Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials

J NEUROL NEUROSURG PSYCHIATRY 2020

- The past few decades have witnessed great global efforts in updating and upgrading the evidence on how to prevent Alzheimer's disease

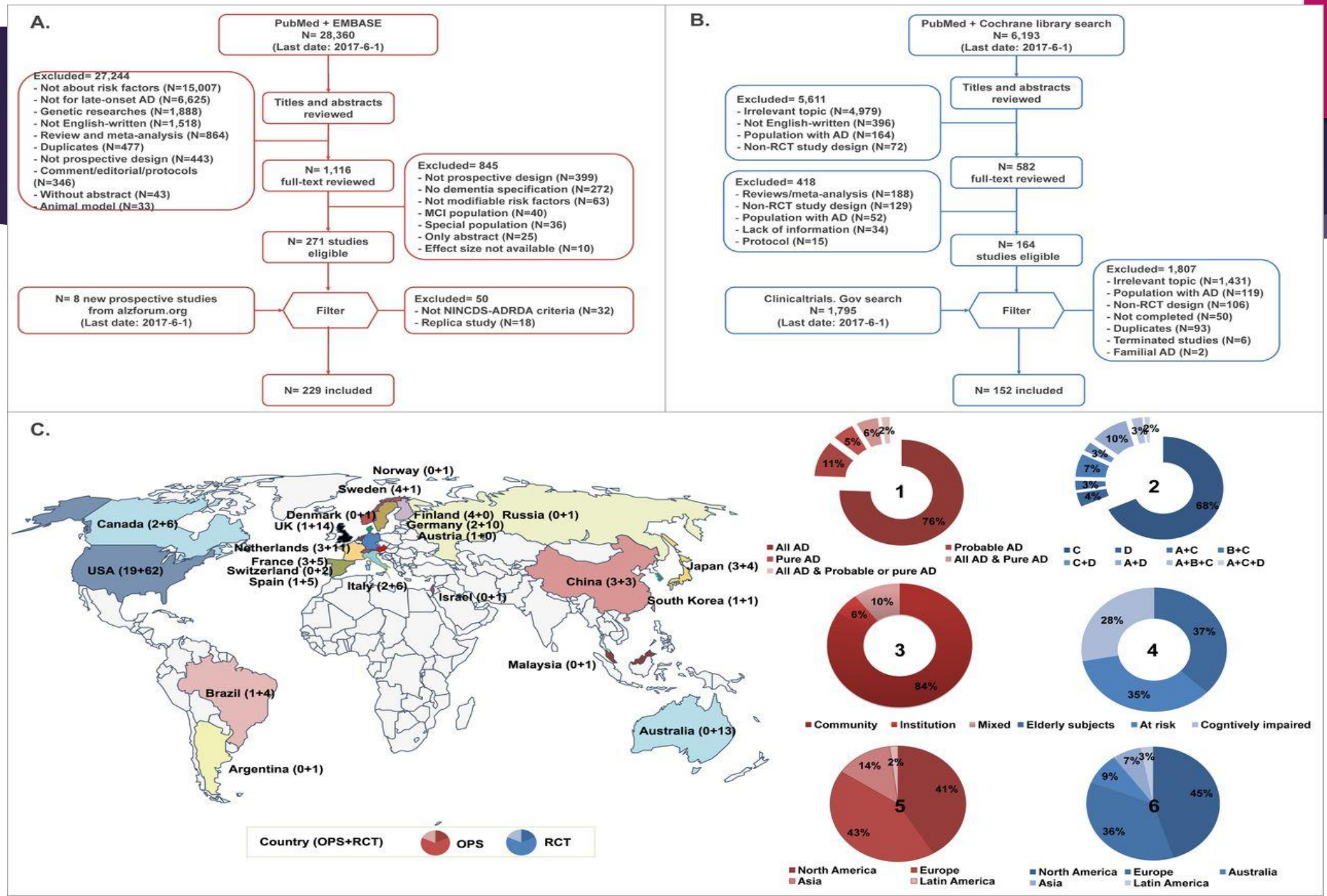
Two types of studies:

Observational prospective studies (OPSs)

which describe temporal relationships with potential causal links and often use large samples recruited from community dwellers

Randomised controlled trials (RCTs)

which possess strong internal validity to infer causality by testing the effects of specific interventions on the incidence of AD.


A.
PubMed + EMBASE
N= 28,360
(Last date: 2017-6-1)
Excluded= 27,244
- Not about risk factors (N=15,007)
- Not for late-onset AD (N=6,625)
- Genetic researches (N=1,888)
- Not English-written (N=1,518)
- Review and meta-analysis (N=864)
- Duplicates (N=477)
- Not prospective design (N=443)
- Comment/editorial/protocols (N=346)
- Without abstract (N=43)
- Animal model (N=33)
Titles and abstracts reviewed
N= 1,116
full-text reviewed
Excluded= 845
- Not prospective design (N=399)
- No dementia specification (N=272)
- Not modifiable risk factors (N=63)
- MCI population (N=40)
- Special population (N=36)
- Only abstract (N=25)
- Effect size not available (N=10)
N= 271 studies eligible
N= 8 new prospective studies from alzforum.org
(Last date: 2017-6-1)
Filter
Excluded= 50
- Not NINCDS-ADRDA criteria (N=32)
- Replica study (N=18)
N= 229 included
B.
PubMed + Cochrane library search
N= 6,193
(Last date: 2017-6-1)
Titles and abstracts reviewed
Excluded= 5,611
- Irrelevant topic (N=4,979)
- Not English-written (N=396)
- Population with AD (N=164)
- Non-RCT study design (N=72)
N= 582
full-text reviewed
Excluded= 418
- Reviews/meta-analysis (N=188)
- Non-RCT study design (N=129)
- Population with AD (N=52)
- Lack of information (N=34)
- Protocol (N=15)
N= 164
studies eligible
Clinicaltrials. Gov search
N= 1,795
(Last date: 2017-6-1)
Filter
Excluded= 1,807
- Irrelevant topic (N=1,431)
- Population with AD (N=119)
- Non-RCT design (N=106)
- Not completed (N=50)
- Duplicates (N=93)
- Terminated studies (N=6)
- Familial AD (N=2)
N= 152 included
C.
Norway (0+1)
Sweden (4+1)
Canada (2+6)
Denmark (0+1)
UK (1+14)
Finland (4+0)
Russia (0+1)
Germany (2+10)
Austria (1+0)
Netherlands (3+11)
France (3+5)
Switzerland (0+2)
Spain (1+5)
USA (19+62)
Italy (2+6)
Israel (0+1)
China (3+3)
Japan (3+4)
South Korea (1+1)
Malaysia (0+1)
Brazil (1+4)
Australia (0+13)
Argentina (0+1)
Country (OPS+RCT)
OPS
RCT
1
11%
5%
6%
2%
76%
All AD
Pure AD
All AD & Probable or pure AD
Probable AD
All AD & Pure AD
2
10%
3%
2%
3%
7%
3%
4%
68%
C
D
A+C
B+C
C+D
A+D
A+B+C
A+C+D
3
10%
6%
84%
Community
Institution
Mixed
4
28%
37%
35%
Elderly subjects
At risk
Cogntively impaired
5
14%
2%
41%
43%
North America
Europe
Asia
Latin America
6
7%
3%
9%
45%
36%
North America
Europe
Australia
Asia
Latin America

Inclusion :

Ops

- An OPS exploring the association between potentially modifiable exposures at baseline and incident AD independently diagnosed according to NINCDS-ADRDA criteria

RCT

- A RCT targeting the impact of modifiable risk factors on the incidence of AD or AD-related clinical endpoints (dementia or cognitive impairment)

Level of evidence

Directness		Credibility	Observational prospective study (OPS)		
			G or G/A+ or A+	A+/- or A-	S/P
Randomized controlled trial (RCT)	Alzheimer's disease (AD)	G or G/A+ or A+	A1	A1	A1
		A+/- or A-	A2	B	B
		S/P or not suitable for RCT	A4	B	C
	Dementia/Cognitive impairment (CI)	G or G/A+ or A+	A2	B	B
		A+/- or A-	A3	B	B
		S/P or not suitable for RCT	A4	B	C

LEVEL A	LEVEL B	LEVEL C *
● LEVEL A1: moderate-to-high level (G or G/A+ or A+) of evidence from RCT, irrespective of evidence from OPS ● LEVEL A2: moderate-to-high level evidence from OPS & low-to-moderate level (A+/- or A-) of evidence from RCT with AD as endpoint or moderate-to-high level of evidence from RCT with dementia/CI as endpoint ● LEVEL A3: moderate-to-high level evidence from OPS & low-to-moderate level of evidence from RCT with dementia/CI as endpoint ● LEVEL A4: moderate-to-high level evidence from OPS & weak (S/P) or no evidence from RCT.	● Situations located between Level A and Level C (it is more complex and thus no further classification is conducted.)	● Credibility of evidence is weak (S/P) for both OPS and RCT, irrespective of the endpoint.

CLASS I (STRONG): Benefit >> Risk | CIASS II (WEAK): Benefit ≈ Risk or uncertain risk | CLASS III (NOT SUGGESTED): Risk >> Benefit

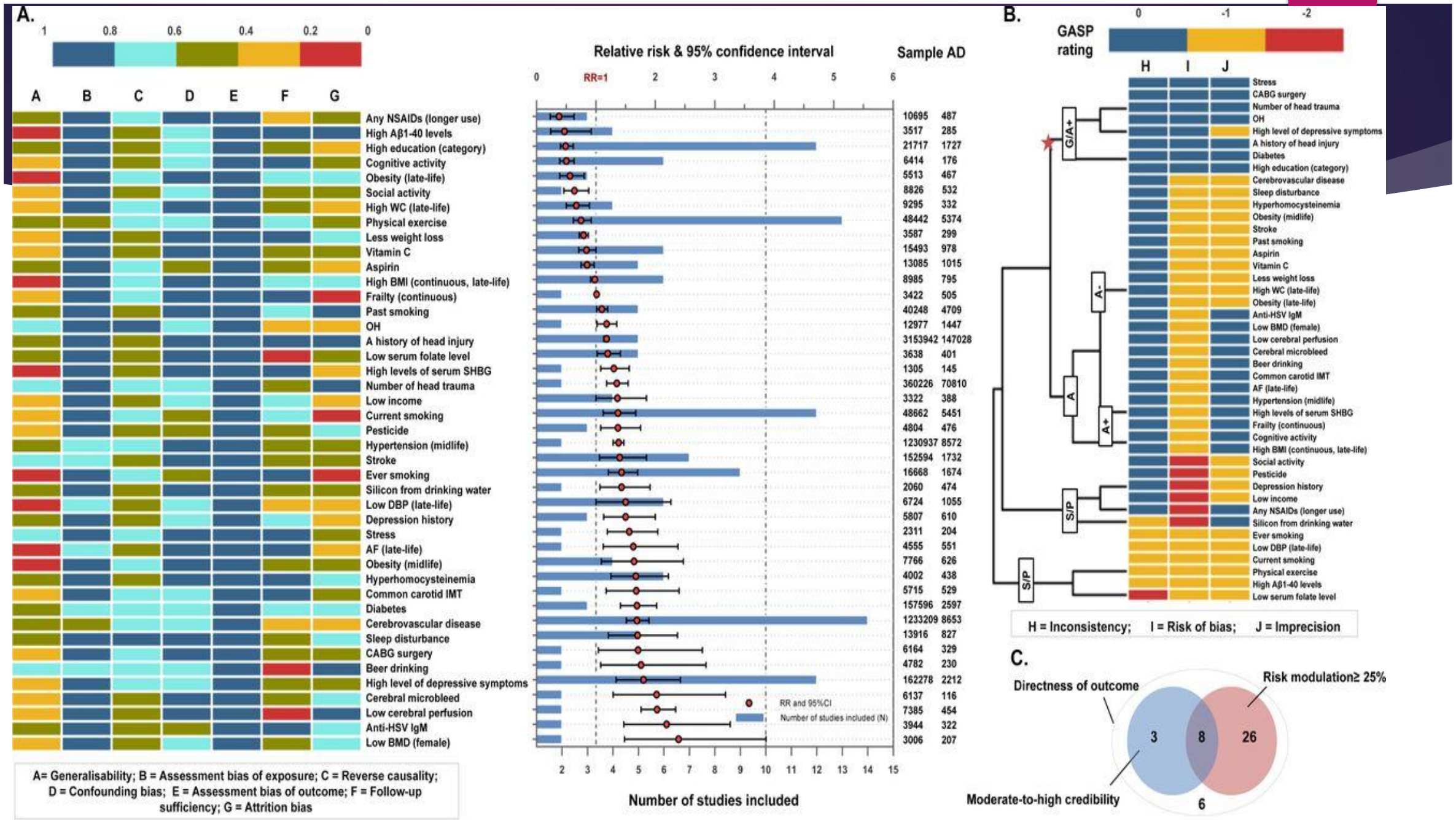
Class (STRENGTH) of suggestions

- Meta-analyses were conducted for 134 risk factors.
- A total of 43 factors showed significant associations with the risk of AD,
- Among which 80% were identified as significantly modifying the risk by at least 25%

- Eight risk factors (diabetes, orthostatic hypotension, hypertension in midlife, head trauma, stress, depression, midlife obesity and coronary artery bypass grafting (CABG) surgery)

- three protective factors (cognitive activity, increased BMI in late life and education) were rated with moderate-to- high level credibility

- 20 factors were rated at a low-to- moderate level and 12 were rated at a very low level


A.
1 0.8 0.6 0.4 0.2 0
A B C D E F G
Any NSAIDs (longer use)
High Aβ1-40 levels
High education (category)
Cognitive activity
Obesity (late-life)
Social activity
High WC (late-life)
Physical exercise
Less weight loss
Vitamin C
Aspirin
High BMI (continuous, late-life)
Frailty (continuous)
Past smoking
OH
A history of head injury
Low serum folate level
High levels of serum SHBG
Number of head trauma
Low income
Current smoking
Pesticide
Hypertension (midlife)
Stroke
Ever smoking
Silicon from drinking water
Low DBP (late-life)
Depression history
Stress
AF (late-life)
Obesity (midlife)
Hyperhomocysteinemia
Common carotid IMT
Diabetes
Cerebrovascular disease
Sleep disturbance
CABG surgery
Beer drinking
High level of depressive symptoms
Cerebral microbleed
Low cerebral perfusion
Anti-HSV IgM
Low BMD (female)
A= Generalisability; B = Assessment bias of exposure; C = Reverse causality;
D = Confounding bias; E = Assessment bias of outcome; F = Follow-up
sufficiency; G = Attrition bias
Relative risk & 95% confidence interval
Sample AD
0 RR=1 2 3 4 5 6
10695 487
3517 285
21717 1727
6414 176
5513 467
8826 532
9295 332
48442 5374
3587 299
15493 978
13085 1015
8985 795
3422 505
40248 4709
12977 1447
3153942 147028
3638 401
1305 145
360226 70810
3322 388
48662 5451
4804 476
1230937 8572
152594 1732
16668 1674
2060 474
6724 1055
5807 610
2311 204
4555 551
7766 626
4002 438
5715 529
157596 2597
1233209 8653
13916 827
6164 329
4782 230
162278 2212
6137 116
7385 454
3944 322
3006 207
RR and 95%CI
Number of studies included (N)
2 3 4 5 6 7 8 9 10 11 12 13 14 15
Number of studies included
B.
GASP rating
0 -1 -2
H I J
Stress
CABG surgery
Number of head trauma
OH
High level of depressive symptoms
A history of head injury
Diabetes
High education (category)
Cerebrovascular disease
Sleep disturbance
Hyperhomocysteinemia
Obesity (midlife)
Stroke
Past smoking
Aspirin
Vitamin C
Less weight loss
High WC (late-life)
Obesity (late-life)
Anti-HSV IgM
Low BMD (female)
Low cerebral perfusion
Cerebral microbleed
Beer drinking
Common carotid IMT
AF (late-life)
Hypertension (midlife)
High levels of serum SHBG
Frailty (continuous)
Cognitive activity
High BMI (continuous, late-life)
Social activity
Pesticide
Depression history
Low income
Any NSAIDs (longer use)
Silicon from drinking water
Ever smoking
Low DBP (late-life)
Current smoking
Physical exercise
High Aβ1-40 levels
Low serum folate level
G/A+
A-
A
A+
S/P
S/P
H = Inconsistency; I = Risk of bias; J = Imprecision
C.
Directness of outcome
Risk modulation≥ 25%
3
8
26
6
Moderate-to-high credibility

- RCTs: 29 meta-analyses covering 11 interventions were conducted.

- Three interventions, including total homocysteine (tHcy)-lowering treatment (using folic acid, vitamin B12 and vitamin B6), cocoa flavanol and physical activity showed significant associations with AD or cognitive endpoints.

- Only five meta-analyses (involving acetylcholinesterase inhibitor, antihypertensive treatment, non-steroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy and ginkgo biloba) examined associations with AD

Class I suggestions were for 19 factors:

- 10 factors with Level A evidence (cognitive activity, hyperhomocysteinaemia, increased BMI in late life, depression, stress, diabetes, head trauma, hypertension in midlife, orthostatic hypotension and education)
- Nine factors with Level B evidence (obesity in midlife, weight loss in late life, physical exercise, smoking, sleep, CVD, frailty, atrial fibrillation and vitamin C)

- Two factors were not recommended (Class III): oestrogen replacement therapy (Level A) and acetylcholinesterase inhibitors (Level B)
- Six factors (diastolic blood pressure management, NSAID use, social activity, osteoporosis, pesticide exposure and silicon from drinking water) were rated as Level C low-strength evidence, with the recommendation that their relationships with AD be confirmed in future studies

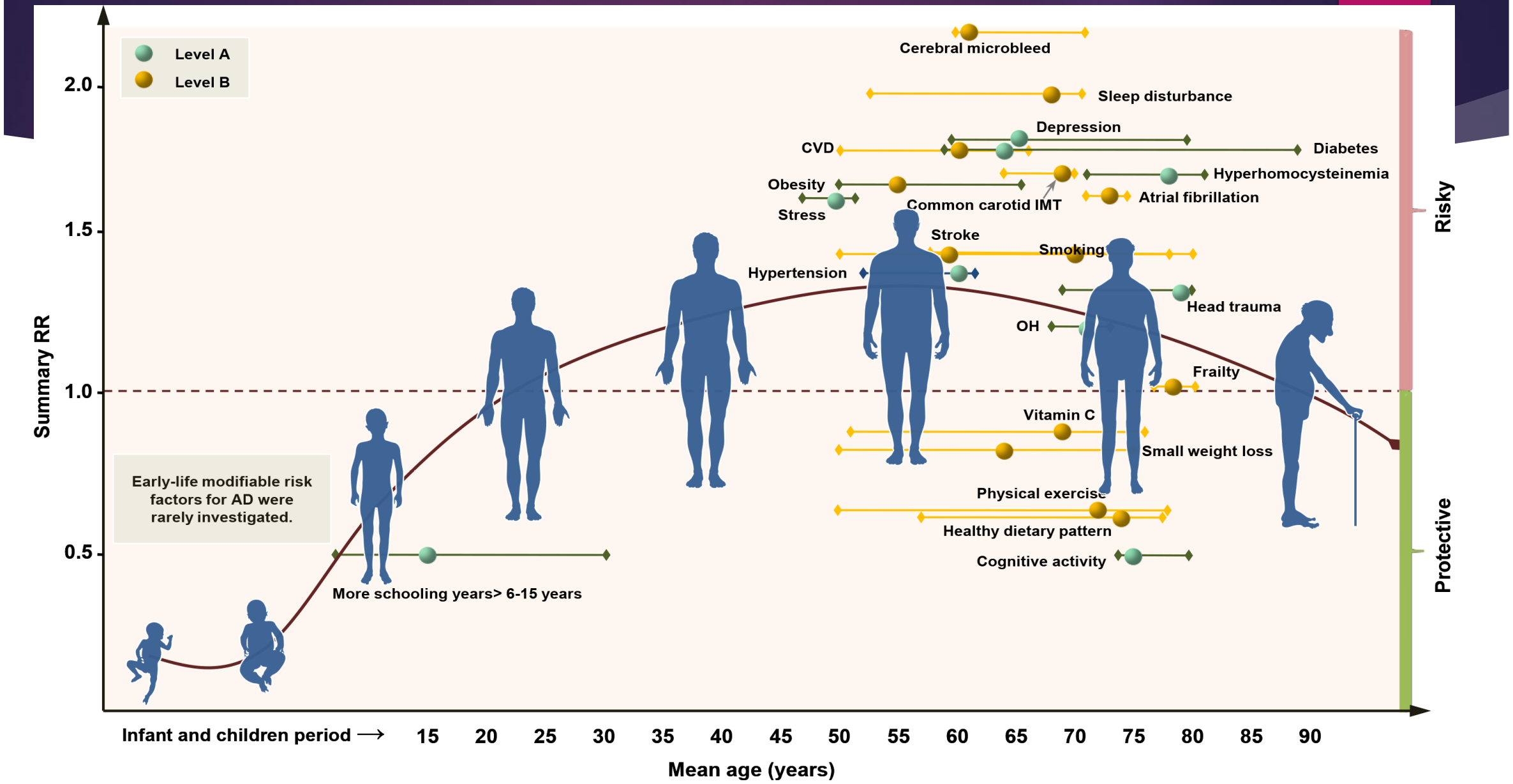
Table 1 Guideline for prevention of AD: preliminary clinical suggestions*

Factors/interventions	Suggestion
Lifestyle	
BMI and weight management	► Adults aged <65 years should maintain or lose weight through an appropriate balance of physical activity, caloric intake and formal behavioural programmes when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2 (*Class I, level B*) ► Adults aged >65 years should not to be too skinny (*Class I, level A4*) ► Adults aged >65 years with a trend of weight loss should be closely monitored for their cognitive status (*Class I, Level B*)
Physical exercise	► Individuals, especially those aged ≥65 years, should stick to regular physical exercise (*Class I, Level B**)
Cognitive activity	► Mentally stimulating activities should be encouraged, such as reading, playing chess, etc (*Class I, Level A4*)
Smoking	► People should not smoke and should avoid environmental tobacco smoke. Ccounselling, nicotine replacement and other pharmacotherapy as indicated should be provided in conjunction with a behavioural programme or formal smoking cessation programme (*Class I, Level B*)
Sleep	► Get sufficient and good quality sleep and consult a doctor or receive treatment when you have problem with sleep (*Class I, Level B*)
Comorbidities	
Diabetes	► Stay away from diabetes via a healthier lifestyle and diabetic patients should be closely monitored for their cognitive decline (*Class I, Level A4*)
CVD	► Maintain a good condition of the cerebral vessels via a healthier lifestyle or medications to avoid atherosclerosis, low cerebral perfusion and any CVD. Individuals with stroke, especially cerebral microbleeding, should be carefully monitored for their cognitive change and take preventative measures as indicated to protect cognition (*Class I, level B*)
Head trauma	► Protect your head from injuries (*Class I, level A4*)
Frailty	► Stay healthy and strong in late life. Those with increasing frailty should be especially monitored for their cognition (*Class I, Level B*)
Blood pressure	► Individuals aged < 65 years should avoid hypertension via a healthier lifestyle (*Class I, Level A4*) ► Individuals with OH should be closely monitored for their cognition (*Class I, Level A4*)
Depression	► Maintain a good condition of mental health and closely keep an eye on the cognitive status for those with depressive symptoms (*Class I, Level A4*)
AF	► Maintain a good cardiovascular condition and manage AF using pharmaceuticals (*Class I, level B*)
Stress	► Relax your mind and avoid daily stress (*Class I, Level A4*)
Other domains	
Education	► Receive as much education as possible in early life (*Class I, level A4*)
Hyperhomocysteinaemia	► Have a regular blood examination for homocysteine level. Individuals with hyperhomocysteinaemia should be treated with vitamin B and/or folic acid and be followed with a focus on their cognition (*Class I, Level A2*)
Vitamin C	► Vitamin C in the diet or taken as supplements might help (*Class I, Level B*)
Not recommended	
ERT	► Oestrogen replacement therapy should not be specifically used for AD prevention in postmenopausal women (*Class III, Level A2*)
ACI	► ACI should not be used for AD prevention in cognitively impaired individuals (*Class III, Level B*)

Table 1 Guideline for prevention of AD: preliminary clinical suggestions*

Factors/interventions	Suggestion
Lifestyle	
BMI and weight management	▶ Adults aged <65 years should maintain or lose weight through an appropriate balance of physical activity, caloric intake and formal behavioural programmes when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2 (*Class I, level B*) ▶ Adults aged >65 years should not to be too skinny (*Class I, level A4*) ▶ Adults aged >65 years with a trend of weight loss should be closely monitored for their cognitive status (*Class I, Level B*)
Physical exercise	▶ Individuals, especially those aged ≥65 years, should stick to regular physical exercise (*Class I, Level B**)
Cognitive activity	▶ Mentally stimulating activities should be encouraged, such as reading, playing chess, etc (*Class I, Level A4*)
Smoking	▶ People should not smoke and should avoid environmental tobacco smoke. Ccounselling, nicotine replacement and other pharmacotherapy as indicated should be provided in conjunction with a behavioural programme or formal smoking cessation programme (*Class I, Level B*)
Sleep	▶ Get sufficient and good quality sleep and consult a doctor or receive treatment when you have problem with sleep (*Class I, Level B*)
Comorbidities	
Diabetes	▶ Stay away from diabetes via a healthier lifestyle and diabetic patients should be closely monitored for their cognitive decline (*Class I, Level A4*)
CVD	▶ Maintain a good condition of the cerebral vessels via a healthier lifestyle or medications to avoid atherosclerosis, low cerebral perfusion and any CVD. Individuals with stroke, especially cerebral microbleeding, should be carefully monitored for their cognitive change and take preventative measures as indicated to protect cognition (*Class I, level B*)
Head trauma	▶ Protect your head from injuries (*Class I, level A4*)
Frailty	▶ Stay healthy and strong in late life. Those with increasing frailty should be especially monitored for their cognition (*Class I, Level B*)

Blood pressure	▶ Individuals aged < 65 years should avoid hypertension via a healthier lifestyle (*Class I, Level A4*) ▶ Individuals with OH should be closely monitored for their cognition (*Class I, Level A4*)
Depression	▶ Maintain a good condition of mental health and closely keep an eye on the cognitive status for those with depressive symptoms (*Class I, Level A4*)
AF	▶ Maintain a good cardiovascular condition and manage AF using pharmaceuticals (*Class I, level B*)
Stress	▶ Relax your mind and avoid daily stress (*Class I, Level A4*)
Other domains	
Education	▶ Receive as much education as possible in early life (*Class I, level A4*)
Hyperhomocysteinaemia	▶ Have a regular blood examination for homocysteine level. Individuals with hyperhomocysteinaemia should be treated with vitamin B and/or folic acid and be followed with a focus on their cognition (*Class I, Level A2*)
Vitamin C	▶ Vitamin C in the diet or taken as supplements might help (*Class I, Level B*)
Not recommended	
ERT	▶ Oestrogen replacement therapy should not be specifically used for AD prevention in postmenopausal women (*Class III, Level A2*)
ACI	▶ ACI should not be used for AD prevention in cognitively impaired individuals (*Class III, Level B*)


Level A
Level B
2.0
1.5
1.0
0.5
Summary RR
Early-life modifiable risk factors for AD were rarely investigated.
More schooling years> 6-15 years
Cerebral microbleed
Sleep disturbance
Depression
CVD
Diabetes
Hyperhomocysteinemia
Obesity
Common carotid IMT
Atrial fibrillation
Stress
Stroke
Smoking
Hypertension
Head trauma
OH
Frailty
Vitamin C
Small weight loss
Physical exercise
Healthy dietary pattern
Cognitive activity
Risky
Protective
Infant and children period ⟶
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
Mean age (years)

Strengths and weaknesses of this study

The hypotheses for the underlying mechanisms

- brain reserve theory,
- the hypoperfusion hypothesis,
- one-carbon methabolism,
- hypomethylation theory,
- inflammation and the oxidative stress hypothesis.

- The combination of multiple recommendations is most likely the best approach to delay the onset of AD, as indicated by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER).

Future Research

- cognitive activity and stroke
- follow-up insufficiency (stroke and smoking)
- Well- designed clinical trials are needed to verify the effects on AD of several promising interventions, including sleep improvement, smoking cessation, antidepression management and antidiabetic
- RCT