Dairy and fish consumption and the risk of mild cognitive impairment and dementia

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Research

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Abstract

Background

There are inconsistent evidence for the association between fish consumption and dementia risk, and emerging evidence suggesting that dairy consumption is associated with lower dementia risk, based on a limited number of prospective cohort studies.

Methods

We investigated the association of dairy and fish consumption with the risk of developing mild cognitive impairment (MCI) and dementia. High intake of daily consumption of milk and dairy products and consumption of fish at least three servings per week were determined at baseline for 1,164 community-living and cognitively normal Chinese individuals aged 55 + in the Singapore Longitudinal Ageing Study (SLAS-1), who were followed-up (average 3.5 years) for incident cases of MCI and dementia determined by established criteria.

Results

The participants' mean (SD) age was 65.1 (6.9) years, 66.8% were female. Controlling for sex, age, low or no education, APOE-e4 status, physical, social and productive activity, depression (GDS ≥ 5), central obesity, prediabetes/diabetes, hypertension, abnormal lipids, cardiac diseases, and daily fruit/vegetable intake in multivariable analysis, daily intake of milk and dairy products was significantly associated with lower risk of incident MCI (OR = 0.61; 95% CI = 0.39–0.96) or MCI-dementia (OR = 0.62; 95% CI = 0.40–0.95). Fish intake was not significantly associated with lowered risk of incident MCI and MCI-dementia, (OR = 0.74, 95%CI = 0.49–1.13 for MCI; OR = 0.76, 95% CI = 0.51–1.14 for MCI-dementia).

Conclusions

High dairy intake was associated with approximately 40% reduced risk of MCI or dementia. There is weak support in this study of an association between fish intake and MCI-dementia risk.

Trial Registration:

ClinicalTrials.gov NCT03405675. Registered 23 January 2018 (retrospectively registered).

Introduction

Cognitive decline is a major public health concern of ageing populations worldwide. It is estimated that 50 million people have dementia globally and nearly 10 million new cases are reported each year (1). With effective disease modifying therapies lacking, and as the aetiology of dementia continues to be explored, identifying factors that may slow or prevent the development of cognitive decline is crucial for decreasing its burden to public health.

Diet is potentially a modifiable risk factor that may protect against cognitive decline and dementia. A growing body of literature suggests that specific food intakes and nutrients, food intake patterns and dietary interventions may delay the onset of dementia or reduce the rate of cognitive decline (2–6). Initially, there were reports suggesting that consumption of fish with high level of n-3 polyunsaturated fatty acids (PUFAs) may be protective against the risk of dementia but this was not consistently supported by other studies (7–13). More recently, emerging evidence suggest an association between consumption of dairy products and cognitive disorders, but the findings are also mixed (14–24). While some researchers

have reported that lower intake of milk is significantly associated with increased risk of cognitive disorders (16–18, 20–22), other studies did not support the inverse association (19, 23, 24).

There are few studies that have investigated these associations using prospective cohort designs or assessed cognitive outcome using established criteria for diagnosis of neurocognitive disorders (MCI and dementia). We examined the association of dairy and fish consumption at baseline with the subsequent risk of developing MCI and dementia over 3.5 years in a prospective cohort of cognitively normal Chinese participants aged 55 years and above in the Singapore Longitudinal Aging Study (SLAS-1).

Methods

Study Design and Population

The SLAS-1 is a population-based study of aging and health of community-dwelling older Singaporeans aged 55 years and above. Recruitment and baseline assessments for 2,804 participants were conducted between 2003 and 2004. These participants were followed-up from 1 January 2006 to 31 December 2009. The mean length of follow-up was 3.5 years (median 3.8 years). Details of the population sampling and study methods have been described previously (25). Briefly, each participant underwent comprehensive structured interviews, clinical evaluation, blood sampling, and performance-based assessments for an extensive range of demographic, medical, biological, psychosocial, and neurocognitive characteristics. The study was approved by the National University of Singapore Institutional Review Board, and written informed consent was obtained from all participants.

The present study was restricted to 1,164 Chinese participants with baseline normal cognition (no MCI or dementia) and known cognitive status at follow-up (normal cognition, MCI, or dementia). Participants with stroke, central nervous system diseases, unknown cognitive status at baseline and follow-up were excluded. See **Flowchart**. The mean age of the study population was 65.1 years (SD ± 6.9) and 66.8% of the participants were female.

Measurements

Clinical measurements were based on self-reports of a diagnosis and/or treatment of diabetes mellitus, hypertension, cardiac diseases, and stroke, with details of medications ascertained by review of medication packages. Blood pressure was determined by the mean of three readings with participants seated and recorded using a standard mercury sphygmomanometer. Waist circumference was measured in centimetres at the midpoint between the lowest rib margin and the top of the iliac crest at minimal respiration to the closest 0.1 cm (26). Overnight fasting serum samples were analysed for blood glucose and lipid levels using standard laboratory techniques.

Assessment of Dairy and Fish Intakes

High dairy intake was defined as having at least one serving of milk product daily and high fish intake was defined as having at least three servings of fish each week. Participants were asked to provide self-reported “yes” or “no” responses to the questions: “I consume a lot of milk products (at least one serving per day)”; and “I eat a lot of fish (at least three servings per week)”. Dairy products refer to milk, yogurt, probiotic drinks, cheese, butter, and ice-cream, while fish refers to all edible fish species available in Singapore, excluding shellfish.

Neuropsychological Evaluation

Screening and assessment of cognitive impairment were performed according to a standard protocol of clinical assessment for dementia. A previously validated, highly sensitive and specific Chinese modified version of the Mini-Mental State Examination (MMSE) with education-stratified norms (27) was used to screen for MCI and dementia (28). Participants with a MMSE score below 27 or a MMSE score decline of at least one to two points per year underwent comprehensive neuropsychological testing and the Clinical Dementia Rating (CDR).

The neuropsychological evaluation used a standardized test battery assessing: memory (Rey Auditory Verbal Learning Test immediate and delayed recall and visual reproduction immediate and delayed recall; executive function (Symbol Digit Modality Test, Design Fluency and Trail Making Test Part B); language (categorical verbal fluency); visuospatial skills (block design); and attention (digit span forward and backward and spatial span forward and backward). The assessment was administered by trained psychology research assistants in English, Mandarin, or Chinese dialects. Details of the neuropsychological tests and their normative values have been described previously (29). Trained research nurses conducted and scored the CDR (https://biostat.wustl.edu/adrc/cdrpgm/). Functional ability was assessed by dependency in performing ten basic activities of daily living: bowels, bladder, grooming, toilet use, feeding, transferring, mobility, dressing, stairs, and walking.

MCI and dementia diagnoses were determined by established diagnostic criteria (30, 31). MCI was defined by cognitive concern expressed by the participant or informant, cognitive impairment in one or more domains (executive function, memory, language, or visuospatial); normal functional activities, and absence of dementia, and operationalized as follows:

1. Subjective cognitive complaints from a single question asking whether the participant had more problems with memory than most, or an informant report of memory decline, “Do you think your family member’s memory or other mental abilities have declined?” or Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) ≥ 3.0;
2. Cognitive deficits defined as Modified Chinese MMSE score of 24–27, or decline of 2 more points from baseline, a neurocognitive domain score that was 1–2 SD below the age-and-education adjusted means, or decline from baseline of 0.5 SD from serial measurements;
3. No functional dependency in performing instrumental daily living activities (Lawton IADL scale);
4. CDR scale score of 0 or 0.5;
5. No dementia

Dementia was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, DSM-4R (32), with evidence of cognitive deficit from objective assessment (MMSE ≤ 23 or neuropsychological domain scores < 2 SD of age-education-adjusted mean), and evidence of social or occupational function impairment (dependency in one or more IADL or CDR score ≥ 1). Participants who did not meet these criteria for MCI or dementia were classified as cognitively normal.

Covariates

Analyses included as covariates: age, sex, education level (none or primary education), APOE-ε4 genotype, level of leisure time activities (based on the number and frequencies of usual participation in 18 different categories of physical, social and productive activities) (33), smoking status at baseline (ever smoker or current smoker), daily alcohol consumption, Geriatric Depression Scale (GDS ≥ 5), central obesity (waist circumference of ≥ 100 cm and ≥ 90 cm in males and females respectively), prediabetes and diabetes, hypertension, lipid abnormality, cardiac diseases and daily intake of at least two servings of fruits and vegetables.

Statistical Analysis

Statistical software (SPSS, version 25, IBM Corporation) was used to perform the data analysis. Comparison of baseline risk factor variables by high level dairy and/or fish intake categories was performed using Chi-squared test for categorical variables and ANOVA test for continuous variables. Logistic regression analysis was used to estimate the odds ratios (OR) and 95% confidence interval (95% CI) of association between dairy and fish consumption and risk of incident MCI or MCI-dementia in multivariable models adjusting for baseline covariates. The outcome variable combined MCI and dementia since the follow-up of these cognitive normal participants identified incident cases of MCI as well as a small number of dementia cases (N = 14) who were diagnosed without known progression from MCI. Statistical significance was set at $p < 0.05$.

Results

The demographics and baseline risk factors of the study participants across the categories of high dairy and/or fish intake are summarized in Table 1. The mean age of the participants was 65.1 (SD = 6.9) years and 66.8% were female. Over a third (37.2%) of the study population reported low dairy and fish intake at baseline. These participants, compared to their high dairy and fish intake counterparts tend to be female, were less educated, had lower levels of physical, social and productive activities, were more likely to be centrally obese and hypertensive, and reportedly consumed less than two servings of fruits and vegetables daily but did not differ on age, APOE- ε4 status, smoking, alcohol, depression, prediabetes and diabetes, lipid abnormality and cardiac diseases.

The estimated ORs of association between baseline dairy and fish intake and incident MCI and MCI-dementia from follow-up are summarized in **Table 2**. A total of 9.5% of the study population were found to have MCI while 1.0% was diagnosed with dementia.

There was a significant inverse relationship between high dairy intake and risk of incident MCI (OR = 0.59; 95% CI = 0.39–0.90) or MCI-dementia (OR = 0.60; 95% CI = 0.40–0.90). The estimated OR of the association remained significantly elevated after adjusting for age, sex low or no education, APOE- ε4 status, physical, social and productive activity, depression (GDS ≥ 5), central obesity, prediabetes/diabetes, hypertension, abnormal lipids, cardiac diseases, and fruit/vegetable and fish intake in multivariable analysis **(**Table 3**)**.

Fish intake was also associated with a lower risk of incident MCI and MCI-dementia, but the estimated ORs of association were not statistically significant in univariate and multivariable analysis (OR = 0.74, 95% CI = 0.49–1.13 for MCI; OR = 0.76, 95% CI = 0.51–1.14 for MCI-dementia).

Participants who reported both high dairy and fish intake showed significantly lower ORs of association with MCI (OR = 0.50; 95% CI = 0.34–0.97) and MCI-dementia (OR = 0.60; 95% CI = 0.37–0.98), compared to those with neither high fish nor dairy intake. However, these ORs were comparable to those in participants with only high dairy intake, suggesting little or no additive interaction effect.

Discussion

This follow-up study of a Chinese cohort of cognitively normal older adults aged 55 years and above in Singapore showed that those with daily consumption of milk or other dairy products were about half as likely to develop MCI or dementia compared to those with less dairy consumption. To the best of our knowledge, five prospective cohort studies published to date have reported the association between milk or dairy intake and risk of cognitive impairment with conflicting findings (20–24).

Our findings concur with two prospective cohort studies of Japanese men and women which showed a significant association between a higher level of milk and dairy intake with lower risk of Alzheimer's disease but not vascular dementia in one study (20), and with vascular dementia in another study (21). On the other hand, one study of Caucasian and African Americans suggest that milk intake at midlife may be associated with greater rate of cognitive decline from midlife to late life (22). Additionally, two other cohort studies of Australian men and French women found that regular consumers of full-cream milk was associated with poorer cognitive function assessed by MMSE (23) and higher intakes of dairy desserts and ice-cream was associated with cognitive decline (24). A meta-analysis involving a total of 10,941 participants from four cohort studies and three cross-sectional studies concluded that there is an inverse relationship between milk consumption and cognitive disorders (Alzheimer's disease, dementia, and cognitive decline/impairment) but this was limited to Asian participants who are noted to have relatively lower intake of overall milk and dairy products (14). Milk consumption is relatively low among Singaporeans (34), as it is among Japanese, which reinforces the evidence that among Asians, high dairy intake reduced the risk of MCI or dementia.

This may possibly be explained by genotypic differences among populations in lactase persistence (LP), a trait in which lactose can be digested throughout adulthood, and lactase non-persistence (LNP) which can cause lactose intolerance and

influence dairy consumption. Asians are known to have higher prevalence of intolerance than other ethnicities. It has been reported that in all ethnic populations and especially among Caucasians, LP individuals tend to consume more cheese and recent total dairy intake (35). In LP, lactose is broken down by the enzyme lactase in the small intestine, resulting in the formation of D-galactose, which has been extensively shown to induce neurodegeneration through oxidative stress in animal models. Thus, Caucasians with a higher frequency of LP may be more susceptible to the neurotoxic effects of galactose-induced oxidative stress and cognitive decline. However, findings from a study fail to support the hypothesis that milk intake was associated with greater cognitive decline among Caucasians with the LP versus LNP genotype (22). Hence, more studies are needed.

There are many other proposed biological mechanisms for the protective effect of dairy intake against the risk of dementia. Prospective studies have reported that dairy intake was associated with a lowered risk of developing type 2 diabetes mellitus (36), hypertension (37) and obesity (38), and these same factors are also known risk factors for dementia (39). The reduced risk of cognitive impairment from milk intake could be attributed to modified neurovascular dysfunction, weight reduction and lowered metabolic risks (40, 41). Another possible mechanism could be the benefits from bioactive constituents present in milk and dairy products. It has been postulated that phospholipids in the milk fat globule membrane are active transporters of essential fatty acids that could improve brain health by reducing endoplasmic reticulum stress (42), which is known to increase the risk of cognitive disorders such as Alzheimer's disease. Furthermore, milk and dairy products are important sources of vitamin B12 which is known to reduce plasma homocysteine levels (20). As low serum vitamin B12 and elevated plasma homocysteine levels are reportedly risk factors for the development of dementia (43, 44), milk and dairy consumption could lower the risk of dementia because of the presence of these nutrients. Numerous bioactive peptides are present in milk and dairy products that possess important biological activities and functionalities, including antihypertensive, antioxidative, immunomodulatory and other activities that influence physiological and metabolic functions with ultimate beneficial health effects (45). Recently, a novel oleamide identified from a fermented dairy product was demonstrated to be able to reduce amyloid beta accumulation via enhanced microglial phagocytosis, and to suppress microglial inflammation after amyloid beta deposition (46).

In this study, we found no statistically significant reduced risk of MCI or dementia in participants who reported high fish intake. Evidence from previous studies have suggested inconsistent results, as only four of eight observational studies that used incidence of Alzheimer's disease or dementia outcomes reported positive findings (11). On its own, our data does not strongly support an association; however, our data taken together with existing data across studies does favour a role for fish consumption in delaying or preventing the onset of cognitive disorder in elderly individuals without dementia. A recent meta-analysis in 2015 of six prospective cohort studies reported the pooled relative risks associated with fish intake for dementia of 0.84 (95% CI = 0.71–1.01) and an associated 36% (95% CI = 8–56%) lower risk of Alzheimer's disease (12). In our study population, we did not distinguish between fish types (high fat versus low fat, wild versus farmed) and preparation methods of fish (baked, fried, or steamed) which may influence the fatty acid content and obscure a true association. Inaccuracies in self-reporting frequencies of fish intake may also cause misclassification errors and bias risk estimation towards the null. Additionally, dairy and fish intakes were assessed only at baseline and possible changes after the baseline interview may attenuate estimates of risks.

In summary, our study provided strong support that among Asian older adults in this Singapore population, consumption of milk and dairy products but not fish consumption was significantly associated with lower risk of incident MCI or dementia. These findings have strong implications for future research and public health policy in terms of dietary interventions for the early prevention of dementia. Further research in populations with diverse genetic polymorphisms in LP and milk tolerance should be conducted to elucidate the ethnic population-specific effects of dairy consumption on cognitive decline and dementia risk.

List Of Abbreviations

Mild Cognitive Impairment, MCI

Singapore Longitudinal Ageing Study, SLAS-1

Geriatric Depression Scale, GDS

Mini-Mental State Examination, MMSE

Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE

Diagnostic and Statistical Manual of Mental Disorders, DSM-4R

Instrumental Activities of Daily Living, IADL

Lactose Persistence, LP

Lactose Non-Persistence, LNP

Declarations

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the National University of Singapore Institutional Review Board (NUS-IRB; Reference Code: 04-140).

Consent for Publication

Not applicable.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors’ Contributions

DQLC and TPN designed research, wrote paper and had primary responsibility for final content; XYG, QG, MSZN, PY, TSL, MSC, WSL, KBY designed and conducted research, including clinical assessment of MCI and dementia; TPN analysed data and performed statistical analyses; All authors reviewed and approved the final manuscript for publication.

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Tables

Table 1. Baseline risk factor variables by high-level dairy (milk products) and fish intake categories

	High-level of dairy and/or fish intake								
	None		Dairy only		Fish only		Both dairy and fish		P
	%	(n)	%	(n)	%	(n)	%	(n)	
Total		433		136		256		339	
Age, mean ± SD	65.5	± 6.9	65.2	± 7.2	64.4	± 6.3	64.9	± 7.1	0.180
Female sex	69.3	(300)	64.0	(87)	60.2	(154)	69.6	236	0.046
None or primary education	54.0	(234)	33.1	(45)	34.8	(89	41.6	141	0.001
APOE-ε4	17.8	(77)	15.4	(21)	16.8	(43	16.5	56	0.923
Leisure time activities tertiles: Low	22.4	(97)	25.0	(34)	19.1	(49)	17.1	(58)	
Mid	45.7	(198)	45.6	(62)	42.6	(109)	45.1	(153)	
High	31.9	(138)	29.4	(40)	38.3	(98)	37.8	(128)	0.014
Smoking: Ex-smoker	9.2	(40)	10.3	(14)	7.8	(20)	6.5	(22)	
Current smoker	5.5	(24)	4.4	(6)	7.0	(18)	5.9	(20)	0.696
Daily alcohol drinking	9.5	(41)	6.6	(9)	7.4	(19)	8.6	(29)	0.675
Depression (GDS ≥ 5)	12.0	(52)	9.6	(13)	8.2	(21)	71.	(24)	0.111
Central obesity	48.7	(211)	45.6	(62)	43.4	(111)	38.6	(131)	0.046
Prediabetes and diabetes	14.5	(63)	13.2	(18)	14.5	(37)	14.2	(48)	0.984
Hypertension	59.8	(259)	55.1	(75)	47.7	(122)	51.6	(175)	0.012
Lipid abnormality	60.0	(260)	57.4	(78)	59.4	(152)	60.5	(205)	0.934
Cardiac diseases	8.3	(36)	5.9	(8)	3.1	(8)	7.4	(25)	0.057
Fruits and vegetables intake of ≥ 2 servings daily	91.2	(395)	89.0	(121)	92.6	(237)	96.8	(328)	0.005

Table 2. Association of baseline dairy (milk products) and fish intake with MCI and dementia from follow-up

Dairy (milk products) and fish intake at baseline	At risk	Incident cases				Bi-variable analysis			
		MCI		Dementia		MCI	P	MCI-dementia	P
	n	%	(n)	%	(n)	OR (95%CI)	P (trend)	OR (95%CI)	P (trend)
Whole sample	1164	9.5	(110)	1.0	(12)				
Daily dairy consumption: Yes	475	6.9	(33)	0.8	(4)	0.59 (0.39 – 0.90)	0.016	0.60 (0.40-0.90)	0.014
Daily dairy consumption: No	689	11.2	(77)	1.2	(8)	1		1	
Fish intake ≥3 servings a week: Yes	569	7.9	(47)	1.0	(6)	0.69 (0.46-1.02)	0.065	0.71 (0.49-1.03)	0.074
Fish intake ≥3 servings a week: No	595	11.1	(63)	1.1	(6)	1		1	
Both dairy (daily) and fish (≥3 servings a week)	339	7.4	(25)	1.2	(4)	0.54 (0.33-0.90)	0.017	0.57 (0.36-0.91)	0.019
Dairy daily only	136	5.9	(8)	0.0	(0)	0.43 (0.20-0.91)	0.028	0.38 (0.18-0.82)	0.013
Fish ≥3 servings a week only	256	8.6	(22)	0.8	(2)	0.64 (0.38-1.08)	0.095	0.63 (0.38-1.04)	0.071
None of above	433	12.7	(55)	1.4	(6)	1	(0.026)	1	0.015

Table 3. Association of dairy (milk products) and fish intake with MCI and dementia from follow-up

	Multivariable analysis[1]			
	MCI	P	MCI-dementia	P
	OR (95%CI)	P (trend)	OR (95%CI)	P (trend)
Daily dairy consumption: Yes	0.61 (0.39-0.96)	0.031	0.62 (0.40-0.95)	0.027
Daily dairy consumption: No	1		1	
Fish intake ≥3 servings a week: Yes	0.74 (0.49-1.13)	0.166	0.76 (0.51-1.14)	0.193
Fish intake ≥3 servings a week: No	1		1	
Both dairy (daily) and fish (≥3 servings a week)	0.50 (0.34-0.97)	0.037	0.60 (0.37-0.98)	0.042
Dairy daily only	0.51 (0.23-1.13)	0.098	0.43 (0.19-0.95)	0.038
Fish ≥3 servings a week only	0.77 (0.44-1.34)	0.349	0.73 (0.43-1.24)	0.246
None of above	1	(0.115)	1	(0.069)

[1]Multivariable analysis includes the follow covariates: sex, age, low or no education, APOE-ε4 status, leisure time (physical, social and productive activity tertiles), depression (GDS≥5), central obesity, prediabetes/diabetes, hypertension, abnormal lipids, cardiac diseases, daily fruit and vegetable intake.

Figures

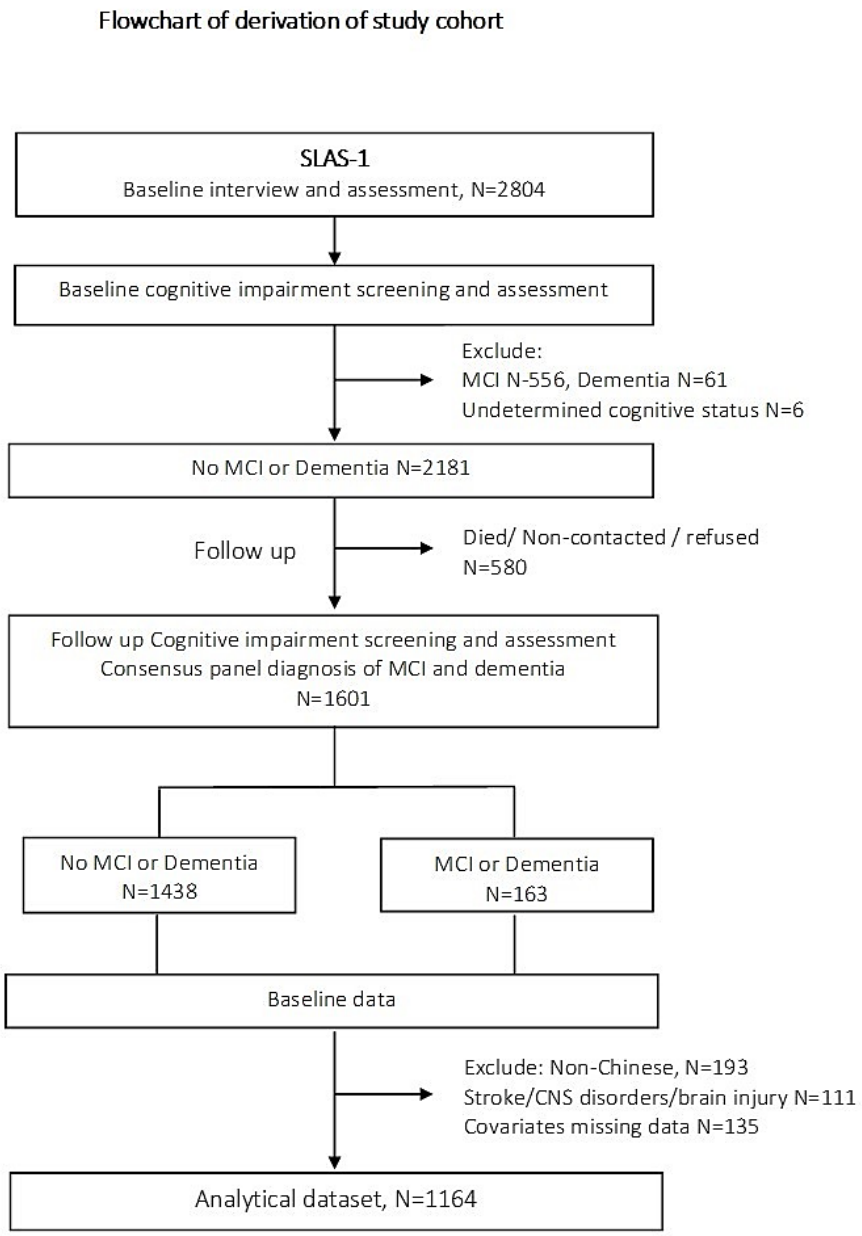

Figure 1

Flowchart of derivation of study cohort.