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Original Article

Ultra-processed food consumption and risk of dementia and Alzheimer's disease: The Framingham Heart Study

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ABSTRACT

Background: Ultra-processed food consumption is emerging as a risk factor for various cardiometabolic diseases, however its association with dementia and Alzheimer's disease has rarely been explored.
Objectives: We sought to examine whether ultra-processed food consumption is associated with risk of all-cause dementia and Alzheimer's disease among middle-age and older adults.
Design: A prospective cohort study.
Setting: The Framingham Heart Study, a single-site, community-based cohort study.
Participants: Offspring cohort participants who attended examination cycles 5 (1991-1995) and 7 (1998-2001) at age ≥60 years and who were dementia-free at baseline.
Measurements: Nutritional information was retrieved from food frequency questionnaires, and ultra-processed food was categorized based on the NOVA system. Participants were followed-up for all-cause dementia and Alzheimer's disease. Cox regression models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) adjusting for potential confounders.
Results: The study sample included 1,375 participants free of dementia and stroke at baseline (mean age 68 ± 6y, 54 % females). During a mean follow-up of 12.7 ± 6.0 years, 224 and 172 individuals were diagnosed with all-cause dementia and Alzheimer's disease, respectively. An interaction of ultra-processed food consumption with age was observed with regard to dementia and Alzheimer's disease (p for interaction = 0.02 and 0.007, respectively). Therefore, all analyses were stratified by the median age of 68 years. Among participants who were <68 years of age at baseline, each serving per day of ultra-processed food was associated with 13 % increased risk for Alzheimer's disease (HR = 1.13, 95 % CI:1.03-1.25), and consumption of ≥10 servings/day vs. <10 servings/day of ultra-processed food was associated with a 2.7-fold increase in Alzheimer's disease risk (HR = 2.71, 95 % CI:1.18-6.24), after adjustment for age, sex, education, total energy, metabolic factors and diet quality. The associations with all-cause dementia were less robust, and no significant findings were observed when age at baseline was 68 years or above.
Conclusions: Our findings suggest that consumption of ultra-processed food in middle-age may be linked with an increased risk for Alzheimer's disease. Future clinical studies are warranted to assess whether reduction of ultra-processed food consumption improves brain health.

1. Introduction

Dementia, including Alzheimer's disease (AD) as its major subtype, is highly prevalent and is expected to increase substantially due to aging of the population, thus posing enormous and increasing physical, financial, and social burdens to patients, families, caregivers and societies [1]. Because treatment options for AD are limited, a great emphasis has been put on identifying risk and protective factors [2]. Accumulat-

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ing evidence suggests that life-style factors play an important role in the prevention of cognitive impairment and dementia [3]. Among those factors, healthy diet patterns, such as the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH diet Intervention for Neurological Delay (MIND) as well as caloric restriction, have shown promising results in dementia and AD prevention [4–7]. Moreover, specific food items and groups, as well as macro-and micronutrients have been related to AD development. Some examples include the possible protective effects of fish consumption and n-3 PUFA, and the possible harmful effects of red meat and saturated fat [7].

In recent years, ultra-processed foods (UPFs) have gained substantial attention as determinants of health [8]. UPFs are industrially-processed formulations containing multiple food-based and synthesized substances that maximize profitability, convenience and palatability [9]. Although a modest decrease in UPF consumption over a period of 17 years has been demonstrated among participants from the Framingham Heart Study (FHS) cohort in the US [10], UPFs make up more than half of the total dietary energy consumed in high-income countries, with the largest share in the US (57.9 %) [11]. Further, UPF consumption is expected to increase substantially, particularly in developing countries [12]. High UPF consumption has been linked with an increased risk of mortality [13,14] and health outcomes, including obesity [15], diabetes [16] and cardiovascular diseases [17,18]. Emerging evidence further suggested that UPF consumption may be associated with poorer cognitive function [19,20] and with a faster rate of cognitive decline [21]. Several studies have explored the association of diet with cognitive impairment and dementia, including specific UPF food items (e.g. processed meats, artificially sweetened beverages) or a western dietary pattern. However, few studies have focused specifically on the overall consumption of UPF [22,23]. Moreover, dementia ascertainment in studies exploring UPF and cognitive health was based solely on cognitive assessments [22] or electronic health records [23].

In the current study, we aimed to assess the relationship of UPF consumption at middle and old-age with the clinical diagnosis of all-cause dementia and AD among community-dwelling participants of the FHS.

2. Methods

De-identified data are available through formal data request application procedures by qualified investigators. More information is presented in framinghamheartstudy.org or biolincc.nhlbi.nih.gov/studies/framcohort/.

2.1. Study sample

The study sample is based on participants from the Offspring Generation of the FHS, who attended both the 5th (1991-1995) and the 7th (1998-2001) examination cycles [24]. A flow chart of the study sample is presented in Fig. 1. Of 3,295 attendees of the 5th and 7th examination cycles, 3,117 were dementia-free at baseline and had information on incident dementia. We excluded 554 individuals who did not complete the Food Frequency questionnaire (FFQ), or had invalid FFQ defined as >13 missing items or implausible total energy intake (<600 or >3,999 kcal for women and <800 or >4,199 kcal for men). Additionally, we excluded 1,173 who were younger than 60 years at examination cycle 7 (baseline) and 15 with no education information. Therefore, our final sample consisted of 1,375 participants. Data were obtained under a protocol approved by the institutional review board of the Boston University Medical Center, and written informed consent was obtained from all participants.

2.2. UPF assessment

The Harvard semi-quantitative FFQ was used to assess the consumption frequency of 126 food items and nine categories over the past year at examination cycles 5 and 7. This FFQ has shown good validity compared to 7-day diet records [25,26]. Data from the FFQ was then used to categorize all the food and beverage items into NOVA categories, which are based on the nature, extent and purposes of the industrial processes they undergo [27]. We classified all the food items into NOVA group 4 (i.e. UPF) or not (i.e. Group 1: Unprocessed or Minimally Processed Foods; Group 2: Processed Culinary Ingredients; Group3: Processed Foods) [27]. Due to the FFQ lack of detailed information on exact food types and preparation methods, it is limited in the extent to which it can correctly categorize all food items into the NOVA UPF category. Therefore, for our primary analyses we used a conservative categorization, where food items with no conclusive classification (i.e. yogurt, cream, bacon, pancakes, waffles, chips, popcorn, chowder, cream soup and tomato sauce) were not included as UPFs (Supplementary Table 1). The quantity of UPF intake for each participant was assessed in servings/day. We averaged the UPF servings/day across examination cycles 5 and 7 to create a measure of UPF intake over a maximum of a 10 year period. The food items included as UPFs by food category are listed in Supplementary Table 1.

2.3. Dementia and AD ascertainment

Screening and surveillance methods for incident all-cause dementia and AD were reported in detail previously [28,29]. In brief, all FHS participants undergo continuous surveillance for cognitive impairment. Participants are identified as having possible cognitive impairment based on their performance on repeated screening tests, a report of the participant or family member on subjective cognitive decline, a referral by a physician or FHS ancillary investigators, or a review of outside medical records. Those who are flagged for possible cognitive impairment are invited for further annual neurologic and neuropsychological examinations. If these examinations indicate possible dementia, the relevant neuropsychological and medical information (e.g. neuroimaging, autopsy, interviews with caregivers) is reviewed by a dementia review committee, which includes a neurologist and a neuropsychologist, where a decision is reached on whether the person had dementia, the dementia subtype and date of onset. Dementia was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria. This criteria requires impairment in memory and at least one other domain of cognitive function, along with impaired functional ability [30]. AD diagnosis was reached based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association for definite, probable, or possible AD [31].

2.4. Covariate assessment

Educational achievement was defined as a four class variable (no high-school degree, high-school degree only, some college, or at least a college degree). Diabetes was defined as a fasting blood glucose concentration >7 mmol/L, a previous diagnosis of diabetes mellitus, or the use of a hypoglycemic agent or insulin. Body mass index (BMI) was defined by weight (in kilograms) divided by the square of height (in meters). High-density lipoprotein (HDL) cholesterol was measured from fasting morning blood samples. We used the Dietary Approaches to Stop Hypertension (DASH) diet score as an indicator of overall diet quality [32]. Construction of the DASH diet score in the FHS Offspring Cohort has been previously described [33]. The final DASH score was used as a continuous measure ranging from 8 to 40, with a higher score indicating higher adherence and therefore increased diet quality. Total daily energy intake was derived from the FFQ.

2.5. Statistical analysis

Multivariable Cox regression models were used to examine the associations between UPF consumption and incident dementia and AD. We

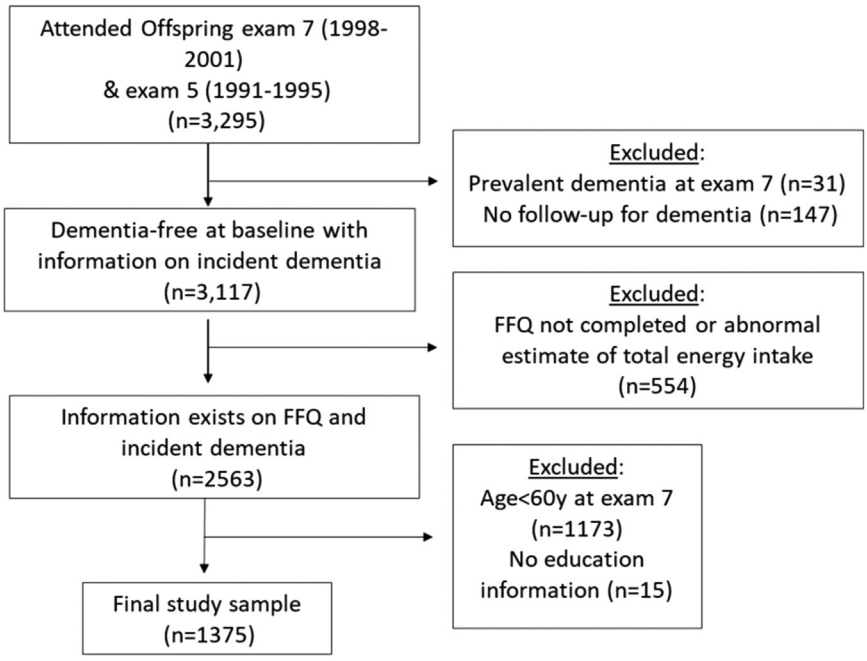

Fig. 1. Flow chart of the study sample.

tested whether age modified the associations between UPF consumption and the study's outcomes based on the evidence that midlife health behaviors, including exposure to healthy diet [34,35], is critical for a subsequent amelioration of dementia risk. UPF consumption was examined as a continuous variable, with Hazard Ratios (HRs) indicating risk for dementia/AD associated with increment in 1 energy-adjusted serving per day as well as quintiles of UPF with the bottom category used as the reference. To examine whether excessive UPF consumption may be associated with an increased dementia/AD risk, we additionally assessed the dementia/AD risk, comparing those who consumed 10 servings/day or more to those who consumed less than 10 servings/day.

The basic model included age, sex, education and total calories as covariates. In the second model, we additionally adjusted for BMI, prevalent diabetes and total to HDL ratio (metabolic measures) in addition to covariates from the basic model. Lastly, we added diet quality as a covariate to the basic model.

We ran two sensitivity analyses: 1. excluding dementia cases diagnosed in the first three years of follow-up to mitigate the possibility that our findings are due to reverse causality (i.e. that cognitive impairment has led to an increase in UPF consumption); 2. including discordant food items in the UPF NOVA category.

All models were tested for violation of the proportional hazards assumption using the zph option in PROC PHREG, which uses weighted Schoenfeld residuals. A two-sided p-value of <0.05 was considered statistically significant. Analyses were performed using Statistical Analyses System software Version 9.4 (SAS Institute, Cary, NC).

3. Results

During a mean follow-up of 12.7 ± 6.0 years, 224 (16 %) and 172 (13 %) developed all-cause dementia and AD, respectively. The mean age of the total study sample was 68 ± 6 years, 46 % were men and 98 % were of European ancestry. The total energy intake was 1,799 ± 557 kcal per day, and ultra-processed food consumption was on average 6.2 ± 3.4 servings per day. Of the total sample, 185 (13 %) consumed at least 10 servings per day of UPF. Additional demographic, clinical and nutritional characteristics overall and by UPF consumption categories are presented in Table 1. Additionally, the baseline characteristics of the subsample of participants who were not included in our analyses are presented in Supplemental Table 2.

In the total sample, no significant associations were observed between UPF consumption and dementia or AD risk (Supplemental Table 3). However, a significant interaction was observed between UPF consumption and age with respect to their association with risk of dementia and AD (p for interaction = 0.02 and 0.007, respectively). Therefore, a stratified analysis was performed using the median age of 68 years as the cutoff. The proportional hazard assumption was met in each age strata. Baseline characteristics separately for participants aged <68 years and ≥68 years are presented in Supplemental Tables 4 and 5. As expected, older individuals were less healthy (e.g. had higher rates of diabetes, hypertension, CVD), but no substantial differences were observed in nutritional factors (e.g. diet quality, total calories). Mean follow-up durations for participants aged <68y and ≥68y were 14.3 ± 5.8 and 11.2 ± 5.8 years, respectively.

Among participants 68 years of age and older, no statistically significant associations were found between continuous or quintiles of UPF consumption and dementia or AD risk. Yet, comparing ≥10 to <10 servings/day, a significant decreased risk for dementia and AD were observed, only in the models adjusted for all the study's covariates (HR = 0.58, 95 % CI:0.34, 0.99 and HR = 0.53, 95 % CI:0.29, 0.97, respectively) (Supplementary table 6). Among individuals aged <68 years at the time of the second dietary assessment (i.e. baseline; examination cycle 7), each serving/day was associated with increased risk for all-cause dementia (HR = 1.10, 95 % CI:1.01, 1.20; p = 0.02) after controlling for age, sex, education and total energy (Table 2). These results remained similar after additional adjustment for metabolic measures (i.e. BMI, diabetes and total to HDL cholesterol ratio). However, the associations slightly attenuated and became non-significant after further adjustment for overall diet quality (HR = 1.08, 95 % CI:1.00, 1.18; p = 0.08). More robust associations were observed for incident AD. After adjustment for age, sex, education and total calories, each serving/day of UPF was associated with an increased risk of AD (HR = 1.13, 95 % CI:1.03, 1.25; p = 0.01), and these associations remained similar after further adjustment for metabolic factors (model 2) and diet quality (model 3). Furthermore, excessive UPF intake (≥10 servings/day) compared to <10 servings/day was associated with a 2.7 higher AD risk (HR = 2.76, 95 % CI:1.21, 6.29) in the basic model, and this association remained similar after adjustment for metabolic factors and diet quality (Table 2 and Fig. 2).

Our findings were similar after excluding dementia and AD cases that occurred at the first 3 years of follow-up (Supplementary table 7).

Table 1.
Baseline characteristics of the study sample overall and by UPF quintiles and excessive consumption (≥10 servings/day).

		Total n = 1375	Q1 (0.5-4.1 S/D) n = 275	Q2 (4.1-5.5 S/D) n = 275	Q3 (5.5-6.9 S/D) n = 275	Q4 (6.9-9.0 S/D) n = 275	Q5 (9.0-25.6 S/D) n = 275	<10 S/D n = 1190	≥10 S/D n = 185
Age (years)		68.3 ± 5.6	68.1 ± 5.8	67.6 ± 5.4	68.5 ± 5.7	68.4 ± 5.3	68.7 ± 5.9	68.1 ± 5.6	69.2 ± 5.7
Men, n (%)		635 (46)	88 (32)	121 (44)	131 (48)	137 (50)	158 (57)	522 (44)	113 (61 %)
Education	No high-school degree, n (%)	79 (6)	15 (5)	9 (3)	19 (7)	15 (5)	21 (8)	63 (5)	16 (9 %)
	High-school degree, n (%)	465 (34)	113 (41)	89 (32)	82 (30)	93 (34)	88 (32)	401 (34)	64 (35 %)
	Some college, n (%)	392 (29)	83 (30)	77 (28)	81 (29)	75 (27)	76 (28)	345 (29)	47 (25 %)
	College graduate, n (%)	439 (32)	64 (23)	100 (36)	93 (34)	92 (33)	90 (33)	381 (32)	58 (31 %)
Body mass index, kg/m^2		27.4 [24.5,30.6]	27.1 [24.0,29.8]	26.8 [24.4,30.1]	27.5 [24.9,30.4]	27.6 [25,31.5]	27.5 [24.5,31.3]	27.3 [24.5, 30.5]	27.5 [25.1,31.4]
Current smoking, n (%)		104 (8)	16 (6)	19 (7)	24 (9)	19 (7)	26 (9)	86 (7)	18 (10)
Physical activity index		38.2 ± 6.4	38.6 ± 6.7	38.9 ± 6.3	37.9 ± 6.2	37.8 ± 6.4	37.6 ± 6.4	38.3 ± 6.9	37.5 ± 6.9
Diabetes, n (%)		193 (14)	29 (11)	34 (12)	48 (17)	43 (16)	39 (14)	171 (14)	22 (12)
Fasting blood glucose, mg/dL		99 [92,109]	97[90,105]	98[92,108]	101 [94,113]	100 [92,113]	101 [94,111]	99 [92, 109]	101 [94,110]
Hypertension, n (%)		794 (58)	150 (55)	161 (59)	161 (59)	160 (58)	162 (59)	685 (58)	109 (59)
Systolic blood pressure, mean mmHg ± SD		132.7 ± 19.2	131.4 ± 20.3	131.9 ± 19.8	133.7 ± 19.8	133.7 ± 18.2	132.7 ± 17.8	132.6 ± 19.4	133.6 ± 17.7
Diastolic blood pressure, mean mmHg ± SD		72.6 ± 9.7	72.6 ± 10.4	72.1 ± 8.5	73.4 ± 10.2	72.1 ± 9.9	72.6 ± 9.5	72.6 ± 9.8	72.4 ± 9.1
Prevalent CVD, n (%)		253 (18)	39 (14)	52 (19)	51 (19)	55 (20)	56 (20)	213 (18)	40 (22)
Total cholesterol, mg/dL		199.1 ± 36.1	204.2 ± 33.9	201.3 ± 37.2	201.2 ± 36.9	195.6 ± 36.7	193.0 ± 34.7	200.2 ± 36.1	191.8 ± 35.1
HDL-cholesterol, mg/dL		53.6 ± 16.9	56.2 ± 17.6	53.3 ± 16.9	54.1 ± 17.0	53.1 ± 16.1	51.1 ± 16.9	54.1 ± 16.9	50.2 ± 16.6
Triglycerides, mg/dL		138.1 ± 77.4	131.1 ± 65.4	137.4 ± 75.6	141.5 ± 88.1	136.8 ± 68.0	143.5 ± 86.9	137.4 ± 75.6	142.5 ± 87.8
ApoE4, n (%)		295 (22)	49 (18)	74 (27)	58 (22)	55 (21)	59 (22)	255 (22)	40 (22)
NOVA classification (servings/day)*	Unprocessed/ Minimally processed	10.9 ± 4	10.1 ± 4.2	11.0 ± 4.0	11.1 ± 4.2	11.1 ± 3.7	11.4 ± 3.8	11.0 ± 3.7	11.4 ± 3.9
	processed culinary ingredients	3.2 ± 3	2.4 ± 2.2	2.9 ± 2.9	3.3 ± 2.9	3.4 ± 2.9	4.0 ± 3.6	3.1 ± 2.4	4.1 ± 3.9
	Processed	2.5 ± 1.6	2.1 ± 1.4	2.3 ± 1.3	2.7 ± 1.6	2.7 ± 1.6	3.1 ± 1.8	2.5 ± 1.3	3.2 ± 1.8
	Ultra-processed	6.2 ± 3.4	2.8 ± 1.0	4.5 ± 1.2	5.8 ± 1.6	7.4 ± 2.0	10.6 ± 3.8	5.8 ± 2.1	11.5 ± 4.0
Total energy intake, kcal/day		1798.6 ± 557.4	1399.1 ± 402.5	1632.0 ± 403.9	1818.7 ± 527.2	1919.6 ± 498.0	2223.7 ± 567.6	1720.3 ± 509.7	2302.5 ± 588.1
Carbohydrates (grams)		228.5 ± 81.6	180.3 ± 67.7	209.1 ± 65.8	232.9 ± 75.6	241.0 ± 74.9	279.1 ± 87.8	219.3 ± 75.8	287.5 ± 92.9
Proteins (grams)		76.6 ± 25	64.7 ± 22.0	72.1 ± 22.1	77.8 ± 26.1	79.7 ± 22.7	88.7 ± 25.5	74.3 ± 24.1	91.0 ± 26.2
Fat (grams)	SFA	19.8 [14.5,25.5]	13.8 [10.6,18.7]	17.4 [13.9,21.5]	19.9 [15.1,25.1]	22.5 [17.6,28.5]	25.4 [20.5,33.2]	18.8 [13.9, 24.1]	26.7 [21.4,34.7]
	MUFA	21.1 [15.8,27.3]	15.2 [11.3,19.9]	19.0 [14.5,23.3]	21.2 [16.5,26.4]	23.5 [18.9,29.8]	27.8 [22.1,35.6]	20.2 [15.1, 25.4]	28.9 [24.0,37.9]
	PUFA	10.9 [8.1,14.2]	8.2 [6.5,11.0]	9.9 [7.5,12.3]	10.9 [8.2,13.6]	11.6 [9.2,15.1]	14.6 [10.9,18.3]	10.4 [7.8, 13.2]	15.0 [11.5,18.8]
	Trans	2.4 [1.7,3.2]	1.6 [1.1,2.0]	2.0 [1.6,2.6]	2.4 [1.7,3.1]	2.8 [2.1,3.5]	3.4 [2.5,4.5]	2.2 [1.6, 2.9]	3.5 [2.7,4.7]
Fruits & Vegetables, Servings/week		37.5 ± 19.3	36.8 ± 20.6	38.6 ± 19.3	38.1 ± 19.8	36.9 ± 17.6	37.2 ± 19.0	37.8 ± 19.1	35.9 ± 20.1
Fibers, grams/1000kcal		10.6 ± 3.3	11.7 ± 4.1	11.0 ± 3.1	10.7 ± 3.0	10.2 ± 2.8	9.5 ± 3.0	10.9 ± 3.4	9.1 ± 2.5
Fast food (Servings/week)		1.5 [0.9,3.4]	0.9 [0.5,1.5]	1.5 [0.9,2.5]	1.5 [0.9,3.0]	1.9 [1.0,3.5]	2.9 [1.4,4.5]	1.5 [0.9,2.5]	3.5 [1.5,4.5]
Fried food (Servings/week)		0.5 [0.0,1.0]	0.0 [0.0,0.5]	0.5 [0.0,0.5]	0.5 [0.0,1.0]	0.5 [0.0,2.0]	0.5 [0.0,2.5]	0.5 [0.0, 0.5]	0.5 [0,2.5]
Red meat (Servings/week)		3.9 [2.4,6.5]	2.9 [1.4,4.4]	3.9 [2.4,5.5]	4.4 [2.4,6.9]	4.9 [2.9,7.4]	5.9 [3.5,8.9]	3.9 [2.4, 6.0]	6.5 [3.9,10]
Sugar sweetened beverages (Servings/week)		0.5 [0.0,2.0]	0.0 [0.0,0.9]	0.5 [0.0,1.5]	0.5 [0.0,3.0]	0.5 [0.0,3.0]	0.5 [0,3.5]	0.5 [0.0, 2.0]	0.5 [0.0,3.5]
Alcohol (grams)		2.8 [0.0,12.7]	1.8 [0.0,9.5]	3.0 [0.0,12.3]	2.8 [0.0,12.4]	3.5 [0.0,13.7]	2.0 [0.0,15.6]	2.8 [0.0, 12.2]	1.9 [0.0,15.8]
Sodium (mg/day)		2045.6 ± 727.4	1516.2 ± 495.3	1827.2 ± 515	2067.7 ± 695.8	2220.3 ± 614.4	2596.6 ± 784.8	1942.7 ± 654.2	2707.3 ± 822.7
Whole grain (g/day)		13.7 [5.7,27.2]	10.4 [4.3,25.8]	13.2 [5.2,26.3]	16.9 [6.3,29.6]	16.2 [5.9,27.8]	14.0 [6.6,26.7]	13.5 [5.5, 27.3]	14.0 [6.7,26.7]
Diet quality*		23.8 ± 4.1	25 ± 4.1	24.4 ± 4.1	24.2 ± 4.1	23.2 ± 3.8	22.3 ± 4.1	24.1 ± 4.1	21.9 ± 4.0

* Average consumption reported in examination cycles 5 & 7; †Based on the DASH diet score (continuous measure ranging from 8 to 40 with higher scores indicating higher adherence)UPF, Ultra-processed Food; S/D, Servings per day; CVD, Cardiovascular Disease; HDL, High-Density Lipoprotein; ApoE, Apolipoprotein E.

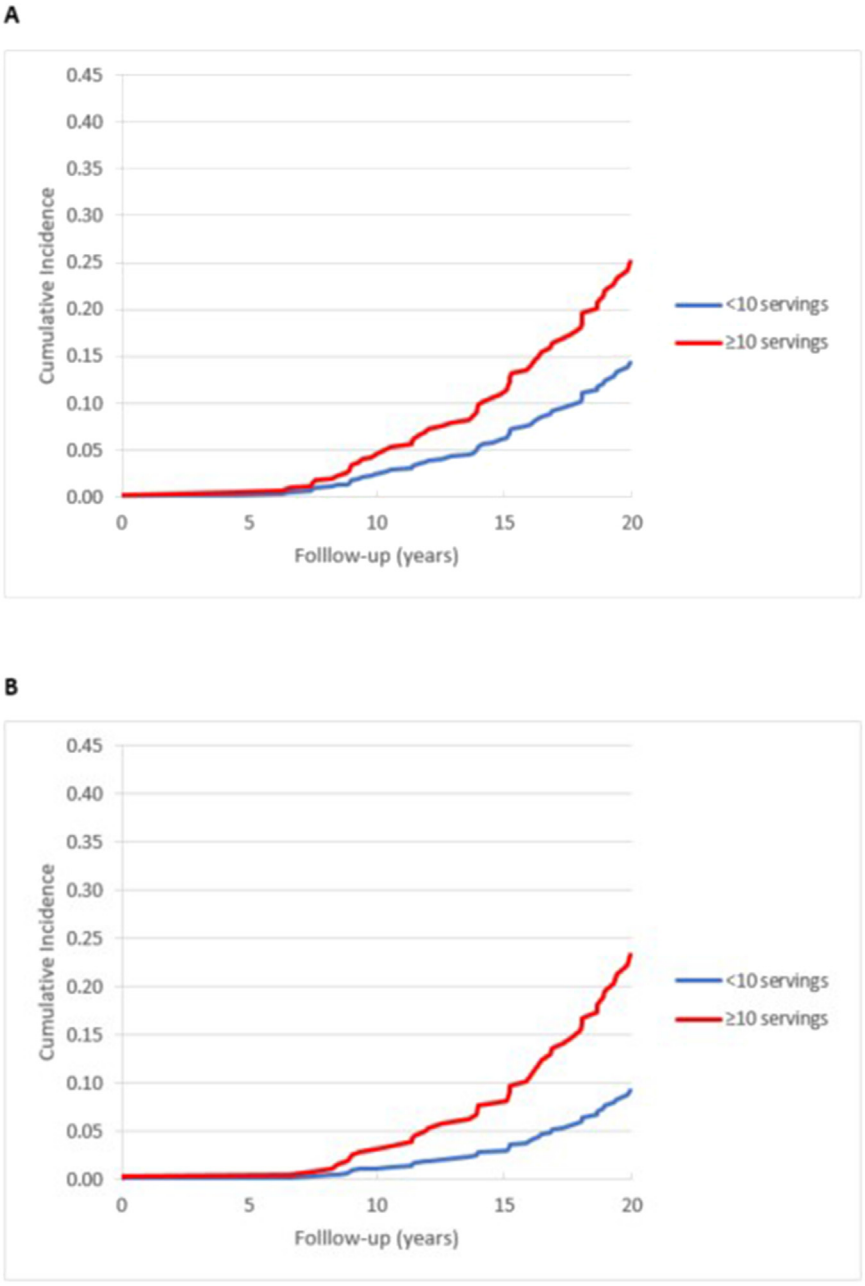

Fig. 2. Adjusted Cumulative Incidence of all-cause dementia (A) and Alzheimer's disease (B) by UPF intake categories among participants aged <68 y, n = 675. Adjustments were made for age, sex, education and total energy intake.

However, no statistically significant associations were observed when discordant food items were included in the UPF category (Supplementary tables 8 and 9).

4. Discussion

This community-based cohort study with a mean follow-up time of ~13 years did not identify significant associations between UPF consumption and dementia or AD risk overall. However, the current study suggests that UPF consumption in midlife may be associated with a higher risk of AD. The association was non-linear, and was driven by excessive consumption, with a high AD risk of more than 2.5-fold observed among those who consumed 10 or more servings per day. The association between UPF consumption in midlife and AD risk remained robust after controlling for potential confounders, including diet quality. However, no associations were found when UPF was reported at older ages or when the outcome was all-cause dementia.

Our findings are generally supported by a previous study among participants of the UK biobank that demonstrated significant associations between UPF consumption and dementia risk [23]. Yet, in contrast to our findings of significant associations with AD but not all-cause dementia, the former study reported less profound associations with AD and stronger associations with all-cause and vascular dementia. This discrepancy may stem from methodological differences between the studies, including dementia ascertainment that in the previous study was based on hospital admissions and death registries, the UPF data derived from a 24 h dietary questionnaire compared to FFQ in the current study and differences in participants' characteristics.

Despite the scarcity of evidence linking UPF consumption to dementia risk, a plethora of evidence indirectly supports our findings. First, a western-style diet, which is characterized by high consumption of UPF, has been previously associated with AD-related biomarkers among dementia-free adults [36]. Moreover, among 115 participants from the Women's Health Aging Project, adherence to "junk food" predicted Amyloid-β deposition in the brain [37]. Second, previous literature showed that consumption of specific UPF products, including sugary and artificially-sweetened beverages [38], added saturated and trans fats [39] and processed meat [40] may be associated with increased de-

Table 2
Association between UPF consumption and risk for dementia and Alzheimer's disease, ages <68 years.

	Continuous HR (95 % CI)	P-value	Q1 HR (95 % CI)	Q2 HR (95 % CI)	Q3 HR (95 % CI)	Q4 HR (95 % CI)	Q5 HR (95 % CI)	≥10 vs. <10 servings/day HR (95 % CI)	P for trend
All-cause dementia	62 cases/675		10 cases/143	10 cases/155	15 cases/126	12 cases/130	15 cases/121	10 cases/71	
Model 1	**1.10 (1.01, 1.20)**	**0.02**	1.00 (ref.)	0.92 (0.38, 2.25)	1.68 (0.72, 3.91)	1.47 (0.61, 3.57)	2.02 (0.81, 5.04)	1.86 (0.88, 3.95)	0.08
Model 2	**1.10 (1.01, 1.20)**	**0.03**	1.00 (ref.)	0.904 (0.37, 2.21)	1.65 (0.71, 3.84)	1.43 (0.59, 3.49)	2.01 (0.80, 5.03)	1.86 (0.88, 3.94)	0.09
Model 3	1.08 (1.00, 1.18)	0.08	1.00 (ref.)	0.871 (0.36, 2.13)	1.54 (0.66, 3.61)	1.26 (0.51, 3.09)	1.73 (0.67, 4.46)	1.67 (0.78, 3.60)	0.2
Alzheimer's disease	45 cases/675		8 cases/143	9 cases/155	10 cases/126	5 cases/130	13 cases/121	9 cases/71	
Model 1	**1.13 (1.03, 1.25)**	**0.01**	1.00 (ref.)	1.14 (0.43, 3.01)	1.51 (0.57, 4.02)	0.83 (0.26, 2.65)	2.41 (0.86, 6.79)	**2.76 (1.21,6.29)**	0.2
Model 2	**1.14 (1.03, 1.25)**	**0.01**	1.00 (ref.)	1.13 (0.43, 3.00)	1.49 (0.56, 3.97)	0.80 (0.25, 2.60)	2.36 (0.83, 6.68)	**2.73 (1.20, 6.23)**	0.2
Model 3	**1.13 (1.03, 1.25)**	**0.01**	1.00 (ref.)	1.12 (0.42, 2.98)	1.48 (0.55, 3.95)	0.70 (0.24, 2.57)	2.32 (0.81, 6.66)	**2.71 (1.18, 6.24)**	0.2

UPF, Ultra-processed Food; HR, Hazard Ratio.
Model 1: Adjusted for age, sex, education and total calories.
Model 2: model 1 + BMI, prevalent diabetes and total to HDL ratio.
Model 3: Model 1 + diet quality.

mentia risk. Lastly, emerging evidence demonstrates a link between UPF consumption and cognitive function, in cross-sectional [41] and longitudinal [19,21] studies.

In our sample of older adults, increased UPF consumption was related to dementia risk only among the younger participants. This finding is in agreement with a previous study demonstrating a stronger association between UPF consumption and cognitive decline in younger (<60y) compared to older participants [21]. The stronger association in younger ages is concordant with the rationale that to be efficient, risk reduction in dementia should target modifiable risk factors, particularly nutrition, in mid- rather than late-life, due to the long pre-morbid period of the disease [42,43]. Further, our findings may imply that excessive UPF consumption may be protective for dementia and AD among the older age group. These unexpected findings may reflect a possible influence of cognitive decline with aging on nutritional parameters (e.g. total energy intake), and require exploration in future studies.

The associations between UPF intake and AD attenuated when discordant food items were included in the UPF NOVA category. This discrepancy underscores the challenge of applying the NOVA classification to the FFQ, when the latter lacks detailed information on exact food types and preparation methods [44]. Moreover, UPFs represent a heterogeneous group of foods. Although many UPF foods are considered to have a poor nutrient density while being energy rich, others may be a source of under consumed nutrients and food components. For example, a higher intake of whole grain, regardless of processing, may be associated with healthier aging [45] and reduced dementia risk [46]. Future cohort studies with more detailed dietary assessments and hence reduced NOVA misclassification are needed to determine a refined measure of UPF intake and its association with health outcomes, including dementia and AD [44].

Accumulating evidence suggests that various aspects of food processing and formulation that characterize UPF may lead to insulin resistance, metabolic dysregulation, oxidative stress and systemic inflammation, which in turn may contribute to AD development [47]. Among those aspects are, for example, several potential toxic compounds such as advanced glycation end products, industrial trans-fatty acids and acrylamide, all are present in high concentrations in UPF products. Additional potentially harmful UPF factors include food additives such as emulsifiers, sweeteners and colorant, and various contaminants that migrate from contract packaging to foods [48]. According to emerging literature, the gut microbiome may have a central role as a potential mediator of the association between consumption of UPF and chronic diseases [48]. Specifically, the above mentioned factors in UPF have been shown to directly cause changes to the gut microbiota composition and microbial metabolism, which in turn lead to neuroinflammation and cognitive decline [47,48]. Further, a recent study showed that the gut microbiome composition was related to *in vivo* measures of Amyloid and tau pathology in brain of cognitively healthy individuals, but no associations were found in relation to vascular brain injury [49]. These findings suggest that changes to the gut microbiome may occur early in the disease process, and stand in line with our observations of associations between UPF intake and AD but not all-cause dementia.

An additional plausible explanation for our findings is that, regardless of the degree of food processing, diet characterized by excessive amount of UPF is also high in energy intake and poor in nutritional quality. Hence, individuals who consume large amounts of UPF are also less adherent to diet types such as the Mediterranean, DASH and MIND, and consume less nutrients such as n-3 PUFA, all have been associated with slower rates of cognitive decline and a reduction of AD rate [50]. Yet, the fact that our findings remained similar after adjustment for total energy intake and diet quality implies that the degree of processing *per se* may play a detrimental role in brain health, and is supported by findings from previous studies that found significant associations of UPF consumption with dementia [23] and other health outcomes, while also considering energy intake and nutritional quality of the diet [48].

The strengths of our study include the prospective cohort design with a long follow-up. Of note, the long follow-up, particularly in the younger subsample, may suggest that our results are not wholly influenced by reverse causality. Indeed, some studies assessing the relationship of dietary patterns with dementia risk found significant associations only when the follow-up periods were short, possibly because dietary habits deteriorate in the years preceding dementia diagnosis (i.e. reverse causality) [51–53]. Moreover, the sample included middle-aged and older individuals from the community, with a comprehensive assessment of clinical all-cause dementia and AD. Further, we averaged UPF consumption over two examination cycles to estimate the amount consumed over a ~10 years period. However, our findings should be interpreted in light of several study limitations. First, the FFQ has limited validity to assess UPF consumption due to incomplete information on the degree of processing [44]. Furthermore, self-report of diet patterns is subjected to misclassification. Yet, considering the cohort study design that included a sample of cognitively healthy individuals at baseline and a long follow-up duration, the possible misclassification of participants into the NOVA categories is expected to be non-differential and thus to result in attenuation of the true associations. Second, despite the adjustment for potential confounders, including BMI, total energy and diet quality, residual confounding may still remain. Third, although our findings remained significant after excluding the first years of follow-up and despite the long follow-up, reverse causality may still explain our findings. Lastly, some baseline characteristics of participants included in our analyses were different from the characteristics of those excluded, and the study external validity may be limited due to the inclusion of participants of mainly European ancestry, from one geographic area and of a relatively high socioeconomic status.

In summary, our study showed that individuals who consume large amounts of UPF at midlife may be prone to AD in older ages. If replicated by additional studies, these findings imply that limiting UPF consumption in middle-age may be an efficient preventive strategy aiming to reduce AD burden. Future observational studies and randomized clinical trials are warranted to replicate our results in diverse populations, using long follow-up durations and focusing on UPF consumption during midlife. Future studies are also needed to clarify biological mechanisms that underlie the link of UPF consumption with AD risk.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2024.100042.

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