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Non-pharmacologic prevention of Alzheimer's disease: nutritional and life-style risk factors

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Summary We conducted a review of cohort studies and interventional studies on nutritional and life-style risk factors and primary prevention of Alzheimer's Disease. Studies were assessed by the Oxford classification. Interventional studies exist for mental training and vitamin supplementation. For alcohol, fat and fish intake, mediterranean diet, homocysteine, overweight/caloric intake, physical and social activity, hypercholesterolemia, diabetes and smoking, currently there is only evidence from cohort studies. Cognitive stimulation by mental training increases mental functions and can be recommended on the basis of positive interventional studies. Vitamin supplementation cannot prevent AD on the basis of interventional studies. Hyperlipidemia, hyperhomocysteinemia, diabetes and typical life-style factors (alcohol, smoking, obesity etc.) modestly increased AD risk, fish, mediterranean diet and unsaturated fat or n-3 fatty acids and social activity are protective in observational cohorts, but interventional studies are lacking.

Keywords: Dementia, cognitive decline, mild cognitive impairment

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder with the clinical hallmarks of cognitive decline, impaired daily activities and neurological/neuropsychological abnormalities. Neuropathologic features are intraneuronal neurofibrillary tangles containing abnormally phosphorylated tau protein, extracellular β-Amyloid plaques and functional impairment of neurotransmitter systems like acetylcholine. In 2000, AD affected approximately 4.5 million people in the US and 3.3 million people in Europe (Hebert et al. 2003; Lobo et al. 2000). According to a recent consensus study, the number of demented patients will double every 20 years (Ferri et al. 2005). The annual costs for patients with AD are approximately 40,000 USD. Often patients initially present with mild cognitive impairment (MCI) which exceeds aging-associated memory decline and which can be separated from AD.

Between 6 and 25% of patients with MCI annually convert to AD (Petersen et al. 2001). Since there is no proven medical therapy for MCI, patients often ask what else can be done to prevent progression to AD. Now, the availability of several longitudinal data from large cohort studies allows assessing the impact of possible life-style factors on the risk to develop AD.

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Material and methods

Relevant studies were identified by systematic search of following data sources: MEDLINE ("Alzheimer + Disease"[MeSH] AND (randomized controlled study OR risk factor OR cohort study)); Embase, Current contents, the Cochrane database and www.clinicaltrialresults.org for articles published from January 1966 to June 2006. Search was limited to English abstracts and human studies. We identified additional articles and studies by hand-searching referenced articles or reviews on this topic and also personal contacts with investigators. The studies can be appraised as additional material to this article on the web.

Inclusion criteria were:

- Adequate description of the study type and population under study.
- Description of the intervention in therapeutic studies.
- Description of risk factor determination, AD diagnosis.
- Time of follow-up, principal measure of effect given (hazard or relative risk).
- Covariates stated.
- Description of outcome.
- Primary prevention.

Table 1. *Protective factors and risk factors for Alzheimer's Disease: hierarchy of evidence*

Risk factor	Oxford classification (Centre for Evidence-Based Medicine, 2001)
Cognitive stimulation	1a
Vitamins	
E	1b
Folate	1a
B6	1a
B12	1a
Alcohol	2b
Fat intake	2b
Fish intake	2b
Homocysteine	2b
Overweight	2b
Caloric intake	2b
Physical activity	2b
Hypercholesterolemia	2b
Diabetes	2b
Smoking	2b

Oxford classification for prevention and therapy.
1a: Systematic review or meta-analysis of interventional studies.
1b: At least one randomized intervention study.
2a: Systematic review of cohort studies.
2b: At least one cohort study or randomized controlled study.
2c: Outcome Research; Ecological studies.

Exclusion criteria were:

- Studies that did not address AD (e.g. only cognitive decline).
- Editorials and Letters.
- Studies in defined populations with pre-existing disease (e.g. coronary artery disease or stroke).
- Pharmacological studies.

Grading quality of evidence

After the literature search, relevant studies were graded according to a scheme proposed by the Oxford Centre for Evidence-based Medicine (see Table 1). In this scheme, evidence is ranked higher for interventional studies than for cohort studies. If studies with higher Oxford levels of evidence were found, further literature search was stopped. Studies were included if they had data available on risk factor (defined measure and criteria), age, gender, and if AD was diagnosed by standard criteria. More detailed quality assessment, like standardized assessment of limitation, inconsistencies or probability of reporting bias was not performed.

Results

1. Interventional studies

Cognitive stimulation, leisure activity, social contacts

Several cohort studies consistently showed a protective effect of increased leisure and social activities against AD (see additional material; relative risk 0.46–0.93).

In an older meta-analysis of controlled studies mnemonic training in healthy elderly subjects showed a modest but significant effect size of 0.73 (Verhaeghen et al., 1992) on cognition but not incidence of AD. A controlled trial of cognitive and psychomotor training (SIMA-Project) showed a beneficial effect on memory performance in elderly patients (Oswald et al., 1996). In patients with MCI, no studies have been published. For secondary prevention there are 5 randomized studies which investigated cognitive stimulation. Most of them showed improvement of behavioral problems, depression or quality of life but not progression of AD. Taken together, there is cumulating evidence from many cohort studies and some interventional studies (without AD as an endpoint) that an active, mental-challenging and social lifestyle might protect against cognitive decline and possibly also AD (Review by Fratiglioni et al. (2004) and Livingston et al. (2005), evidence level 1a).

Micronutrients

In a recent double-blind, placebo-controlled study by Petersen et al., published in the New England Journal of Medicine, treatment with Vitamin E showed no delay in the progression from MCI to AD (evidence level 1b) (Petersen et al., 2005). For AD, a randomized placebo-controlled study investigated whether selegiline, vitamin E (alpha-tocopherol) or both delayed death, institutionalization, daily activities or severe dementia. After correction for baseline Mini-Mental Test results, vitamin E significantly delayed institutionalization (risk ratio 0.42) but not cognitive endpoints, death, daily activities or severe dementia (Sano et al., 1997). It is currently unclear whether a combination of vitamin C and E is protective.

For folic acid and B12, there are four small randomized placebo-controlled trials (Cochrane reviews by Malouf, evidence level 1a (Malouf et al., 2003; Malouf and Areosa, 2003). For vitamin B6 supplementation, there is no evidence for short-term benefit in improving cognitive function (Malouf and Grimley, 2003) (evidence level 1a).

In the Framingham study, AD was associated with elevated homocysteine (relative risk 1.8 (1.3–2.5) per increase of 1 SD at baseline) (Seshadri et al., 2002). Recent interventional trials for cardiovascular outcomes (recurrent myocardial infarction, stroke and vascular death) consistently showed no benefit for lowering Homocysteine with vitamin B (Bonaa et al., 2006; Lonn et al., 2006; Toole et al., 2004).

Low folic acid doubles AD risk (relative risk 2.1 (1.2–3.5)) (Wang et al., 2001). Interventional studies to prevent progression of MCI are currently on the way therefore clear recommendations cannot be given.

2. Cohort studies

Diet

The impact of diet on AD has recently been reviewed by Luchsinger and Mayeux (2004). Several cohort studies investigated an association between fat and fish intake and AD (Table 2). Total fat (relative risk 0.9 (0.4–1.8)) and dietary cholesterol (relative risk 0.9 (0.4–2.4)) did not increase risk (Morris et al., 2003a). The Rotterdam study showed no association between total dietary fat and various subtypes of fat and AD (odds ratio 0.9 (0.8–1.1)) (Engelhart et al., 2002a). Fish intake was a protective factor (relative risk 0.3 (0.1–0.9)) (Kalmijn et al., 1997). The Chicago Health and Aging Project showed that polyunsaturated and unhydrogenated fat is protective and conversely, saturated or trans- unsaturated (hydrogenated) fats increase AD risk (Morris et al., 2003a). The Rotterdam studies found no significant association between saturated fat intake and AD (Engelhart et al., 2002a; Kalmijn et al., 1997). A recent follow-up of the WHICAP study found Mediterranean diet (rich in vegetables, legumes, fruits, cereals, unsaturated fatty acids, low intake of saturated fatty acids, moderate intake of fish) protective (Hazard 0.6 (0.4–0.9))(Scarmeas et al., 2006).

Whereas several studies showed a decrease of weight immediately before and after onset of AD, it has been shown that a high BMI in middle age carries an increased risk for developing AD in later ages: In the study of Gustafson et al. (2003), which had a long follow-up period of 18 years, the relative risk for AD increased to 1.4 (1.2–1.6)/BMI-Point in women. However, the study had few patients with dementia and was not controlled for APOE and physical activity. In the HAAS cohort, the relative risk for dementia after more than 20 years (but not for AD) was 1.2 (1.1–1.4) for each 1-point increase of BMI (Kalmijn et al., 2000). Other studies confirmed the effect of obesity on AD (Whitmer et al., 2005) or found no significant association (Yoshitake et al., 1995). However, all of these studies were not controlled by APOE, which is an important link between fat metabolism and AD risk. For caloric intake, to our knowledge there is only the WHICAP (Luchsinger et al., 2002) study which found a relative risk for AD in the upper quartile of caloric intake of 1.5 (1.0–2.2) (Evidence level 2b; see Table 2).

Alcohol

Alcohol is a neurotoxin. Alcohol abuse or heavy use is a clear risk factor for dementia (Fratiglioni et al., 1993; Saunders et al., 1991). Several cohort studies searched for the relation between alcoholic drinks and AD (see supplemental data). Most studies showed that high alcohol intake increased dementia risk and moderate alcohol intake could reduce dementia (combined relative risk 0.55, evidence level 2b). However, there are no randomized studies.

Hypercholesterolemia

The role of hypercholesterolemia in AD remains unclear (Table 2; evidence level 2b). Some cohort studies found an increased AD or dementia risk with increased cholesterol, where others found decreased risk or no association. The findings might be explained by different timing of cholesterol determination in relation to age and assessment of dementia (Mielke et al., 2005).

Diabetes

Several cohort studies addressed an association of diabetes with AD (see Table 2). Interventional studies with dementia as an endpoint are lacking (evidence level 2b). According to the latest position statement of the American Diabetes Association, screening for diabetes is recommended in 3-year intervals above an age of 45 years and at a BMI below $25\,kg/m^2$. Obese subjects (BMI above $25\,kg/m^2$), physical inactive, hypertensive, hyperlipidemic persons or persons with a history of vascular disease should be tested for diabetes even at younger ages and more frequently (2006).

Smoking

The interaction between smoking and dementia is complex. Smoking is a clear risk factor for cardiovascular disease and stroke. Initial case-control studies suggested a protective effect of smoking on AD. An earlier review of 19 case-control studies of AD and smoking showed a protective effect (relative risk 0.60, 95% CI 0.5–0.8) (Lee, 1994). However, in prospective population based cohort studies like the Rotterdam study, smoking was a risk factor for AD. Overall, in this study smoking doubled AD (relative risk 2.3). The risk was much higher in individuals without an APOE4 allele (relative risk 4.6 (1.5–14.2)) (Ott et al., 1998). Other cohort studies confirmed this effect (Launer et al., 1999; Merchant et al., 1999) with a smaller relative risk, but did not control for the APOE-effect. Further cohort studies, like CSHA (Lindsay et al., 2002) or the Hisayama study (Yoshitake et al., 1995) were negative (evidence level 2b).

Table 2. *Cohort studies on Alzheimer's disease and risk factors (sorted in alphabetical order and chronologically): Studies with significant associations are in bold; no association: roman*

Name	Study size, age AD cases	AD diagnosis	Mean follow up (years)	Risk factor diagnosis	Relative risk or hazard ratio	Dose response	Controlled covariates
Alcohol							
Hisayama (Yoshitake et al., 1995)	N = 828, >65 y 42 AD	DSM-IIIR NINCDS-ADRDA	7	Interview (yes/no)	0.56 (0.22–1.43)	No	Age
PAQUID (Orgogozo et al., 1997)	**N = 3777, >65 y 66 AD**	**DSM-III-R NINCDS-ADRDA**	**3**	**Structured questionnaire at baseline**	**0.55 (0.31–0.99) Mild 0.28 (0.08–0.99) Moderate alcohol**	**Yes**	**Age, gender, education, occupation, MMSE**
CSHA (Lindsay et al., 2002)	**N = 4615, >65 y 194 AD**	**NINDS-AIREN**	**5**	**Self administered questionnaire at baseline**	**Alcohol: 0.68 (0.47–1.00) Wine: 0.49 (0.28–0.88) (at weekly consumption)**	**No**	**Age, gender, education**
Rotterdam (Ruitenberg et al., 2002)	N = 5395, >55 y 146 AD	DSM-IIIR NINCDS-ADRDA	6	SFFQ, baseline	0.72 (0.43–1.2) at 1–3 drinks/day	Yes	Age, gender, systolic blood pressure, education, smoking, BMI; Type of drink
CCHS (Truelsen et al., 2002)	**Nested Case-control N = 1709, >65 y 83 Dementia**	**DSM-IIIR NINCDS-ADRDA**	**15**	**Self report**	**0.43 (0.23–0.82) monthly wine 0.33 (0.13–0.86) weekly wine 2.28 (1.13–4.6) monthly beer**	**No**	**Age, gender, education, stroke, income, hypertension, smoking**
CHS (Mukamal et al., 2003)	**Case Control, >65 y 258 AD**	**DSM-IV NINCDS-ADRDA**	**6**	**Baseline and yearly**	**0.6 (0.4–0.9) <1 drink/ week 0.4 (0.3–0.7) 1–6 drinks/week**	**Yes**	**Age, gender, race, diabetes, APOE, Stroke**
WHICAP (Luchsinger et al., 2004)	**N = 980, >65 y 199 AD**	**DSM IV**	**4.1**	**SFFQ, between baseline and 1st year**	**0.59 (0.38–0.91) ≥3 servings wine/day**	**Yes**	**Age, gender, APOE, education**
CAIDE (Anttila et al., 2004)	N = 1464, >65 y 37 AD	DSM-IV NINCDS-ADRDA	23	Questionnaire (never, infrequently, frequently) at baseline	AD: 0.91 (0.39–2.14) Never drinkers MCI: 2.1 (1.01–4.59) Never drinkers	Yes	APOE, age, gender, education, follow-up tine, BMI, cholesterol, blood pressure, smoking, MI, stroke
Cognitive stimulation, leisure activity, social contacts							
PAQUID (Fabrigoule et al., 1995)	**N = 2040, >65 y Dementia 84**	**DSM-IIIR NINCDS-ADRDA**	**3**	**Baseline ADL questionnaire (Lawton-Brody)**	**0.46–0.53 (0.24–0.99)**	**Yes**	**Age, MMSE**
Kungsholmen (Fratiglioni et al., 2000)	**N = 1203 126 AD**	**DSM-III-R**	**3**	**Baseline interview**	**0.67 (0.42–1.0) social contacts**	**Yes**	**Age, gender, education, MMSE, depression**
Scarmeas (Scarmeas et al., 2001)	**N = 1772, >65 y AD 153 Dementia: 207**	**DSM-III-R NINCDS-ADRDA**	**2.9**	**Baseline interview on 13 activities**	**0.62 (0.46–0.83) High vs. low**	**No**	**Age**
CHAP (Wilson et al., 2002a)	**N = 1249, >65 y 139 AD**	**NINCDS-ADRDA**	**4.1**	**7 activities at baseline**	**0.36 (0.2–0.65)/1 point increase**	**Yes**	**Age, education, gender, race, APOE**
Religious Orders Study (Wilson et al., 2002b)	**N = 801 111 AD**	**NINCDS-ADRDA**	**4.5**	**Baseline: 7 activities**	**0.67 (0.49–0.92)/1 Point composite score**	**Yes**	**Age, gender, education, physical activity**
Einstein Aging Study (Verghese et al., 2003)	**N = 469, >75 y 61 AD**	**DSM-IIIR NINCDS-ADRDA**	**5.1**	**Structured questionnaire of 6 activities at baseline**	**0.93 (0.9–0.97)/1 point increment**	**Yes**	**Age, gender, education, chronic illness, base line cognitive status**

Cholesterol							
Hisayama (Yoshitake et al., 1995)	N = 828, >65 y 42 AD	DSM-IIIR NINCDS-ADRDA NINDS-AIREN	7	Serum	1.10 (0.80–1.51)	Yes	Age
Seven Countries (Notkola et al., 1998)	**N = 444 Men, >70 y 27 AD**	**DSM-IIIR**	**>10**	**Serum; every 5 years**	**3.1 (1.2–8.5) >6.5 mol/l**	**No**	**Age, APOE4**
Moroney (Moroney et al. 1999)	N = 1111 225 AD	NINCDS-ADRDA	2.1	Initial; serum	LDL-Cholesterol >3.7 mol/dl RR: 0.77 (0.51–1.15)	No	Demographic factors
Romas (Romas et al., 1999)	Cross-sectional prospective N = 1238 307 AD	NINCDS-ADRDA	2.5	Baseline serum	1.3 (0.8–2.1) for Cholesterol <177 mg/dl	No	Age
HAAS (Kalmijn et al., 2000)	3734 Men 215 Dementia AD numbers not given	DSM-IIIR NINCDS-ADRDA	Appr. 25	Single; baseline	Dementia: 1.10 (0.95–1.26)	No	Age; education
FIN-MONICA (Kivipelto et al., 2002)	**N = 1449, 65–79 y 48 AD**	**DSM-IV NINCDS-ADRDA**	**21**	**4x Serum**	**2.8 (1.2–6.7) >6.5 mol/l**	**No**	**Age, APOE, education, gender, smoking, alcohol.**
Framingham (Tan et al., 2003)	N = 1026 77 AD	DSM-IV NINCDS-ADRDA	8	Biennial	0.95 (0.87–1.04)/ 10 mg/dl rise		Age, gender, APOE, smoking, BMI, CAD, diabetes
Reitz et al. (2004)	Cross-sectional N = 4316, >65 y 119 AD	NINCDS-ADRDA	Not given	Baseline serum	Elevated total cholesterol 0.89 (0.59–1.35) for Prevalence	No	Age, gender, education, ethnicity.
H70 (Mielke et al., 2005)	**392, >70 y 93 dementia**	**DSM-III-R NINCDS-ADRDA**	**9–18**	**Baseline serum**	**0.31 (0.11–0.85) upper quartile, sample at age 70 for dementia**	**Yes**	BMI, blood pressure, sex, education, smoking.
Diabetes							
Hisayama (Yoshitake et al., 1995)	N = 828, >65 y 42 AD	DSM-IIIR NINCDS-ADRDA NINDS-AIREN	7	Interview	2.18 (0.97–4.9)	No	Age
Rochester (Leibson et al., 1997)	**N = 1455 77 AD**	**DSM-III**	**6.8**	**Fasting serum level**	**1.66 (1.34–2.05) for all dementia**	**No**	**Age, gender**
Rotterdam (Ott et al., 1999)	**N = 6370, >55 y 89 AD**	**NINCDS-ADRDA NINDS-AIREN**	**2.1**	**Serum/WHO**	**1.9 (1.2–3.1)**	**No**	**Age, gender**
WHICAP (Luchsinger et al., 2001)	N = 1262 Black/ Hispanic, >65 y 157 AD	DSM-IV NINCDS-ADRDA	4.3	Self report, medication, clinical history	1.3 (0.8–1.9) AD **1.6 (1.2–2.1) AD + MCI**	No	Gender, ethic group, Education, APOE4
HAAS (Peila et al., 2002)	**N = 2574 Men 65 AD**	**DSM-IIIR NINCDS-ADRDA**	**2.9**	**Self report, medication, serum level**	**1.8 (1.1–2.9) APOE4: 5.5**	**No**	**Age, Education, APOE, Medication, Alcohol, smoking, Blood pressure, Cholesterol, BMI**
CSHA (MacKnight et al., 2002)	N = 5574, >65 y 267 AD	DSM-IV NINCDS-ADRDA	5	Interview, medication, serum level	1.3 (0.83–2.03)	No	Demographics, Stroke, hypertension, heart disease.
Religious orders (Arvanitakis et al., 2004)	**N = 824, >55 y 151 AD**	**CERAD/ NINCDS-ADRDA**	**5.4**	**Self report; medication**	**1.65 (1.1–2.5)**	**No**	**Age, gender, educational level**
Kungsholmen (Xu et al., 2004)	N = 1301, >75 y 260 AD	ICD-8; DSM-III-R	6	Serum, medication	1.3 (0.9–2.1)	No	

(*continued*)

Table 2 (*continued*)

Name	Study size, age AD cases	AD diagnosis	Mean follow up (years)	Risk factor diagnosis	Relative risk or hazard ratio	Dose response	Controlled covariates
Fat, fish, diet							
Rotterdam (Engelhart et al., 2002a; Kalmijn et al., 1997)	N = 5395, >55 y 146 AD	DSM-III-R NINCDS-ADRDA	2.1 resp. 6	SFFQ	Total fat 0.93 (0.81–1.07) Saturated fat 1.9 (0.9–4.0) **Fish: 0.3 (0.1–0.9)/ Upper tertile**	Yes	Age, gender, education, Energy intake
WHICAP (Luchsinger et al., 2002)	N = 980 242 AD	DSM-IV NINCDS-ADRDA	4	SFFQ	Fat 1.4 (0.93–2.13) upper quartile	Yes	Age, Gender, APOE4, Education, ethnic group
Chicago Health and Aging Project (Morris et al., 2003a, b)	**N = 815, >65 y 131 AD**	**NINCDS-ADRDA + coexisting dementia**	**3.9**	**SFFQ 2.3 y before clinical evaluation**	**Saturated Fat 2.2 (1.1–4.7) Trans-unsaturated fats 2.4 (1.1–5.3) Total fat (RR 0.9 (0.4–1.8) Dietary cholesterol 0.9 (0.4–2.4) upper Quintile Fish 0.4 (0.2–0.9) n-3 Fatty Acid 0.4 (0.1–0.9)/Upper Quintile**	**No**	**Age, gender, race, education, APOE**
PAQUID (Barberger-Gateau et al., 2002)	N = 74 135 AD	DSM-IIIR	7	Food frequency	0.69 (0.47–1.01) fish at least once a week	Yes	Age, sex
WHICAP (Scarmeas et al., 2006)	**N = 2258 262 AD**	**DSM-IIIR NINCDS-ADRDA**	**4**	**SFFQ**	**0.6 (0.4–0.9) highest tertile Mediterranean diet**	**Yes**	**Age, sex, ethnicity, education, APOE, caloric intake, smoking, BMI**
Smoking							
Hisayama (Yoshitake et al., 1995)	N = 828, >65 y 42 AD	DSM-IIIR NINCDS-ADRDA NINDS-AIREN	7	Interview	0.73 (0.34–1.57)	No	Age
Rotterdam (Ott et al., 1998)	**N = 6870, >55 y 105 AD**	**DSM-III-R**	**2.1**	**Baseline habits**	**2.3 (1.3–4.1) for current smoking**	**Yes**	**APOE, age, gender, alcohol intake; education**
EURODEM (Launer et al., 1999)	**N = 16334, >65 y 352 AD**	**DSM-IIIR NINCDS-ADRDA**	**2.0–2.8**	**Baseline habits**	**1.74 (1.21–2.50) for current smoking**	**No**	**Age, gender, education**
Merchant et al. (1999)	**N = 1062 142 AD**	**DSM-IV NINCDS-ADRDA**	**2**	**Structured interview at baseline**	**1.7 (1.1–2.8) for current smoking**	**No**	**Education, ethnicity**
CSHA (Lindsay et al., 2002)	N = 4615, >65 y 194 AD	NINDS-AIREN	5	Baseline questionnaire	0.82 (0.57–1.17)	No	Age, gender, education

Study-design and name	Study size, age AD cases	AD diagnosis	Mean follow up (years)	Risk factor diagnosis	Relative risk or hazard ratio	Dose response	Controlled covariates
Overweight/caloric intake							
Hisayama (Yoshitake et al., 1995)	N = 828, >65 y 42 AD	DSM-IIIR NINCDS-ADRDA NINDS-AIREN	7	Interview	0.75 (0.54–1.03)/SD BMI	Yes	Age
HAAS (Kalmijn et al., 2000)	**N = 3734 Men 45–68 y 215 Dementia**	**DSM-IIIR NINCDS-ADRDA**	**25**	**Baseline BMI**	**1.21 (1.05–1.4)/SD BMI**	**No**	**Age, education**
WHICAP (Luchsinger et al., 2002)	**N = 980 242 AD**	**DSM-IV NINCDS-ADRDA**	**4**	**SFFQ**	**1.5 (1.0–2.2)/highest quintile caloric intake**	**Yes**	**Age, gender, APOE4, education, ethnic group**
H70 (Gustafson et al., 2003)	**N = 392 93 Dementia**	**DSM-IIIR; NINCDS-ADRDA**	**18**	**Baseline BMI**	**1.36 (1.16–1.59)/1 BMI increase, for women**	**No**	**Blood pressure, cardiovascular disease, smoking, socioeconomic status, hypertension.**
Whitmer et al. (2005)	**N = 10276 713 Dementia**	**ICD-9**	**27**	**Baseline multiphasic exam**	**1.74 (1.34–2.26) BMI > 30 1.35 (1.14–1.6) BMI 25–30**	**Yes**	**Age, ethnicity, gender, marital status, hypertension, cholesterol, stroke, diabetes, cardiac disease, hyperlipemia**
Physical activity							
Hisayama (Yoshitake et al., 1995)	**N = 828, >65 y 42 AD**	**DSM-IIIR NINCDS-ADRDA NINDS-AIREN**	**7**	**Interview**	**0.20 (0.06–0.68)**	**No**	**Cardiovascular risk factors; age, gender.**
CSHA (Lindsay et al., 2002; Laurin et al., 2001)	**N = 4615, >65 y 194 AD**	**DSM-IIIR NINCDS-ADRDA NINDS-AIREN**	**5**		**0.5–0.69 (0.28–0.96) for high activity**	**Yes**	**Age, gender, education**
Religious Orders Study (Wilson et al., 2002b)	N = 801 111 AD	NINCDS-ADRDA	4.5	Baseline questionnaire	0.61 (0.35–1.05)/ highest quartile	Yes	Age, gender, education, physical activity
Religious Orders Study (Wilson et al., 2002b)	N = 1249, >65 y AD 139	NINCDS-ADRDA	4.5	Baseline questionnaire	0.61 (0.35–1.1)	Yes	Age, education, gender, race, APOE
Einstein Aging Study (Verghese et al., 2003)	N = 469, >75 y 61 AD	DSM-IIIR NINCDS-ADRDA	5.1	11 physical activities at baseline	1.27 (0.78–2.06)	Yes	Age, gender, education, chronic illness, base line cognitive status
CHS (Podewils et al., 2005)	N = 3375, >65 y 245 AD	NINCDS-ADRDA	5.4	Baseline minnesota leisure time activity questionnaire	0.7 (0.44–1.13) highest quartile	Yes	Age; education, gender, ethnicity, APOE, MMSE, MRI, ADL, social support
ACT (Larson et al., 2006)	**N = 1740, >65 y 107 AD**	**DSM-IV NINCDS-ADRDA**	**6.2**	**Baseline self report**	**Dementia: 0.68 (0.48–0.96)** AD: 0.69 (0.45–1.05)	**Yes**	**Alcohol, smoking, supplement use, education, APOE, diabetes, hypertension, vascular disease, depression.**

(*continued*)

Table 2 (*continued*)

Study-design and name	Study size, age AD cases	AD diagnosis	Mean follow up (years)	Risk factor diagnosis	Relative risk or hazard ratio	Dose response	Controlled covariates
Dietary vitamin E, C and homocysteine							
Rotterdam Study (Engelhart et al., 2002b)	**N = 5395, >55 y 146 AD**	**NINCDS-ADRDA**	**6**	**SFFQ**	**Vitamin E: 0.82 (0.66–1.00) Vitamin C: 0.82 (0.68–0.99)/1 SD**	**No Yes**	**Age, Sex, MMSE, alcohol, education, smoking, BMI**
HAAS (Masaki et al., 2000)	N = 3734 men >70 y 47 AD	NINCDS-ADRDA	3–5	Questionnaire	Vitamin E + C: 1.81 (0.91–3.63)	No	Age, education, APOE, stroke
CHAP (Morris et al., 2002)	N = 815, >65 y 131 AD	NINCDS-ADRDA	3.9	SFFQ 1.7 y after baseline	**Vitamin E 0.3 (0.10–0.92)** Vitamin C: 1.03 (0.41–2.56) Beta Carotene 0.55 (0.22–1.35) lowest quintile	Yes	Age, education, gender, race, APOE, length of follow up.
Framingham (Seshadri et al., 2002)	**N = 1092 83 AD**	**DSM-IV; CDR NINCDS-ADRDA**	**8**	**Plasma at 16th or 20th biennial examination**	**Homocysteine: 1.8 (1.3–2.5)/ SD > 14mcmol: 1.6 (1.2–2.1)**	**Yes**	**Gender, age, APOE, B-Vitamins, folate, education; blood pressure; diabetes smoking, alcohol, BMI, stroke**

NINCDS-ADRDA National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association.
SFFQ Semi quantitative food frequency questionnaire.
Study acronyms:
CAIDE Cardiovascular risk factors, aging and dementia (Anttila et al., 2004).
CCHS Copenhagen City Heart Study (Truelsen et al., 2002).
CSHA Canadian Study of Health and Aging (Lindsay et al., 2002).
CHAP Chicago Health and Aging Project (Morris et al., 2002).
CHS Cardiovascular Health Study (Mukamal et al., 2003).
EURODEM European Studies of Dementia (Launer et al., 1999).
H70 Gerontological and Geriatric Population Studies (Gustafson et al., 2003).
HAAS Honolulu-Asia Aging Study (Peila et al., 2002).
PAQUID Personnes âgées Quid (Orgogozo et al., 1997).
WHICAP Washington Heights Inwood-Columbia Aging Project (Luchsinger et al., 2004).

Physical activity

Several cohort studies now indicate that physical activity is capable of reducing deficits associated with AD (see additional material on the web). In the Hisayama Study this was confirmed by a high number of autoptic proven AD (Yoshitake et al., 1995). In some smaller studies, there was no significant association between physical activity and AD (Wilson et al., 2002b; Verghese et al., 2003) (evidence level 2b).

Discussion

Evidence from mainly observational studies suggests that life-style risk factors increase the risk for Alzheimer's Disease (AD). Due to ethical reasons, there are no randomized studies for life-style risk factors. Most observational studies showed only modest associations of AD with relative risks usually below 2 or 0.5, respectively.

Still the real impact of life-style and other risk factors might be overestimated due to publication bias. Our literature showed that there is benefit of cognitive stimulation on cognitive functioning in elderly, but whether AD can be prevented is not known. Cognitive training has not been investigated in larger trials, but can be recommended to patients with MCI on the basis of the currently available studies.

There is good evidence from observational studies that physical activity may reduce AD risk and associated symptoms.

A recent trial showed no benefit for Vitamin E in mild cognitive impairment. Data regarding Vitamin C are inconclusive. Folate, Vitamin B6 and B12 can be recommended to prevent neuropathy and pernicious anemia in patients at risk but not to prevent cognitive decline or AD.

There is evidence from cohort studies that hyperlipidemia, hyperhomocysteinemia and diabetes increase AD risk, but there are no interventional non-pharmacologic studies that would support that treatment is preventive.

For alcohol, most observational studies showed a dose-dependent effect on AD: High alcohol intake increases dementia risk; moderate alcohol intake (several alcoholic drinks per week) reduces dementia risk.

Cohort studies showed that high calorie and fat intake (total, saturated and trans-unsaturated fat) intake, obesity and smoking increases AD risk. There is also good evidence from cohort studies that mediterranean diet, fish and n-3 unsaturated fat might be protective.

There is no evidence whether randomized interventions that favour protective life-style factors are beneficial. The amount of publication bias and the causality in all these observations and associations is not known. The possible underlying biological effects and mechanisms of an active and socially integrated lifestyle have been recently reviewed by Fratiglioni et al. (2004). They encompass effects of increased cognitive reserve in an enriched environment, vascular protection and stress reduction as an psychological mechanism.

Our literature search was not as complete, methodologic and systematic as proposed by the Cochrane Collaboration, which might limit its validity. We cannot rule out that extending of the search term probably would bring up more studies that are relevant. Still, we think that we covered the relevant literature and this might help both clinicians and researchers to see the current status of studies regarding prevention of Alzheimer's disease. Still, we cannot rule out that we missed more relevant or unpublished studies. Since mainly cohorts, but not interventional studies were cited, the recommendations drawn have to be interpretated with caution.

The research in this field will be improved by performing carefully controlled long-term interventional studies on life-style factors since Alzheimer's disease is chronic and neurodegenerative with long observational periods.

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