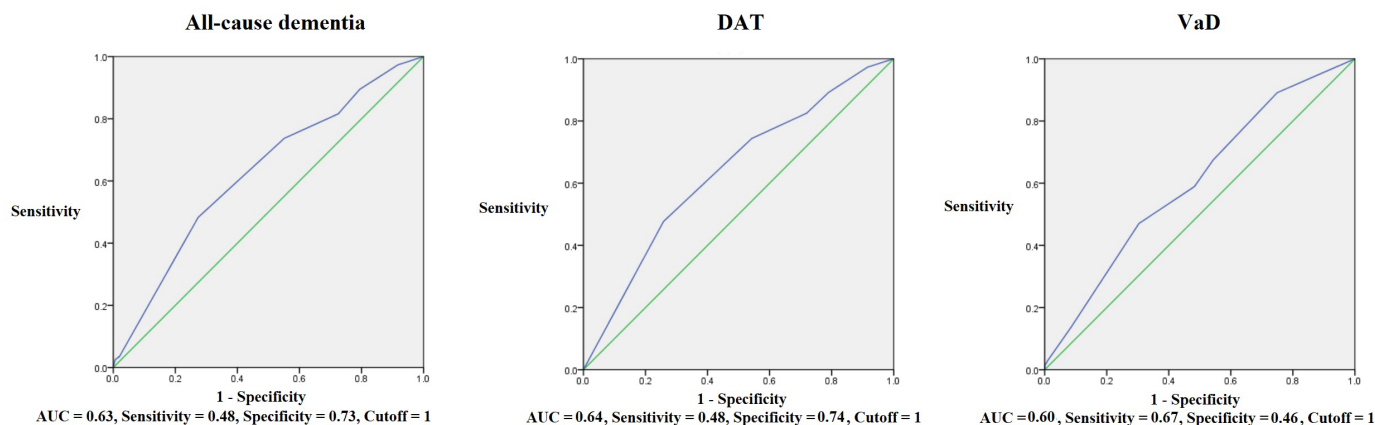Researchers have recently suggested that cholesterol also plays a role in preventing inflammation.[21] It

Figure 4. ROC analysis.

appears that oxidized low-density lipoprotein (LDL) promotes the development of arthrosclerosis and chronic inflammation in the intima of arteries. High-density lipoprotein may facilitate cholesterol efflux and inhibit the process of molecular adhesion in the formation of artherosclerotic plaques.[21] In a meta-analysis paper, Shepardson *et al.*[7] reported that total serum cholesterol levels are correlated with the risk of dementia throughout life and with incident dementia during middle adulthood. By contrast, total serum cholesterol levels were negatively correlated with incident dementia in late adulthood (e.g. over 70 years). Our discovery that hypercholesterolemia may be protective against incident dementia among elderly individuals is in line with the findings in Shepardson *et al.*[7] Note that the mean age of participants in this study was 72.35 years. Among the elderly, the integrity of the white matter tends to decrease, due to changes in small blood vessels.[22] Thus, the role of lipids in reducing myelin loss may be of greater importance to the elderly than to middle-aged individuals. Researchers have previously determined that the accumulation of amyloid plagues (key etiology in DAT), tends to increase rapidly after 60 years old.[23] It has been suggested that the clearance of A β_{42} proteins depends on the function of blood vessels.[24] Thus, compromised blood vessel function due to lipid depletion could undermine the clearance of A β_{42} proteins. It follows that hypercholesterolemia in elderly individuals could lead to lipid depletion, thereby slowing the accumulation of the amyloid plagues with a corresponding negative effect on the risk of incident dementia.

Guidelines for the control of cerebrovascular disease suggest lowering low-density lipoprotein cholesterol (LDL-c) levels;[25] however, the beneficial effects on cognitive function among the elderly remain unclear.[26–28] Cholesterol is a precursor in the formation of various hormones, including estradiol and testosterone,[29] both of which have been implicated in AD and cerebrovascular diseases.[30] Researchers have reported that estradiol can reduce the oxidation of LDL and thereby decrease arthrosclerosis and chronic inflammation in the intima of blood vessels. Estradiol has been identified as a neuroprotective agent against AD. Estradiol also interacts with lipids and regulates reproductive functions. Thus, hypercholesterolemia may counter the depletion of estradiol caused by menopause among elderly women. Stable free testosterone levels have been associated with a reduced risk of incident DAT. Testosterone suppression for the management of prostate cancer in elderly men has been shown to increase plasma A β levels two-fold.[30] Taken together, it appears that cholesterol may exert important neurotrophic and neuroprotective effects modulating cerebrovascular abnormalities and A β biochemistry. In fact, several recent studies have suggested that cholesterol may have beneficial effects on cognitive functions among the elderly.[27,28]

In the current study, we determined that after controlling for the effects of silent stroke, hypercholesterolemia was associated with an elevated risk of slow progression DAT. This can perhaps be attributed to the fact that most of the protective effects of hypercholesterolemia are associated with a reduced risk of vascular insult.[21] Note, however, that we did not measure serum cholesterol levels. Thus, it is possible that these results

observed in DAT patients could be attributed to severe hypercholesterolemia and the corresponding effects on brain functions (i.e. beyond the effects on the vascular system).

The role of a vegetarian diet in the development of dementia remains a contentious issue.[8] Several studies have reported that a vegetarian diet is protective against incident dementia.[31] Researchers have argued that the nutrients in a vegetarian diet, including antioxidants (e.g. vitamins C and E), phytochemicals, and dietary fiber, may decrease neuroinflammation with a corresponding decrease in the risk of dementia.[32] In the current study, we identified a vegetarian diet as a risk factor for incident dementia and significant predictor of incident VaD. Researchers have previously reported that among the elderly, a vegetarian diet is correlated with lack of cobalamin, a vitamin important in the metabolism of homocysteine.[33] The accumulation of homocysteine in the blood has been shown to have vasculotoxic and neurotoxic effects, which could increase the risk of developing incident dementia. The inconsistencies between our findings and those in previous studies can perhaps be attributed to the fact that the participants in this study were older. There is also a high likelihood of confounders associated with a vegetarian diet, such the fact that vegetarians tend to lead a more healthy lifestyle and are more likely to take nutritional supplements.[8] Note, however, that the prevalence of vegetarians in this study was low ($n = 36$). Further research using larger samples and/or a randomized design will be required to confirm our findings indicating that a vegetarian diet can have detrimental effects on cognition.

In the current study, a combination of vegetarians and hypertension presented significant predictive values for incident all-cause dementia and VaD, compared with other participants. These results may be attributed to the importance of a balanced diet in preserving brain functions.[3,34] It is possible that a cobalamin deficiency could compromise endothelial cells in the arteries.[35]

Hypertension has been identified as a risk factor for VaD.[9] Our findings are in line with previous work indicating that the management of hypertension is crucial to the prevention of VaD and dementia.[6] Researchers have determined that anti-hypertensive usage can have a profound effect on efforts to predict incident dementia based on hypertension. Joas *et al.*[9] found that among individuals who were not taking hypertensives, the systolic blood pressure of those with incident dementia was consistently higher than that of individuals without incident dementia up to 80 years old. Among patients who were taking anti-hypertensives, changes in systolic blood pressure (lower in middle adulthood but higher in late adulthood) were more pronounced among those with incident dementia than among those without incident dementia. These results illustrate the degree to which anti-hypertensives can reduce the risk of incident dementia. Note that in predicting incident dementia, it is important to consider whether the patient is or has been taking anti-hypertensives. Future research will be required to investigate this issue.

Education has been recognized as a protective factor against incident dementia.[4] Researchers have proposed education as a proxy of cognitive reserve to explain why many highly educated individuals sustain their cognitive functions even in instances involving etiologies associated with dementia.[36] Thus, it is possible that education level may play a role in moderating the effects of modifiable factors on incident dementia. This study also revealed that educational levels were a protective factor in the risk models for all-cause dementia and DAT. Note that our findings are not necessarily applicable to individuals with higher educational levels as the sample in the current study had lower educational levels than individuals recruited in studies conducted in many Western countries.

This study shed light on the effect of modifiable factors in predicting the onset of incident dementia, which may play a key role in early interventions for dementia. However, this study was subject to several limitations. First, the participants in this study were recruited from a clinical setting and the rate of conversion to dementia was high. This could reflect the vulnerability of the participants to dementia, due perhaps to their low educational level. In addition, the sample sizes of the incident DAT and VaD subgroups were small. Thus, our findings are not necessarily generalizable to other populations. Second, vascular risks were evaluated using self- or informant-reported data or a review of medical charts. Thus, we were unable to assess the severity of vascular factors or

the dosages or adherence to drugs used to treat them. Note also that we did not address all of the risk or modifiable risk factors addressed in previous studies.[5] In the future, it will be necessary to investigate the effects of *APOE* genotype, physical activity, depression, social isolation, and exposure to air pollution on efforts to predict the onset of dementia. Third, the participants in this study were older than those in many previous studies and the educational level of participant was lower. Fourth, our analysis of individuals with hypercholesterolemia did not include separate analyses of total cholesterol levels and LDL-c levels. Fifth, further research will be required to elucidate the reasons underlying the protective effects of myocardial infarction on DAT or the detrimental effects of anti-platelet medication on VaD. Sixth, the sensitivity of the risk scores in the prediction of dementia was low. Future researchers should formulate prediction models using behavioral and/or physiological indices of higher sensitivity. Finally, this study was limited to patients in Taiwan. Cross-validation studies in other countries will be required to further confirm our findings.

Conclusion

This study identified several modifiable factors that are related to incident dementia and the effects of drugs used to treat them, after controlling for vascular- and lifestyle-related factors. It appears that these findings could be used as markers in predicting dementia in clinical settings, especially among elderly individuals with low educational level. Future studies that include larger more heterogeneous samples will be required to validate these findings and improve the sensitivity in the prediction.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Show Chwan Memorial Hospital (SCMH_IRB1081006). Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Consent for publication

Not applicable.

Availability of data and materials

Data available on request due to privacy/ethical restrictions. Requests to access these datasets should be directed to H-TC, changht@cycu.edu.tw.

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Supplemental material

Supplemental material for this article is available online.

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