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Association Between Later Life Lifestyle Factors and Alzheimer's Disease Biomarkers in Non-Demented Individuals: A Longitudinal Descriptive Cohort Study

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Abstract.
Background: Lifestyle factors have been associated with the risk of dementia, but the association with Alzheimer's disease (AD) remains unclear.
Objective: To examine the association between later life lifestyle factors and AD biomarkers (i.e., amyloid-β 1–42 ($A\beta_{42}$) and tau in cerebrospinal fluid (CSF), and hippocampal volume) in individuals with subjective cognitive decline (SCD) and mild cognitive impairment (MCI). In addition, to examine the effect of later life lifestyle factors on developing AD-type dementia in individuals with MCI.

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Methods: We selected individuals with SCD ($n = 111$) and MCI ($n = 353$) from the DESCRIPA and Kuopio Longitudinal MCI studies. CSF $A\beta_{42}$ and tau concentrations were assessed with ELISA assay and hippocampal volume with multi-atlas segmentation. Lifestyle was assessed by clinical interview at baseline for: social activity, physical activity, cognitive activity, smoking, alcohol consumption, and sleep. We performed logistic and Cox regression analyses adjusted for study site, age, gender, education, and diagnosis. Prediction for AD-type dementia was performed in individuals with MCI only.
Results: Later life lifestyle factors were not associated with AD biomarkers or with conversion to AD-type dementia. AD biomarkers were strongly associated with conversion to AD-type dementia, but these relations were not modulated by lifestyle factors. Apolipoprotein E (APOE) genotype did not influence the results.
Conclusions: Later life lifestyle factors had no impact on key AD biomarkers in individuals with SCD and MCI or on conversion to AD-type dementia in MCI.

Keywords: Alcohol consumption, Alzheimer's disease, amyloid-β (1–42), cerebrospinal fluid, cognitive reserve, exercise, hippocampus, lifestyle, mild cognitive impairment

INTRODUCTION

The prevalence of Alzheimer's disease (AD) is rising across the world, which increases the need for opportunities to delay or prevent the development of the disease. Population studies have found that targeting midlife lifestyle factors such as physical and cognitive activity may decrease the risk for AD-type dementia [1, 2]. AD-type dementia is the most common form of dementia and is characterized by an accumulation of amyloid-β plaques, aggregation of tau tangles and hippocampal atrophy [3, 4]. These AD biomarkers are abnormal up to 25 years before the onset of AD-type dementia, which makes them valuable for early detection of AD ([5–7].

Previous research did not find an association between AD biomarkers and cognitive and physical activity in non-demented individuals [8], but the association between a variety of later life lifestyle factors and AD biomarkers in individuals with normal cognition or mild cognitive impairment (MCI) have not been extensively examined. Understanding the relation between lifestyle factors and AD biomarkers in non-demented individuals at the time of diagnostic assessment at a memory clinic may be useful for the design of prevention studies in early stages of AD, and may be of direct value in advising later life lifestyle changes.

In this study, we examined the association between the potential modifiable risk factors social activity [9], physical activity and cognitive activity [1, 2, 10], alcohol consumption [11], current smoking [1, 2] and sleep problems [1, 2, 12, 13] with cerebrospinal fluid (CSF) tau and amyloid-β 1–42 ($A\beta_{42}$) and hippocampal volume in individuals with subjective cognitive decline (SCD) and MCI. Secondly, we examined the effect of these lifestyle factors on the risk for AD-type dementia and whether these factors modulated the risk of AD biomarkers for conversion to AD-type dementia in individuals with MCI. We hypothesized that lifestyle factors at diagnostic assessment are associated with AD biomarkers in individuals with SCD and MCI and with progression to AD-type dementia in individuals with MCI. Furthermore, we expected that lifestyle factors modulate the risk of AD biomarkers for conversion to AD-type dementia in individuals with MCI.

METHODS

Individuals

We selected in total 464 individuals. 111 SCD and 254 MCI individuals were from the DESCRIPA study [14] and 99 individuals with MCI were from the Kuopio longitudinal-MCI (Kuopio L-MCI) study [15–18]. The DESCRIPA study ($n = 881$) recruited individuals from eleven memory clinics across Europe between 2003 and 2005. The KUOPIO L-MCI study ($n = 145$) pooled individuals from two population-based studies in Eastern Finland between 1996 and 2001 [15, 17–19].

Inclusion criteria for SCD were age above 55 years, referral to the memory clinic for an evaluation of complaints, no cognitive impairment on neuropsychological tests, and absence of dementia.

Inclusion criteria for MCI in DESCRIPA were similar to the criteria for SCD except that a cognitive impairment was required on a neuropsychological test. Impairment was defined as age, gender, and education corrected z-score below –1.5 in any cognitive domain [20]. In Kuopio L-MCI, MCI was defined as: 1) memory complaint by patient, family, or physician; 2) normal activities of daily living; 3) normal global cognitive function; 4) objective impairment

below –1.5 SD in any cognitive domain; 5) CDR score of 0.5; and 6) absence of dementia [20, 21].

For both studies, the diagnosis of AD-type dementia was based on the NINCDS-ADRDA criteria [22]. From both studies, we selected individuals based on the availability of CSF data or hippocampal volumes and at least one lifestyle factor.

Baseline and follow-up assessment

At baseline we performed an assessment of clinical history, Mini-Mental State Examination (MMSE [23]), lifestyle factors, and APOE $\varepsilon 4$ genotyping, and performed medical, neuropsychological, neuroimaging, and CSF assessments. At follow-up, the clinical and neuropsychological assessments were repeated. The average follow-up time was 2.4 years (SD = 1.3).

Lifestyle factors

Data on physical activity, alcohol consumption, and current smoking were available in both the DESCRIPA study and the Kuopio L-MCI study. Data on social activity, cognitive activity, and sleep problems were only collected in DESCRIPA. All measures were self-reported and collected in a clinical interview unless reported otherwise.

Being *socially active* was defined as having at least one social activity reported several times a week or having at least two activities several times a month. Social activities included visiting family and friends, babysitting, going to church/church choir, club membership (e.g., pensioners, garden, social or golf club) and volunteer's work.

Being *physically active* was defined in DESCRIPA as either: 1) every day or about every day walking or cycling, or 2) at least several times a week one of the following self-reported activities: dancing, badminton, tennis, swimming, water exercise, squash, skating, or going to the gym. In KUOPIO L-MCI, being physically active was defined as either 1) a physical activity at least several times a week causing breathlessness or sweating, or 2) a physical activity of at least 2–4 h or 15–30 km per week. This definition was more or less equivalent to the amount of exercise recommended by the Centers for Disease Control (CDC), the American College of Sports Medicine (ACSM) and the American Heart Association (ASA) (i.e., at least five days per week of 30 min moderate intensity activity or 3 days of 20 min vigorous intensity activity) [24, 25].

Cognitive activity was measured with the 7-item Cognitive Activity Scale (CAS) [26]. Cognitive activities measured in this CAS are viewing television; reading newspapers; reading magazines; reading books; playing games such as cards, checkers, crosswords, or other; and going to museums. For every activity, the individual had to rate the frequency on the following 5-point Likert scale: once a year or less (1), several times a year (2), several times a month (3), several times a week (4), every day or about every day (5). Individuals with an average frequency rating >3.9 were considered cognitively active. Individuals ($n = 4$) with more than 2 missing items on the CAS were excluded.

Mild to moderate alcohol consumption was defined in DESCRIPA as consumption of maximum two alcoholic units a day and in Kuopio L-MCI a consumption of maximum 14 alcoholic units per week. We compared individuals with mild to moderate alcohol consumption ($n = 249$) with individuals with no alcohol consumption ($n = 169$), and with individuals with severe alcohol consumption (i.e., more than two units a day or more than 14 per week, $n = 39$).

Current smoking was defined as any present smoking in DESCRIPA and Kuopio-L MCI.

Sleep problems was defined as sleep problems reported by the patient and/or caregiver in clinical interview or a total score (i.e., frequency x severity) of more than two on the sleep item on the Neuropsychiatry Inventory (NPI [27]).

CSF collection, storage, and analysis

In DESCRIPA, CSF samples were collected in 10 mL polypropylene tubes and stored at –80°C. CSF analyses were centrally performed at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Sweden. $A\beta_{42}$ and total tau (t-tau) were measured with single-parameter ELISA kits (Fujirebio, formerly, Innogenetics, Ghent, Belgium). Concentrations below 550 pg/ml for $A\beta_{42}$ and above 375 pg/ml for t-tau were considered abnormal according to local cut-off values [28].

In Kuopio L-MCI, CSF samples were collected in 10 mL polypropylene tubes and stored at –70°C. CSF analyses were measured with commercial ELISA (Fujirebio, formerly, Innogenetics, Ghent, Belgium). Concentrations below 452 pg/ml for $A\beta_{42}$ and above 399 pg/ml for t-tau were considered abnormal according to local cut-off values [29]. In both studies, investigators were blinded to the CSF results.

Hippocampal volume

The scanning was performed at 1.0 or 1.5 Tesla and included for DESCRIPA 3D T1 weighed gradient echo and a fast fluid attenuated inversion recovery (FLAIR) sequence and for Kuopio L-MCI anatomical high-resolution T1-weighed images using a 3D-MPRAGE sequence [21, 30]. The hippocampal volumes were computed from segmentations generated by a multi-atlas segmentation tool [31]. Age and gender corrected continuous hippocampal volumes were used, which were calculated by a linear regression model [32]. In addition, a cutoff was calculated in an independent cohort (Alzheimer's Disease Neuroimaging Initiative) that could best discriminate controls from individuals with AD-type dementia when corrected to age of 70 years. Abnormal hippocampal volume was defined as a volume <4216 mm^3 for males and <3930 mm^3 for females (left and right side summed).

APOE genotype

In DESCRIPA, apolipoprotein E (APOE) $\varepsilon 4$ genotyping was determined with polymerase chain reaction (PCR) of genomic DNA extracted from coagulated blood.

In Kuopio L-MCI, the APOE genotype was determined from blood leukocytes and extracted by standard phenol-chloroform extraction, and analyzed by PCR and *HhaI* digestion [33].

Statistical analyses

Statistical analyses were conducted with IBM SPSS statistics version 24. Group differences at baseline were examined with independent *t*-tests for continuous variables and with χ^2 tests for categorical variables. All lifestyle factors were dichotomized into present versus absent. The association between lifestyle factors and dichotomous AD markers (i.e., abnormal $A\beta_{42}$, abnormal tau, and abnormal hippocampal values) were analyzed by logistic regression analyses corrected for age, gender, education, diagnosis and center in all individuals with SCD and MCI. The moderator effect of all lifestyle factors on continuous AD markers (i.e., CSF $A\beta_{42}$ pg/ml concentrations, CSF t-tau pg/ml concentrations, corrected hippocampal volumes) in converting to AD-type dementia were analyzed by performing survival analyses with Cox Regression corrected for age, gender, education, and center (the 11 single centers) in individuals with MCI. Assumptions of Cox regression were met.

Post-hoc, analyses were repeated with correction for APOE $\varepsilon 4$ carriership to control for a possible genetic predisposition for AD-type dementia. In addition, for lifestyle factors with data from both the DESCRIPA and Kuopio L-MCI study (i.e., physical activity, alcohol consumption, and current smoking) analyses were repeated with correction for study (DESCRIPA versus Kuopio L-MCI). Furthermore, logistic regression analyses were also performed with age and gender corrected hippocampal volumes [32] as a continuous outcome measure.

RESULTS

We included 464 individuals (SCD $n = 111$, MCI $n = 353$). Baseline characteristics are presented in Table 1. Individuals were on average 70 years old (SD = 7.3), had 9 years of education (SD = 4.0) and the majority was female (57%). Individuals with MCI were slightly older than individuals with SCD, but did not differ on years of education and gender. As expected, individuals with MCI had lower MMSE scores, lower hippocampal volumes, higher CSF t-tau concentrations and converted more often to AD-type dementia. However, individuals with MCI did not differ on CSF $A\beta_{42}$ concentrations and APOE $\varepsilon 4$ carriership from individuals with SCD. With regard to lifestyle factors, individuals with MCI were less socially active and fewer individuals consumed mild to moderate quantity of alcohol than individuals with SCD. APOE $\varepsilon 4$ carriership did not differ between groups. There was no difference between individuals with MCI from DESCRIPA ($n = 254$) and Kuopio L-MCI ($n = 99$) on age (mean (SD): 70.3 (7.7) versus 71.5 (4.2)) and gender (44.1% versus 33.3% male), but they did differ on educational years (mean (SD): 9.4 (4.0) versus 7.1 (2.2), $p < 0.001$) and MMSE scores (mean (SD): 27.1 (2.3) versus 23.8 (2.7, $p < 0.001$)).

Lifestyle factors and AD biomarkers

Social activity, physical activity, cognitive activity, mild to moderate alcohol consumption, current smoking and sleep problems at time of diagnosis were not associated with abnormal $A\beta_{42}$, abnormal tau or abnormal hippocampal volumes in individuals with SCD and MCI at baseline. Table 2 lists the relations between these lifestyle factors and AD markers.

Table 1
Baseline characteristics

	All ($n = 464$)	SCD ($n = 111$)	MCI ($n = 353$)
Age	69.8 (7.3)	67.0 (7.6)	70.6 (6.9)*
Male, *n* (%)	199/464 (43%)	54/111 (49%)	145/353 (41%)
Years of Education, mean (SD)	9.4 (4.0)	11.4 (4.1)	8.7 (3.8)
MMSE score, mean (SD)	26.7 (2.8)	28.5 (1.5)	26.2 (2.9)***
APOE-ε4+, *n* (%)	185/407 (46%)	41/90 (46%)	144/317 (45%)
Socially active, *n* (%)	53/119 (45%)	27/47 (57%)	26/72 (36%)*
Physically active, *n* (%)	166/349 (48%)	46/85 (54%)	120/264 (46%)
Cognitively active, *n* (%)	22/231 (10%)	12/85/(14%)	10/146 (7%)
Alcohol consumption, *n*	457	111	346***
None, *n* (%)	169 (37%)	24 (22%)	145 (42%)
Mild to moderate, *n* (%)	249 (55%)	79 (71%)	170 (49%)
Severe, *n* (%)	39 (9%)	8 (7%)	31 (9%)
Current smoking, *n* (%)	52/457 (11%)	13/111 (12%)	39/346 (11%)
Sleep problems, *n* (%)	79/349 (23%)	27/108 (25%)	52/241 (22%)
Abnormal CSF aβ42, *n* (%)	101/205 (49%)	26/65 (40%)	75/140 (54%)
Abnormal CSF t-tau, *n* (%)	107/205 (52%)	23/65 (35%)	84/140 (60%)**
Abnormal CSF aβ42 + t-tau, *n* (%)	63/205 (31%)	10/65 (15%)	53/140 (38%)**
HCV, mean (SD)	3939 (606)	4190 (520)	3869 (610)*
Abnormal HCV, *n* (%)	216/402 (54%)	28/88 (32%)	188/314 (60%)***
Converted to AD-type dementia, *n* (%)	101/464 (22%)	2/111 (2%)	99/353 (28%)***
Converted to Non-AD dementia, *n* (%)	17/464 (4%)	2/111 (2%)	15/353 (4%)

Number of individuals for dichotomous variables: individuals with abnormal score or individuals that were active/individuals with measurement. Abbreviations: MMSE, Mini-Mental State Examination; APOE, Apolipoprotein E; CSF, Cerebrospinal fluid; aβ42, beta amyloid 1–42; t-tau, total tau; HCV, hippocampal volume; SCD, Subjective Cognitive Impairment; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease. Data are mean (SD) or valid percent. $^{*}p < 0.05$, significantly different from the SCD group $^{**}p < 0.01$, significantly different from the SCD group $^{***}p < 0.001$, significantly different from the SCD group.

Table 2
The effect of lifestyle factors on AD markers

	Abnormal $A\beta_{42}$		Abnormal t-tau		Abnormal HCV	
	OR (95% CI)	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*
Social Activity	1.904 (0.642 to 5.645)	0.25	0.529 (0.186 to 1.504)	0.23	0.504 (0.154 to 1.648)	0.26
Physical activity	1.397 (0.745 to 2.620)	0.30	0.673 (0.342 to 1.324)	0.25	0.959 (0.576 to 1.597)	0.87
Cognitive activity	1.138 (0.369 to 3.509)	0.82	0.848 (0.252 to 2.846)	0.79	1.168 (0.346 to 3.944)	0.80
Alcohol consumption						
Mild to moderate versus no intake	0.855 (0.446 to 1.638)	0.64	1.159 (0.592 to 2.269)	0.67	0.749 (0.459 to 1.224)	0.25
Mild to moderate versus severe intake	2.213 (0.593 to 8.256)	0.24	0.237 (0.041 to 1.361)	0.11	0.756 (0.341 to 1.678)	0.49
Current smoking	1.668 (0.642 to 4.335)	0.30	0.821 (0.307 to 2.197)	0.69	1.102 (0.564 to 2.151)	0.78
Sleep problems	0.827 (0.379 to 1.802)	0.63	0.771 (0.343 to 1.733)	0.53	1.774 (0.975 to 3.227)	0.06

Values are odds ratios with confidence intervals between brackets and are corrected for age, gender, education, center, and diagnosis. HCV, hippocampal volume; OR, odds ratio.

Similar results were found when analyses were repeated with corrected continuous measures of hippocampal volumes or when analyses were corrected for study (DESCRIPA versus Kuopio L-MCI). Furthermore, there was no moderator effect of diagnosis and results were comparable when correcting for APOE ε4 carriership (data not shown).

The effect of lifestyle factors on conversion to AD-type dementia

Later life lifestyle factors were not associated with conversion to AD-type dementia in individuals with MCI (Table 3). Lower CSF $A\beta_{42}$ concentrations (HR = 0.998, $p < 0.01$), higher CSF t-tau concentrations (HR = 1.002, $p < 0.001$) and lower hippocampal volumes (HR = 0.999, $p < 0.001$) were associated with conversion to AD-type dementia, but these associations were not modulated by lifestyle factors except for mild to moderate alcohol consumption (Table 3). The effect of mild to moderate alcohol consumption relative to no alcohol intake on conversion to AD-type dementia was dependent on the CSF tau status. In individuals with normal tau concentrations, mild to moderate alcohol consumption tended to decrease the risk for conversion to AD-

Table 3
The effect of lifestyle factors on converting to AD-type dementia in individuals with MCI

	Lifestyle		aβ42*lifestyle		t-tau*lifestyle		HCV*lifestyle	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*	*HR (CI)*	*p*
Social activity	0.667 (0.231 to 1.925)	0.45	0.998 (0.989 to 1.007)	0.63	1.000 (0.993 to 1.007)	0.93	1.001 (0.998 to 1.004)	0.46
Physical activity	1.409 (0.889 to 2.233)	0.14	1.001 (0.998 to 1.004)	0.56	0.999 (0.997 to 1.001)	0.34	1.000 (0.999 to 1.001)	0.49
Cognitive activity	1.487 (0.577 to 3.830)	0.41	1.003 (0.996 to 1.011)	0.40	1.000 (0.996 to 1.004)	0.96	1.002 (0.998 to 1.005)	0.40
Alcohol consumption								
Mild to moderate versus no intake	0.927 (0.587 to 1.464)	0.75	1.003 (0.999 to 1.007)	0.22	1.002 (1.000 to 1.005)	0.02*	1.000 (0.999 to 1.001)	0.58
Mild to moderate versus severe intake	0.968 (0.503 to 1.934)	0.97	1.000 (0.996 to 1.004)	0.86	1.000 (0.997 to 1.003)	0.98	0.999 (0.998 to 1.000)	0.05
Current smoking	0.917 (0.440 to 1.913)	0.82	0.999 (0.995 to 1.004)	0.74	1.001 (0.998 to 1.005)	0.44	1.001 (0.999 to 1.002)	0.25
Sleep problems	0.686 (0.360 to 1.307)	0.25	0.995 (0.987 to 1.003)	0.23	1.000 (0.996 to 1.005)	0.86	1.000 (0.999 to 1.001)	0.90

Values are hazard ratios with confidence intervals between brackets corrected for age, gender, education, center, and diagnosis. The AD marker-by-lifestyle factor interaction indicates how the HR differs from the overall AD marker HR for conversion to AD when the protective lifestyle factor is present. CSF, cerebrospinal fluid; $A\beta_{42}$, amyloid-β 1–42; t-tau, total tau; HCV, hippocampal volume; HR, hazard ratio. *$p < 0.05$.

type dementia (HR = 0.178, $p = 0.081$, Fig. 1), but in individuals with abnormal tau mild to moderate alcohol consumption did not decrease the risk for conversion to AD-type dementia (HR = 0.949, $p = 0.908$, Fig. 1). Findings remained similar after correction for APOE ε4 genotype and also after correction for study (DESCRIPA versus Kuopio L-MCI) (data not shown).

DISCUSSION

The main results of this study are that later life lifestyle factors were not associated with AD biomarkers or with conversion to AD-type dementia in non-demented individuals. Lifestyle factors assessed at this stage also did not modify the relationship between AD biomarkers and conversion to AD-type dementia in individuals with MCI.

The association between lifestyle factors and AD biomarkers have not yet been extensively examined. As far as we know, only Vemuri and colleagues [8] tested the association between cognitive and physical activity with amyloid deposition as assessed by Pittsburg compound B (PiB)-positron emission tomography (PET), metabolism as assessed by ^{18}F-fluorodeoxyglucose (FDG-PET), and hippocampal volume in cognitively normal older adults and in individuals with MCI. In line with our study, they could not find an association between these lifestyle factors and AD biomarkers at later life.

Population studies found an association between lifestyle factors and conversion to AD-type dementia [1, 2]. Surprisingly, we could not find such an association. Our findings may be explained by the difference in recruitment and the timing of the assessment of the risk factors. We included individuals who experienced cognitive impairments from either a memory clinic setting (SCD or MCI) or a population-based setting (MCI). In addition, lifestyle factors may be less influential in individuals who already experience cognitive impairments. We collected lifestyle factors at the time of the baseline visit, typically around age 70, while several population-based studies often have tested risk factors at midlife. It is possible that the association with lifestyle factors and dementia risk is different for several age ranges, as lifestyle may also be affected by ongoing cognitive decline, and therefore may play a more important role in midlife, but this needs to be further explored. Furthermore, targeting lifestyle factors is perhaps also more effective in midlife before the

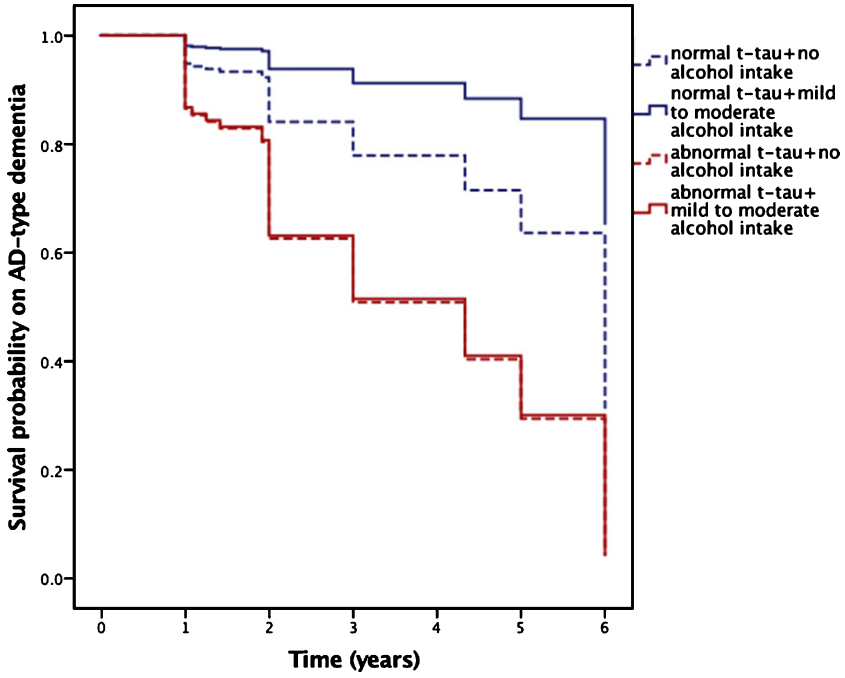

Fig. 1. Association between CSF tau and mild to moderate alcohol consumption. Figure displays Cox regression lines of individuals with normal CSF tau (blue lines) and abnormal CSF tau concentrations (red lines) with mild to moderate alcohol consumption (solid lines) and with no alcohol consumption (dashed lines).

accumulation of AD pathology. Also, lifestyle factors may act mainly via non-AD pathways, for example via cerebrovascular or metabolic routes of damage accumulation. Exposure to cardiovascular risk factors, such as hypertension, hypercholesterolemia and fasting blood glucose, has been linked to late-life cognitive functioning [18, 34, 35], and may be influenced by lifestyle factors as physical activity.

As expected AD biomarkers had a strong effect on conversion to AD-type dementia in individuals with MCI, but lifestyle factors did not have an impact on the predictive accuracy of these biomarkers. Only in individuals with MCI, alcohol consumption modulated the risk of tau for AD-type dementia. However, since the sample size was small (no intake $n = 25$, mild to moderate intake $n = 28$) this finding needs further replication. Protective effects against cognitive decline have been found for mild to moderate alcohol consumption, but these findings are somewhat controversial and further research is needed to confirm this [11, 36–38].

This study has several limitations. First, the follow-up period was relatively short with on average two years. Conceivably, with a longer follow-up period conversion rate to AD-type dementia could be higher. Second, our sample size was relatively small. Since, the influence of lifestyle factors might be subtle, a larger sample may be required to increase power and find an association. Third, like in other studies, participants agreed to undergo a neuroimaging scan and lumbar puncture so they may not be representative of the general population with memory complaints. Fourth, the measurement of lifestyle factors may be somewhat constrained. We only included self-reported questionnaires, which are subjective in nature and can be biased by recall and social desirability. Fifth, like in several others studies, we examined only current later life social-, cognitive- and physical activity and current alcohol consumption and smoking. Examining lifestyle factors over a longer period of time probably gives a better overall indication of the influence of these factors on risk for AD. Furthermore, lifestyle compliance could then be evaluated.

To conclude, our study shows no association between lifestyle factors and AD biomarkers or conversion to AD-type dementia in non-demented individuals. Even though lifestyle factors were not associated with conversion to AD-type dementia, a few intervention studies did find beneficial effects of physical activity on improving cognitive performance in individuals with MCI [39, 40]. But the impact of

lifestyle interventions may be small in size compared to the effect that might be achieved by acting on disease biology. Targeting modifiable lifestyle factors in non-demented individuals with cognitive complaints may still be beneficial to improve overall health, however chances for prognostic effects at the time of diagnostic work-up in memory clinics might be low.

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