Factors Associated with Alzheimer's Disease: An Overview of Reviews

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Abstract

Alzheimer's disease (AD) is a frequent pathology, with a poor prognosis, for which no curative treatment is available in 2018. AD prevention is an important issue, and is an important research topic.

In this manuscript, we have synthesized the literature reviews and meta-analyses relating to modifiable risk factors associated with AD. Smoking, diabetes, high blood pressure, obesity, hypercholesterolemia, physical inactivity, depression, head trauma, heart failure, bleeding and ischemic strokes, sleep apnea syndrome appeared to be associated with an increased risk of AD. In addition to these well-known associations, we highlight here the existence of associated factors less described: hyperhomocysteinemia, hearing loss, essential tremor, occupational exposure to magnetic fields.

On the contrary, some oral antidiabetic drugs, education and intellectual activity, a Mediterranean-type diet or using Healthy Diet Indicator, consumption of unsaturated fatty acids seemed to have a protective effect.

Better knowledge of risk factors for AD allows for better identification of patients at risk. This may contribute to the emergence of prevention policies to delay or prevent the onset of AD.

Key words: Alzheimer's disease, prevention, risk factors, early intervention.

List of abbreviations: AD: Alzheimer's disease; OR: Odds-Ratio; RR: Relative Ratio.

Background

The prevalence of dementia is estimated to be over 45 million people and could reach 115 million by 2050 (1). Alzheimer's disease (AD) accounts for 60-70% of dementias (2). The prevalence of dementia is increasing as the population ages (3). Nevertheless, several studies showed a decrease in the prevalence rate of dementia or severe cognitive impairment after the age of 65 over the last 10 to 30 years in the United States (4–7) and Europe (8–13). The decrease in the prevalence rate could be explained by prevention and better management of risk factors (14).

The main risk factor for AD is age. Another known risk factor is heredity; thus, many genetic determinants have been studied, notably ApoE4, ApoE3 or presenilin S1 and S2 (15, 16).

In 2018, AD remains incurable and prevention is essential: it is based on the management of modifiable risk factors.

Many studies focused on AD "risk factors". In response to the large number of articles, systematic literature reviews focused on classes of risk factors (genetic, environmental, infectious, etc.). For clinicians, it seems important to synthesize these numerous studies and reviews, and provide an overview of literature reviews.

Our aim was to summarize the literature reviews conducted on modifiable risk factors for AD.

Methods

This overview of literature reviews was conducted using the PubMed search engine (MEDLINE database), with the equation: "Alzheimer disease"[MeSH] AND "risk factor" [All Fields] AND (Meta-Analysis[ptyp] OR Review[ptyp]). The research was carried out in February 2017 and checked in November 2017.

The inclusion criteria were literature review or meta-analysis of epidemiological articles.

There was no time limit on the reviews and meta-analyses included.

The exclusion criteria were:
- Descriptive literature reviews
- Literature reviews that do not detail the populations studied
- Pathophysiological literature reviews
- Animal model studies
- Articles not accessible in full
- Articles in a language other than English or French

An additional search was performed on the UpToDate® site. The literature reviews cited, not found via the PubMed query, have been added.

A second additional search was carried out on the French Health Scientific Literature search engine (LiSSa) to look for other risk factors that were not noticed during

the initial searches, via literature reviews published in journals not indexed on MEDLINE.

When the same association was covered by several reviews, we excluded the oldest ones.

As the purpose of this work is to provide an up-to-date synthesis of the literature reviews, most of the main and/or relevant results of the studies have been extracted.

Results

We identified 668 literature reviews and included 86 from PubMed. We included 5 articles with additional research (UpToDate® and LiSSa). Reviews and meta-analysis included are summarized in Table 1.

There are many modifiable risk factors for AD, summarized in Table 2. Levels of evidence are resumed in Table 3.

Cardiovascular

Several literature reviews established a link between hypertension at different life stages and an increased risk of AD (17–21).

A systematic review summarized the findings from population-based observational studies and randomized clinical trials addressing the relations of blood pressure to cognitive function and dementia (20). Concerning "late-life" hypertension, seven longitudinal studies reported an association with AD, three longitudinal studies and two cross-sectional studies found no association, five cross-sectional studies reported an inverse association (potentially protective) (20). Concerning "mid-life" hypertension, an association with AD has been reported in four of five longitudinal studies (20).

Barnes and Yaffe associated «mid-life» hypertension and AD with OR = 1.61 (CI95 [1.16 - 2.24]). «Late-life» hypertension was not associated with an increased risk of AD in 8 of the 13 studies included (22). In another literature review, patients with the highest coefficient of variation in blood pressure were more likely to have an increased risk of cognitive impairment or dementia (17).

In 2006, another review highlighted a link between low diastolic BP (between 65 and 80 mmHg) and increased risk of AD (18).

Most published studies demonstrate associations between atrial fibrillation and impaired cognition, but no atrial fibrillation treatment has yet been associated with a reduced incidence of cognitive decline or dementia (23).

Heart failure was associated with 60% increased dementia risk (RR = 1.60 ; CI95 [1.19-2.13]) (24). Heart failure is associated with increased radiologic brain damage, particularly in the limbic system (which includes the hippocampus), similar to objective damage in AD patients (25).

A meta-analysis o associated hyperhomocysteinemia (> 15 μmol/L) and AD: OR = 3.37 (CI95% [1.90 - 5.95])

(26). This association is suggested in other reviews MA (27, 28). The link between vitamin deficiency (B9 or B12) and hyperhomocysteinemia is known and this could constitute a confounding bias.

Kivipelto et al. associated risk of AD and «mid-life» hypercholesterolemia (not in «late life») (29). In another review, 5 prospective studies were studied: 3 showed a significant association between AD and hypercholesterolemia; on the other hand, 1 study showed no significant association, while the last showed, conversely, a protective effect with a RR estimated at 0.4 (CI95 [0.2 - 0.8]) (18).

Hemorrhagic and ischemic stroke was also considered as risk factors for dementia: an increase in the risk of dementia by 10% after a first episode, and up to more than 20% after several episodes (30). Subclinical brain microbleeds (4 or more) were associated with an increase in cognitive impairment (HR = 2.10 ; CI95 [1.21 - 3.64]) (31).

One review analyzed different types of antihypertensive agents and their possible association with AD: there was no difference between control group, diuretic group or angiotensin 2 antagonist. In contrast, the authors report a decrease in RR dementia in patients using a calcium channel blocker (RR = 0.55; CI95 [0.24 - 0.73]) (32). For ACE inhibitors, the authors reported, at the conclusion of their review, a significant difference between the treatment and control groups in the incidence of cognitive impairment, but no significant difference in the occurrence of dementia (32).

In the review by Miida et al., the included cross-sectional studies showed a significant decrease in the risk of AD in patients using statins; but 3 out of 4 prospective studies did not show a significant decrease in the risk of AD, as did the 8 randomized controlled trials (RCTs) (33).

Habitus, social contact and educational level

Physical activity was associated with a decreased risk of cognitive impairment in 21 of 24 cohorts included (87.5%) and 100% of cross-sectional studies; a meta-analysis of 8 studies reported RR at 0.58 (CI95 [0.49 - 0.70]) for high vs low physical activity (34). In 2011, Barnes and Yaffe concluded that there is an association between physical inactivity and increased risk of dementia in the various reviews and meta-analyses included in their study (19). Wheeler et al. suggest that reducing and replacing sedentary behavior with intermittent light-intensity physical activity may protect against cognitive decline by reducing glycemic variability (35).

Active smoking (versus never smoking) was associated with an increased risk of dementia: RR = 1.79 (CI95 [1.43 - 2.23]) (22). In 2014, Beydoun et al. published a literature review with somewhat more nuanced results on this relationship between smoking and cognitive impairment: 16 of the 29 cohort epidemiological studies

Table 1. Summary of reviews and meta-analysis

Factor studied	Title	Authors	Year	Journal	Type	Number of studies	Years of inclusion	Number of patients	Main results
Alcohol	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	2014	BMC Public Health	Review	18 cohorts 12 cross-sectional studies	January 1990 - October 2012	132,881	8 of the 18 cohorts (44%) and 9 of the 12 cross-sectional studies (75%) associated alcohol with a majoration of cognitive impairment
Alcohol	Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies	Anstey et al.	2009	The American Journal of Geriatric psychiatry	Meta-analysis	15 cohorts	1950 - 2007	14,646	Light to moderate drinkers vs nondrinkers: RR = 0.72; CI95% (0.61-0.86) Heavy / excessive drinkers vs nondrinkers: RR = 0.92; CI95% (0.59-1.45) Drinkers vs nondrinkers: RR = 0.66; CI95% (0.47-0.94)
Aluminium	Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water	Flaten	2001	Brain research bulletin	Review	13 cross-sectional studies	Unknown	Unknown	Possible association between AD and aluminium in drinking water.
Aluminium (anti-acids)	Brief Report: Meta-analysis of Antacid Use and Alzheimer's Disease	Virk et Eslick	2015	Epidemiology	Meta-analysis	2 cohorts 7 case-control studies	Until January 2015	6,310 (842 in cohorts, 5,468 in case-control studies)	OR for case control studies: 1,0 ; CI95% (0,8-1,2) OR for cohorts: 0,8 ; CI95% (0,4-1,8)
Angiotensin receptor antagonists	Hypertension and Dementia	Nagai et al.	2012	American Journal of Hypertension	Review	2 clinical trials (SCOPE, PRoFESS)	Unknown	25,296	No significant difference in cognitive decline or dementia between the treatment and control groups in the 2 studies
Anti-hypertensive agent	Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia	Mc Guinness et al.	2009	Cochrane Database of Systematic Reviews	Review	4 clinical trials	January 2005 - February 2008	15,936	Combined result of the 4 studies: no significant difference in the incidence of dementia between treatment in « late-life » and placebo groups, despite the significant effect of antihypertensive treatment
Anti-oxydative agents and vitamin E	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	2014	BMC Public Health	Review	21 cohorts 6 cross-sectional studies	January 1990 - October 2012	98,350	9 of the 21 cohorts (43 %) and 2 of 6 cross-sectional studies (33 %) associated antioxydative agents and vitamin E with a decreased risk of cognitive impairment
Blood pressure variability	Visit-to-visit blood pressure variability and dementia: Blood pressure variability and dementia	Nagai et al.	2015	Geriatrics & Gerontology International	Review	4 cohorts 1 cross-sectional study	Until June 2015	> 25,000	In all studies, patients with the highest coefficient of variation of BP are significantly associated with a higher risk of cognitive impairment or dementia
Caffeine	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	2014	BMC Public Health	Review	11 cohorts 7 cross-sectional studies	January 1990 - October 2012	43,335	3 of the 11 cohorts (27%) and 4 of the 7 cross-sectional studies (57%) associated caffeine consumption and decreased risk of cognitive impairment 5 cohorts found partial association in subgroups (women, etc.)
Calcium blockers	Hypertension and Dementia	Nagai et al.	2012	American Journal of Hypertension	Review	1 clinical trial	Unknown	2,418	RR = 0.55; CI95% (0.24-0.73)
Chlamydia pneumoniae infection	Alzheimer's disease and infection: Do infectious agents contribute to progression of Alzheimer's disease?	Honjo et al.	2009	Alzheimer's & Dementia	Review	2 cohorts 3 case-control studies	Unknown	146	Possible association between C. pneumoniae infection and AD

Table 1. Summary of reviews and meta-analysis (continued)

Factor studied	Title	Authors	Journal	Year	Type	Number of studies	Years of inclusion	Number of patients	Main results
Conversion enzyme inhibitors	Hypertension and Dementia	Nagai et al.	American Journal of Hypertension	2012	Review	2 clinical trials	Unknown	15,402	The 2 studies show a significant difference between the treatment and control groups in the incidence of cognitive decline but no difference in the incidence of dementia
Depression	Depression: A shared risk factor for cardiovascular and Alzheimer disease	Dylan Windt et al.	Cleveland Clinic Journal of Medicine	2011	Review	Unknown	2010	Unknown	All included studies found an association between depression and increased risk of AD
Depression	Amyloid-beta and depression in healthy older adults: a systematic review	Harrington et al.	Australian and New Zealand Journal of Psychiatry	2015	Review	19 cross-sectional studies	2006 - 2014	Unknown	15 of the 19 cross-sectional studies (79%) found a significant difference between Aβ levels of depressed and non-depressed patients, with a decrease of Aβ42 and an increase in the ratio Aβ40:42
Depression	Depression and Risk for Alzheimer Disease: Systematic Review, Meta-analysis, and Metaregression Analysis	Ownby et al.	Archives of General Psychiatry	2006	Meta-analysis	6 cohorts 5 retrospective cohorts 9 case-control studies	Unknown	102,172	OR = 1.90; CI95% (1.55-2.33) for cohorts OR = 2.03; CI95% (1.73-2.38) for cross-sectional studies
Diabetes mellitus	Facteurs de risque vasculaire et risque de maladie d'Alzheimer : revue d'études épidémiologiques	Cowppli-Bony et al.	Psychologie et Neuropsychiatrie du Vieillissement	2006	Review	11 cohorts	Unknown	34,664	7 of the 11 cohorts (64 %) associated diabetes and increased risk of AD.
Diabetes mellitus	An updated meta-analysis of cohort studies: Diabetes and risk of Alzheimer's disease	Zhang et al.	Diabetes Research and Clinical Practice	2017	Meta-analysis	17 cohorts	Until May 2016	1,746,777	RR = 1.53; CI95% (1.42-1.63) RR for occidental population = 1.36; CI95% (1.18-1.53) RR for oriental population = 1.62; CI95% (1..49-1.75)
Diabetes mellitus	The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence	Barnes & Yaffe	The Lancet Neurology	2011	2 meta-analysis	8 and 9 cohorts (6 duplicates) 5 clinical trials	2005 - 2011	Unknown	In first meta-analysis, 2 of 8 cohorts (25%) associated diabetes and AD. In second meta-analysis, 4 of 9 cohorts (44%) associated diabetes and dementia
Diabetes mellitus	Type 2 Diabetes as a Risk Factor for Alzheimer's Disease: The Confounders, Interactions, and Neuropathology Associated With This Relationship	Vagelatos et al.	Epidemiologic Reviews	2013	Meta-analysis	15 cohorts	1946 - 2013	Unknown	RR =1.57; CI95% (1.41-1.75)
Diet	Alzheimer's disease and diet: a systematic review	Yusufov et al.	International Journal of Neuroscience	2017	Review	46 cohorts 9 cross-sectional studies 6 case-control studies 2 retrospective cohort 1 clinical trial	1995-2015	132,491	50 of 64 studies (78 %) associated diet and decreased risk of AD: 10 of 12 (83 %) for mediterranean diet 1 of 4 (25 %) for beta-carotene 7 of 9 (78 %) for vitamin E 4 of 5 (80 %) for vitamin B9
Diuretics	Hypertension and Dementia	Nagai et al.	American Journal of Hypertension	2012	Review	3 clinical trials	Unknown	10,656	No significant difference in dementia risk between the treated and control groups
Essential tremor	Association between Essential Tremor and Other Neurodegenerative Diseases: What Is the Epidemiological Evidence?	LaRoia & Louis	Neuroepidemiology	2011	Review	6 studies	1966 - March 2011	Unknown	6 of 6 studies presented (100 %) associated essential tremor and AD
HDI diet	Dietary Patterns, Cognitive Decline, and Dementia: A Systematic Review	Van de Rest et al.	Advances in Nutrition	2015	Review	8 cohorts 6 cross-sectional studies 1 clinical trial	Until May 2014	39,499 (21,086 in cohorts, 18,289 in cross-sectional studies, 124 in trials)	6 of 8 cohorts (75%) and 6 of 6 cross-sectional studies SD (100%) associated reduced risk of cognitive impairment and HDI diet

Table 1. Summary of reviews and meta-analysis (continued)

Factor studied	Title	Authors	Journal	Year	Type	Number of studies	Years of inclusion	Number of patients	Main results
Head injury with loss of consciousness	Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication	Fleminger et al.	Journal of Neurology, Neurosurgery & Psychiatry	2003	Meta-analysis	15 case-control studies	1966 - 2006	4,639	OR = 1.58; CI95% (1.21-2.06) OR (men) = 2.29; CI95% (1.47-3.57) OR (femmes) 0.91; IC95% (0.56-1.47)
Hearing impairment	Hearing impairment and risk of Alzheimer's disease: a meta-analysis of prospective cohort studies	Zheng et al.	Neurological Sciences	2017	Meta-analysis	4 cohorts	Until January 2016	7,461	RR = 2,82 ; CI95% (1,47 – 5,42)
Hearing impairment	Age-related hearing impairment a risk factor and frailty marker for dementia and AD	Panza et al.	Nature Reviews Neurology	2015	Review	8 cohorts 6 cross-sectional studies 1 clinical trial (peripherical hearing impairment) 5 cohorts (central hearing impairment)	1991 - 2013	Unknown (> 10,000 for peripherical hearing impairment, > 1000 for central hearing impairment)	Peripheral hearing loss was associated with accelerated cognitive decline in 14 of the 15 studies (93%) at 2 and 8 years Central hearing loss was associated with accelerated cognitive decline in except in 4 of the 5 studies (80%) at 5 years
Heart failure	Structural brain alterations in heart failure: a review of the literature and implications for risk of Alzheimer's disease	Alosco et Hayes	Heart Failure Reviews	2015	Review	9 case-control studies	Unknown	592	In patients with heart failure, there is an increase in brain damage, especially in the middle temporal lobe, a greater atrophy of the limbic system. The alterations are similar to those of AD.
Helicobacter Pylori	Sur la piste infectieuse de la maladie d'Alzheimer. . . Helicobacter pylori ?	Baudron et al.	Gériatrie et Psychologie Neuropsychiatrie du Vieillissement	2016	Review	4 cohorts 2 case-control studies	Unknown	≈ 89,000	Possible association between Helicobacter pylori and AD
Helicobacter pylori infection	Alzheimer's disease and infection: Do infectious agents contribute to progression of Alzheimer's disease?	Honjo et al.	Alzheimer's & Dementia	2009	Review	1 cohort 1 case-control study	Unknown	110	Possible association between H. pylori infection and AD
HHV6 infection	Alzheimer's disease and infection: Do infectious agents contribute to progression of Alzheimer's disease?	Honjo et al.	Alzheimer's & Dementia	2009	Review	2 case-control studies	Unknown	125	HHV-6 does not appear to be an independent risk factor for AD but appears to increase neural damage by HSV1 in patients with APOE4
HSV1 infection	Alzheimer's disease and infection: Do infectious agents contribute to progression of Alzheimer's disease?	Honjo et al.	Alzheimer's & Dementia	2009	Review	12 case-control studies	Unknown	689	0 of 12 studies (0 %) associated HSV1 and AD
Hypercholestérolemia	Cholesterol as a risk factor for Alzheimer's disease–epidemiological evidence	Kivipelto et al.	Acta Neurologica Scandinavica	2006	Review	12 cohorts	1985 - 2005	Unknown	4 of 5 cohorts (80 %) associated mid-life hypertension and AD No clear association between late-life hypertension and AD in 7 cohorts
Hypercholestérolemia	Facteurs de risque vasculaire et risque de maladie d'Alzheimer : revue d'études épidémiologiques	Cowppli-Bony et al.	Psychologie et Neuropsychiatrie du Vieillissement	2006	Review	5 cohorts	Unknown	4,419	2 of the 5 cohorts (40 %) associated hypercholesterolemia and AD, with opposite effects
Hyperhomocysteinemia	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	BMC Public Health	2014	Review	19 cohorts 14 cross-sectional studies	January 1990 - October 2012 janvier 1990 et octobre 2012	35,460	12 of the 19 cohorts (63 %) and 11 of the 14 cross-sectional studies (78 %) associated hyperhomocysteinemia and increased risk of cognitive impairment
Hyperhomocysteinemia	Homocysteine and Alzheimer's disease	Morris	The Lancet Neurology	2003	Review	2 cohorts 4 case-control studies	Unknown	1,615 (1,049 in cohorts, 566 in case-control studies)	2 of the 2 cohorts (100 %) and 3 of the 4 case-control studies (75 %) associated hyperhomocysteinemia and AD

Table 1. Summary of reviews and meta-analysis (continued)

Factor studied	Title	Authors	Journal	Year	Type	Number of studies	Years of inclusion	Number of patients	Main results
Hyperhomocystéinemia	Is High Homocysteine Level a Risk Factor for Cognitive Decline in Elderly? A Systematic Review, Meta-Analysis, and Meta-Regression	Ho Roger et al.	The American Journal of Geriatric Psychiatry	2011	Review	4 cohorts 13 cross-sectional studies	Unknown	6,122	Patients with AD and vascular dementia have higher Hcy levels
Hyperhomocysteinemia	Homocysteine and Alzheimer's Disease: Evidence for a Causal Link from Mendelian Randomization	Hu et al.	Journal of Alzheimer's Disease	2016	Meta-analysis	34 case-control studies	Until September 2015	9,397	OR =3.37; CI95% (1.90–5.95)
Hypertension	Hypertension and Dementia	Nagai et al.	American Journal of Hypertension	2012	2 reviews	First: 7 cohorts Second: 3 cohorts 5 cross-sectional studies 3 case-control studies	Unknown	12,803 and 19,264	6 of 7 cohorts (86 %) in first review and 9 of 11 studies (82 %) in second review associated hypertension (systolic or diastolic) with dementia (first review) or cognitive impairment (second review)
Hypertension	Facteurs de risque vasculaire et risque de maladie d'Alzheimer : revue d'études épidémiologiques	Cowppli-Bony et al.	Psychologie et Neuropsychiatrie du Vieillissement	2006	Review	4 cohorts	Unknown	7,357	1 of 4 cohorts (25 %) associated systolic hypertension and AD. 3 of 4 cohorts (75 %) associated diastolic hypertension and AD
Hypertension	The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence	Barnes & Yaffe	The Lancet Neurology	2011	Meta-analysis	13 studies	2005-2011	15,936	OR for « mid-life » hypertension: 1.61; CI95 (1.16-2.24) Non-significant link between « late-life » hypertension and AD in 8 of 13 studies (62 %)
Intellectual inactivity	The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence	Barnes & Yaffe	The Lancet Neurology	2011	2 reviews	In first review, 22 cohorts In second review, 13 cohorts and 6 case-control studies	2005-2011	21,456	Risk of dementia and AD increased if educational level is low
Lower educational level	Education and Dementia: A Meta-Analytic Study	Caamaño-Isorna et al.	Neuroepidemiology	2006	Meta-analysis	9 cohorts 5 case-control studies	Unknown	28,936 (22,726 in cohorts, 6,210 in case-control studies)	RR =1.80; CI95% (1.43-2.27) RR for cohorts = 1.59; CI95% (1.35-1.86) OR for case-control studies = 2.40; CI95% (1.32-4.38)
Lower educational level	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	BMC Public Health	2014	Review	27 cohorts 25 cross-sectional studies	January 1990 - October 2012	225,989	18 of the 27 cohorts (67 %) and 21 of the 25 cross-sectional studies (84 %) associated lower educational level and risk of cognitive impairment
Magnesium	Magnesium Status in Alzheimer's Disease: A Systematic Review	Veronese et al.	American Journal of Alzheimer's Disease & Other Dementias®	2016	Review	13 case-control studies	Until may 2015	1,066	SMD = -0.35; CI95% (-0.65 - -0.04)
Magnetic field exposure	Magnetic field exposure and neurodegenerative diseases – recent epidemiological studies	Hug et al.	Sozial- und Präventivmedizin SPM	2006	Review	3 cohorts 1 retrospective cohort 4 case-control studies	January 2000 - July 2005	5,566,595 (5,562,429 in cohorts, 4,166 in case-control studies)	5 of 8 studies (63 %) associated magnetic field exposure and AD
Manganese	Association of Serum Manganese Levels with Alzheimer's Disease and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis	Du et al.	Nutrients	2017	Review	17 case-control studies	Unknown	2,090	Possible association between manganese and AD

Table 1. Summary of reviews and meta-analysis (continued)

Factor studied	Title	Authors	Year	Journal	Type	Number of studies	Years of inclusion	Number of patients	Main results
Mediterranean diet	Dietary Patterns, Cognitive Decline, and Dementia: A Systematic Review	Van de Rest et al.	2015	Advances in Nutrition: An International Review Journal	Review	15 cohorts 6 cross-sectional studies 2 interventional studies 3 meta-analysis	Until May 2014	84,481 (64,571 in cohorts, 19,120 in cross-sectional studies, 790 in interventional studies)	8 of the 15 cohorts (53%) and 4 of the 6 cross-sectional studies (67%) associated mediterranean diet and decreased risk of AD HR for 3 meta-analysis = 0.92; CI95% (0.88-0.97)
Metformine	Antidiabetic Drugs and Their Potential Role in Treating Mild Cognitive Impairment and Alzheimer's Disease	Alagiakrishnan et al.	2013	Discovery Medicine	Review	1 cohort 1 case-control study	Until october 2013	Unknown	Opposite results Cohort: HR = 0.76; CI95% (0.58-0.98) Case-control: OR = 1.71; CI95% (1.12-2.60)
Obesity	The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence	Barnes & Yaffe	2011	The Lancet Neurology	Meta-analysis	10 cohorts	2005-2011	Unknown	RR = 1.59; CI95% (1.02-2.48)
Obesity	Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies; BMI and risk of dementia	Anstey et al.	2011	Obesity Reviews	Review	15 cohorts	1950-2009	25,624	Possible association between underweight, overweight and obesity at «mid-life» with dementia
Obesity	Midlife vascular risk factors and Alzheimer's disease: evidence from epidemiological studies	Tolppanen et al.	2012	Journal of Alzheimer's Disease	2 meta-analysis	Unknown	Unknown	Unknown	« mid-life » (45-64 years) BMI < 18.5 or > 30 was associated with increased risk of AD « late-life » BMI was not associated with AD
Physical activity	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	2014	BMC Public Health	Review	24 cohorts 4 cross-sectional studies	January 1990 - October 2012	93,371	21 of the 24 cohorts (88%) and 4 of the 4 cross-sectional studies (100%) associated physical activity with a decreased risk of cognitive impairment
Physical inactivity	The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence	Barnes & Yaffe	2011	The Lancet Neurology	Review	16 cohorts 24 cross-sectional studies	2005 - 2011	167,016	Association between physical inactivity and dementia
Statin	Statins: drugs for Alzheimer's disease?	Eckert et al.	2005	Journal of Neural Transmission	Review	6 cross-sectional studies 3 case-control studies 3 clinical trials	Unknown	59,768 in retrospective studies 308 in prospective studies	Retrospective studies show a significant decrease in the risk of AD if taking statins The effect was not found with prospective studies
Statin	Statins for the prevention of dementia	McGuinness et al.	2016	Cochrane Database of Systematic Reviews	Review	2 clinical trials	Unknown	26,340	Studies did not show any significant difference between the placebo group and the statin group.
Statins	Can statin therapy really reduce the risk of Alzheimer's disease and slow its progression?	Miida et al.	2005	Current Opinion in Lipidology	Review	3 cohorts 3 cross-sectional studies 1 case-control study 8 clinical trials	Unknown	104,745 (9,835 in cohorts and case-control, 66,993 in cross-sectional studies, 27,917 in clinical trials)	3 of 4 cohorts or cases-control study (75 %) did not associated statin and AD. 3 of 3 cross-sectional studies (100 %) associated statin and reduced risk of AD. In clinical trial, there are no association between statin therapy and AD.
Testosterone level	Low Testosterone Level and Risk of Alzheimer's Disease in the Elderly Men: a Systematic Review and Meta-Analysis	Wenshan et al.	2016	Molecular Neurobiology	Meta-analysis	7 cohorts	Until march 2015	5,251	RR = 1.48; IC95% (1.12-1.96)

Table 1. Summary of reviews and meta-analysis (continued)

Factor studied	Title	Authors	Journal	Year	Type	Number of studies	Years of inclusion	Number of patients	Main results
Tobacco use	The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence	Barnes & Yaffe	The Lancet Neurology	2011	3 meta-analysis	19, 23 and 17 studies	2005-2011	Unknown	Current vs never smoking : RR = 1.79; CI95% (1.43 - 2.23) Current vs former smoking : RR = 1.70 CI95% (1.25 - 2.31) In 2 others meta-analysis: RR = 1.59 CI95% (1.15-2.20) and RR = 1.45 CI95% (1.16-1.80)
Tobacco use	Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case-control and cohort studies	Almeida et al.	Addiction	2002	Review	8 cohorts 21 case-control studies	1966 - 2000	49,208 (43,885 in cohorts and 5,323 in cases-control studies)	Possible association between tobacco use and AD
Tobacco use	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	BMC Public Health	2014	Review	29 cohorts 7 cross-sectional studies	January 1990 - October 2012	170,816	16 of the 29 cohorts (55 %) and 2 of 7 cross-sectional studies (29 %) associated smoking and increased risk of cognitive impairment A meta-analysis of 9 studies found: RR (current or ever vs never) = 1.37; CI95% (1.23-1.52)
Unsaturated fatty acids	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Beydoun et al.	BMC Public Health	2014	Review	18 cohorts 5 cross-sectional studies	January 1990 - October 2012	76,046	7 of the 18 cohorts (39%) and 5 of the 5 cross-sectional studies (100%) associated unsaturated fatty acids with a decreased risk of cognitive impairment
Unsaturated fatty acids	n-3 Fatty Acids in the Prevention of Cognitive Decline in Humans	Cederholm et al.	Advances in Nutrition	2013	Review	Unknown	Unknown	Unknown	The results are divergent, but the majority of publications note an association between taking n-3 unsaturated GA, particularly by catching fish, and reducing the risk of cognitive impairment.
Vitamin B supplementation	Efficacy of Vitamin B Supplementation on Cognition in Elderly Patients With Cognitive-Related Diseases: A Systematic Review and Meta-Analysis	Zhang et al.	Journal of Geriatric Psychiatry and Neurology	2017	Review	4 clinical trials	Until may 2015	679	Supplementation significantly reduces homocysteinemia, but there is no significant difference in MMS between the 2 groups, so there is no significant cognitive improvement.
Vitamin D	Vitamin D, cognition, and dementia A systematic review and meta-analysis	Balion et al.	Neurology	2012	Meta-analysis	8 studies	Until August 2010	2,749	4 of 8 studies associated vitamin D concentration > 50 nmol/L and high MMSE: + 1.16 point ; CI95% (0.462-1,85)
Vitamin E	Vitamin E for Alzheimer's dementia and mild cognitive impairment	Farina et al.	Cochrane Database of Systematic Reviews	2017	Review	3 clinical trials (1 analyzed)	Until April 2016	304	Vitamin E does not reduce the number of people with AD in a population with cognitive impairment (CIN)
Zinc	Zinc diet and Alzheimer's disease: a systematic review	Loef et al.	Nutritional Neuroscience	2012	Review	2 reviews 13 clinical trials 4 cohorts 2 cross-sectional studies 15 case-control studies 17 anatomopathological studies 4 uncontrolled studies	Until April 2011	Unknown	No conclusive evidence to allow a recommendation for zinc intake to prevent AD.

Table 2. Modifiable factors associated with AD

Category	Positively associated (risk)	Non-associated	Negatively associated (protective)
Age	Age		
Cardiovascular	Stroke	Diuretics, ACE inhibitors, Angiotensin 2 antagonist Statins	Calcium channels blockers
	Mid-life hypertension		
	Low diastolic blood pressure		
	Mid-life hypercholesterolemia		
	Hyperhomocysteinemia		
	Heart failure		
	Atrial fibrillation		
Habitus, social contact, educational level	Sedentarity	Alcohol consumption	Physical activity
	BMI > 30 ou < 18,5 (mid-life)		High educational level
	Active smoking		Frequent social contact
	Low educational level		Cognitive stimulation
			Caffeine consumption
Pneumology	Sleep apnea syndrom		
Infectiology	C. pneumoniae infection	H. pylori infection	
		HSV1 infection	
		HSV6 infection	
Endocrinology and metabolism	Diabetes	Hypotestosteronemia	Metformine + hypoglycemic sulfonamides
		Plasma vitamin D concentration	
Psychiatry / Neurology / Anesthesia	Depression	General anesthesia	
	Benzodiazepine use		
	Hearing loss		
	Head injury with loss of consciousness		
	Essential tremor		
Environmental	Pesticides		
	Exposure to extremely low frequency electromagnetic fields		
Diet, nutrients	Hypomanganesemia	Antacides (aluminium)	Mediterranean diet
	Lowered level of magnesium within the cerebrospinal fluid	Zinc	HDI diet
			unsaturated fatty acids
			Vitamin E
			Vitamin B9, B12
			Caffeine consumption

included (55.2%) found an association between smoking and increased risk of cognitive impairment, as 2 of the 7 cross-sectional studies included. In a meta-analysis of 9 of 29 studies, the authors calculated a RR of AD for current and former smokers compared to never smokers at 1.37 (CI95 [1.23 - 1.52]) (28).

Concerning alcohol, Beydoun et al. noted an association between alcohol and increased cognitive impairment in 44% of cohorts included and 75% of cross-sectional studies (28).

In 2009, Anstey et al. published a meta-analysis of 15 cohorts whose results suggest that alcohol consumption is associated with a decreased risk of AD: RR = 0.66 (CI95 [0.47 - 0.94]) (36). Confounding factors were possible, particularly due to alcohol-related comorbidities.

There was a moderate association between caffeine consumption and decreased risk of cognitive problems: in one review, 4 of the 7 cross-sectional studies and 3 of the 11 cohorts included found this association. Five other cohorts among the 11 identified this link in a partial way in the subgroup analyses (for example, only among women) (28).

Frequent social contact and cognitive stimulation would be protective factors (37).

Table 3. Summary of evidences concerning associated factors for Alzheimer's dementia

	Convincing association	Suggestive association	Weak or no association
Definition	> 10,000 patients Association in more than 80% studies	> 1,000 patients Association in more than 50% studies	< 1,000 patients or association in less than 50% studies
Cardiovascular	Diabetes mellitus	Hyperhomocysteinemia	Angiotensin receptor antagonists
	High blood pressure variability	Mid-life hypertension	Calcium blockers
		Heart failure	Diuretics
		Tobacco use	Late-life hypertension
			Conversion enzyme inhibitors
			Statin
Habitus, social contact and educational level	Physical activity		Alcohol
	Lower educational level		
Pneumology	Sleep apnea syndrom		Chlamydia pneumonia
Infectiology			Helicobacter pylori
			HHV6
			HSV1
Endocrinology and metabolism		Midlife obesity	Metformine
		Low testosterone level	
Psychiatry, neurology, anesthesia	Hearing impairment	Head injury	General anesthesia
	Depression		Essential tremor
Environmental	Magnetic field exposure		
Diet, nutrients	HDI Diet	Unsaturated fatty acids	Aluminium
		Mediterranean diet	Vitamin B
		Vitamin D	Vitamin E
			Caffeine
			Magnesium
			Manganese
			Zinc

A lower educational level was associated with an increased risk of AD, with an RR estimated at 1.80 (CI95 [1.43 - 2.27]) (38) or 1.99 (CI95 [1.30 - 3.04]) in Beydoun's meta-analysis (knowing that low educational level here means less than 8 years of education) (28).

Pneumology

A meta-analysis of 6 cohort studies (19,940 patients) associated sleep apnea syndrome and dementia (RR = 1.69; CI95 [1.34 - 2.13]). The association is also found in subgroup analyses, with or without polysomnography, adjusted or not on ApoE4 (39).

Infectiology

One of 3 case-control studies and 2 epidemiological studies showed a possible link between Chlamydia pneumoniae infection and AD possibly through chronic neuronal inflammation (40).

The prevalence of Helicobacter pylori was increased in patients with AD in case-control studies; in cohorts patients with H. pylori often have poorer cognitive performance (confounding bias). However, the authors conclude their narrative review with a lack of longitudinal studies to support the association between infection and AD, to explain more precisely the mechanism by which H. pylori would actually intervene in pathogenesis, and to determine the utility of eradication of the bacterium in patients with AD or cognitive disorders (41).

A review of 12 case-control studies did not associated Herpes Simplex Virus 1 infection and AD (40). In the same review, it is suggested that HHV6 is not an independent risk factor for AD. Nevertheless, its presence could increase the neuronal damage caused by HSV1 in patients with ApoE4.

Endocrinology and metabolism

The risk of dementia (especially AD) increased in cases of «mid-life» underweight (BMI < 18.5) or «mid-life» obesity (between 45 and 64 years of age according to the authors); this association is not present after 64 years of age, in late life (42). «Mid-life» obesity was associated with an increased risk of dementia : RR = 1.59 (CI95 [1.02

- 2.48]) (22).

Diabetes is also a risk factor for AD in most studies, with an estimated RR of 1.53 (CI95 [1.42 - 1.63]), or slightly higher in so-called «eastern» populations, with an RR of 1.62 (CI95 [1.49 - 1.75]) (43). Mid-life and late-life diabetes were associated with AD (42); interaction is possible with cerebrovascular risk (18).

The impact of metformin use on the occurrence of cognitive impairment is unclear: protective role in a cohort, risk factor in a case-control study. In one studiy, metformin + hypoglycemic sulfonamide combination therapy is associated with a decrease in AD compared to untreated diabetic patients (HR = 0.65; CI95 [0.56 - 0.74]) (44).

Hypotestosteronemia in elderly men would be associated with an increase in AD (RR = 1.48; CI95 [1.12 - 1.96]). However, the authors do not detail their definition of «elderly male» and report that the studies included in their meta-analysis have different definitions for hypotestosteronemia (45)

Psychiatry, neurology and anesthesia

A meta-analysis associated history of depression and increased risk of AD: RR = 1.90 (CI95 [1.55 - 2.33]) in cohort studies (46). Late-life depression is associated with increased risk of AD (37).

In 2015, Harrington et al. studied the relationship between depression and Aβ plaques in a healthy, older adult population. The majority of included studies found a significant increase in Aβ levels in depressed patients. However, the authors mentioned many biases in the 19 cross-sectional studies included (47).

Long-term benzodiazepine users had an increased risk of dementia compared with never users: RR = 1.49 (CI95 [1.30 - 1.72]). The risk of dementia increased by 22% for every additional 20 defined daily dose per year (RR = 1.22 ; CI95 [1.18 - 1.25]) (48).

Peripheral and central hearing impairment were associated with a risk of AD (49). The RR was estimated at 2.82 (CI95 [1.47 - 5.42]) between hearing impairment and risk of cognitive impairment (50).

Head injury with loss of consciousness could also be a risk factor for AD, according to several studies, with an estimated RR of 1.82 (CI95 [1.26 - 2.67]) (51). In a subgroup analysis, OR is significant only for men (OR = 2.29 ; CI95 [1.47 - 2.06]), not for women (52).

A review of 6 epidemiological studies reports that an essential tremor would be associated with an increased risk of AD (53).

A meta-analysis of 15 case-control studies did not associated general anesthesia and AD (OR = 1.05; CI95 [0.93 - 1.19]) (54).

Environmental

Several literature reviews have highlighted a possible link between AD and exposure to extremely low frequency electromagnetic fields, particularly in a professional context (electrician, electronics technician, welder...) (55–57). The latest meta-analysis (20 studies) highlighted the numerous biases (particularly publication bias) and heterogeneity of the populations being compared, without a dose-response relationship. They suggested a higher risk for train drivers (RR = 2.94; CI95 [1.15 - 7.51]) than for welders (RR = 1.54; CI95 [1.00 - 2.38]) or electricians (RR = 1.18; CI95 [1.01 - 1.37]) (58).

A positive association was observed between pesticide exposure and AD (OR = 1.34; CI95 [1.08 - 1.67]) (59).

Diet, nutrients

Regular use of anti-acids (with aluminium) has no relationship with increased risk of AD: a meta-analysis estimated OR for case-control studies at 1.0 (CI95 [0.8 - 1.2]) and for prospective studies at 0.8 (CI95 [0.4 - 1.8]) (60). A review highlighted a possible relationship between aluminium in drinking water and AD, but noted inconsistencies (61).

A review showed no association or inconsistent associations between vitamin B12 intake and cognitive function (62).

A literature review of 57 studies concluded that there is no evidence to support a possible recommendation for the preventive use of zinc for AD (63).

A decrease in manganese plasma levels may also be associated with an increased risk of AD (64).

In one review, magnesium was not associated with AD, but a lowered level of magnesium within the cerebrospinal fluid increased the risk of AD (65).

A combined meta-analysis of 3 meta-analyses estimates an HR of 0.92 (CI95 [0.88 - 0.97]) in favour of an inverse (protective) relationship between mediterranean diet and risk of AD (66). In 2017, Yusufov et al. published a systematic review of the literature in which 10 of the 12 studies included found an association between Mediterranean diet and reduction in the risk of AD (67).

Van de Rest et al. studied the impact of the Healthy Diet Indicator diet, based on World Health Organization recommendations: 6 of the 6 cross-sectional studies and 6 of the 8 longitudinal studies included found an association between diet adequate to HDI recommendations and decreased risk of cognitive impairment (66).

The intake of unsaturated fatty acids (notably via fish consumption) is associated with a reduction in the risk of AD and dementia (68). This association is mainly found in cross-sectional studies (5/5), less in cohorts (7/18); a meta-analysis of 5 studies estimated RR at 0.67 (CI95 [0.47 - 0.95]) (28). A role of the intestinal flora has been

mentioned in the pathogenesis of Alzheimer's disease (69).

In the review by Yusufov et al. 7 of the 9 studies included found that dietary intake of vitamin E was associated with a decreased risk of AD (67). Beydoun et al. report a similar association, but in 9 of 21 cohort studies and 2 of 6 cross-sectional studies included in their review (34).

An overview of systematic review suggested that Ginkgo biloba extract has potentially beneficial effects for people with dementia when it is administered at doses greater than 200mg/day for at least 5 months (70).

Yusufov et al. note that 4 of the 5 included studies found an association between folate (vitamin B9) intake and decreased risk of AD (67).

Plasma vitamin D concentration greater than 560 ng/mL is associated with minimal gain at the MMSE level estimated at 1.16 points (CI95 [0.46 - 1.85]) in a meta-analysis (71). Several confounding biases are possible, including better sun exposure of non-dementia patients.

An other meta-analysis showed significantly lower plasma levels of folate, vitamin A, vitamin B12, vitamin C, and vitamin E (P < .001), non-significantly lower levels of zinc (P = .050) and vitamin D (P = .075) in AD patients, and non-significant differences for plasma levels of copper and iron; this lower plasma nutrient levels could indicate that patients with AD have impaired systemic availability of several nutrients (72).

Discussion

Principal results

Cardiovascular risk factors are an important part of the reviews selected in this research work. Thus, most of the journals included report an association between the different cardiovascular risk factors and the occurrence of AD.

Medically, several reviews suggest that a history of depressive syndrome is associated with an increased risk of AD. Hearing, central or peripheral impairment also seems to increase the risk of AD. However, the studies do not allow us to conclude whether the risk is corrected with the use of hearing aids.

On the environmental level, intellectual inactivity and low educational level (less than 8 years of study) seem to be the most associated factors in this research with an increased risk of AD.

Unlike intellectual inactivity and low educational level, the authors of the reviews hypothesize that a higher level of education would be associated with a lower risk of AD.

On the drug side, it would appear that the use of calcium channel blockers is associated with a decrease in dementia (but not in AD in particular). For IECs, the results point to a decrease in cognitive disorders, but not in the occurrence of dementia.

In terms of diet, the Mediterranean diet is the most studied, and seems to be associated with a decrease in the risk of AD. The results of the various reviews also seem to point towards a protective role for a diet rich in unsaturated fatty acids ω.

Dietwise, no relationship has been found between plasma or cerebrospinal zinc levels and the incidence of dementia or AD. Similarly, there is no reported link between zinc supplementation and the prevention of AD.

The same applies to vitamin B or vitamin E supplementation. Plasma magnesium levels also do not appear to be associated with a risk of AD.

The absorption of aluminum, through drinking water or medication, does not appear to be associated with the development of AD or dementia.

Medically, the use of ARB2 or diuretics does not appear to affect the onset of dementia. More anecdotally, general anesthesia did not show an association with the occurrence of AD either.

From an environmental perspective, it appears that HSV1 and HHV6 infections are not associated with the occurrence of AD.

Alcohol consumption presents contradictory results. Some studies tend to show a protective effect of alcohol on the occurrence of dementia and AD, while others suggest the opposite relationship.

Strengths and limitations

Alzheimer's disease is a frequent pathology, with a poor prognosis, without curative treatment available in 2018. Knowing how to prevent it better is an important issue, and a lot of research is being carried out in this direction. The large number of literature reviews and meta-analyses carried out on the subject can make a global approach difficult. Our synthesis is intended to be an overview of the various literature reviews in 2018, in order to take stock of what seems likely, what seems doubtful and what is not yet well studied. This is a substantial work based on 90 literature reviews and meta-analyses. Our results are consistent with the previous syntheses carried out on the same subject.

It is likely that the initial research equation may have caused a selection bias in the results presented by the PubMed database.

A publication bias is to be mentioned; in order to limit it, we completed our research with a search in the encyclopedia «UpToDate» and in French-speaking journals not indexed via LiSSa.

An «interpretation» bias is possible in the inclusion of the different reviews.

This study assumes that all included reviews and meta-analyses are of equal quality and value, which is not the case. The various reviews may be sources of bias, which may have influenced the results presented. Many confounding biases can exist in studies and be amplified by literature reviews.

Moreover, the subject matter is vast and complicated, it is not easy to approach it in its entirety, through very heterogeneous publications, which highlight different pathophysiological hypotheses in order to explain in a rational and scientific way the possible suspected association.

Perspectives

We have only studied literature reviews; risk or protective factors may exist, have been studied in retrospective or prospective studies that have not yet been reviewed.

As studies and reviews progress, some clearly identified risk factors can be modified, particularly in the cardiovascular and environmental fields. It may be interesting to study the impact of prevention on targeted modifiable risk factors in order to assess the impact on the incidence of AD and dementia.

On the other hand, some of the factors studied appear to be «doubtful», and it seems appropriate to carry out additional studies. For example, it may be relevant to study the impact of H. pylori eradication on the occurrence of AD, in order to determine whether systematic treatment can be an axis of AD prevention.

Conclusions

Specifying the risk factors for AD is a major issue to better prevent or delay its appearance. Current studies identify many modifiable risk factors. The impact of these modifiable factors appears to be greater and more reliable than genetic factors. Risk factors can induce AD, anticipate it or aggravate it; protective factors can have a specific effect or an effect limiting the impact of a pathology (antidepressant, anti-hypertensive…). To our knowledge, the cumulative effect of the various risk factors has not been studied.

Identifying patients at risk is important in order to prevent or delay the onset of AD, and also to limit high-risk behaviors (driving, treatment management, gas handling), anticipate dependency, limit financial risks (legal protection) or integrate a research protocol.

Synthesizing the literature reviews also highlights doubtful risk factors and unstudied risk factors. In addition, some risk factors have emerged in recent articles, but have not yet been studied in literature reviews. Studying these factors also makes it possible to make physiopathological assumptions that will lead to a better understanding of the mechanisms involved in the development of AD.

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