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INVITED REVIEW

Primary prevention of dementia: from modifiable risk factors to a public brain health agenda?

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Abstract

Introduction With large numbers of people affected, no treatment in sight and continuing demographic change, the prevention of dementia is becoming a central public health issue.

Methods We conducted a systematic meta-review including systematic reviews and meta-analyses of longitudinal observational studies on modifiable risk and protective factors for dementia published over the last 5 years.

Results Compelling evidence on a number of modifiable risk factors, mostly lifestyle factors, is available from longitudinal observational studies to inform primary preventive efforts.

Discussion Evidence stemming from preventive RCTs is limited. However, multi-domain interventions addressing a variety of risk factors at once seem promising with regard to high-risk individuals (selective preventive approach). However, we argue that it is time to move forward and discuss a public brain health agenda as a universal preventive approach. Based on a risk reduction strategy, the public brain health agenda suggests the following ten key actions: (1) increase physical activity, (2) foster social integration, (3) improve education and foster lifelong learning, (4) provide mentally stimulating workplaces, (5) foster a cognitively active lifestyle, (6) propose a healthy Mediterranean-like diet, (7) reduce alcohol consumption, (8) stop smoking, (9) prevent, diagnose and treat chronic conditions, and (10) reduce anticholinergic medication in the elderly.

Keywords Dementia · Risk factors · Systematic review · Brain health agenda · Prevention

Introduction

According to the WHO, around 50 million people worldwide are affected by dementia [1]. The neurodegenerative disease causes progressive damage related to memory and recognition, spatial and temporal orientation and communication. It induces behavioral changes such as aggressive behaviors and results in increased needs for care. Dementia has a strong impact on the lives of those affected and their caring relatives [2–4], and results in a global burden on societies of an estimated 818 billion USD as of 2015 [5]. While Alzheimer's Disease (AD) is seen as the most common form of dementia, most people in old age suffer from mixed forms of dementia [6].

While dementia was previously understood as a disease of the elderly, a life span perspective now increasingly prevails. Today it is well known that AD starts decades before diagnosis [7]. The fact that there is currently no cure for dementia and only limited progress in new treatments has paved way for a new focus on the preservation of cognition and the prevention of dementia. Based on more recent findings of large cohort studies in the Western world on dementia and cognitive disorders which report higher prevalence and incidence rates for earlier cohorts [8–11], the focus on influential lifestyle factors impacting brain health at the population level has gained momentum. This has facilitated research on modifiable risk factors over the life span. The current paper provides an overview on well-established modifiable risk factors for dementia and discusses the implications for a public brain health agenda.

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Methods

We conducted a systematic literature search on dementia risk factors in Medline via the PubMed interface following PRISMA guidelines [12]. The search included English systematic reviews and meta-analyses published in the 5 years before 11 May 2018. Risk factors were searched separately using the following search strings: (review OR meta-analysis) AND (dementia OR alzheimer OR cognitive decline OR cognitive impairment) AND (sport OR exercise OR physical activity OR physical inactivity)/(social activities OR social network OR social support OR social interaction OR social participation OR social isolation OR loneliness)/(education OR mental demand OR mental stimulation OR cognitive demand OR cognitive stimulation OR cognitively AND active)/(nutrition OR diet OR nutrient OR dietary supplement OR mediterranean OR food)/(alcohol)/(smoking OR smoke OR tobacco)/(blood pressure OR hypertension)/(diabetes)/(adiposity OR obesity OR overweight)/(depression OR depressive)/(hearing loss OR hearing impairment OR hearing)/(craniocerebral injury OR cci OR concussion OR brain injury OR brain trauma)/(anticholinergic medication OR anticholinergic OR anticholinergics).

We assessed literature in two steps. In the first step, titles and abstracts of all identified articles were screened, and in the second step the remaining full texts were assessed. The basis for assessment was our predefined list of criteria which included all systematic reviews and meta-analyses with populations above 18 years and all forms of dementia. We excluded articles that solely focused on cognitive impairments or included other disorders like Parkinson`s Disease.

Results

Physical activity

There is a strong evidence base suggesting that physical activity has a protective effect against dementia [13–15] and against AD in particular [15–17]. Moreover, Guure et al. [18] found protective effects of physical activity for all-cause dementia (ACD) and AD, but not for vascular dementia (VaD), and Stephen et al. [17] found a protective effect of leisure time physical activity against AD. Results strongly support the idea that regular physical activity throughout the life course is protective against dementia while physical inactivity poses a risk factor. While it is generally assumed that more physical activity is connected to stronger effects, it remains unclear which activities undertaken at which intensity, duration and frequency are most protective against dementia [5, 19]. There is evidence that even minor physical activity, compared to none, is connected to lower dementia risk [20], suggesting that every step counts.

Social activities

Humans are social beings and social activities contribute to protecting cognitive functioning and reducing dementia risk. One recent meta-analysis addressed the role of social interactions as a protective factor against dementia [21]. Kuiper et al. [21] show that low social participation as well as less-frequent contact and social isolation in later life increase dementia risk. The roles of network size and satisfaction with one's social network are less clear.

Education, mental demands at the workplace and a cognitively active lifestyle

A large body of literature showed that low *education* is linked to increased dementia risk. Two recent meta-analyses demonstrate the protective effect of education against AD [16] and dementia [22]. Focusing on a potential dose–response relationship, Xu et al. [22] showed a 7% reduction in dementia risk for every additional year of education (RR 0.93, 95% CI 0.92–0.94; $p = 0.000$). Results implicate that cognitive activity, starting at a very early age, is a protective factor. This is consistent with the notion that once established, a cognitive reserve may then act as a buffer against age-related impairments [23].

The majority of the population spends a great amount of their time at the *workplace*. Therefore, work has a strong influence on the quantity and quality of daily cognitive activities. However, this field remains under-researched to date. One review reported evidence for a protective effect of high job control and work complexity, relating to people and data, against cognitive decline and dementia [24]. Further studies point to the relevance of mentally stimulating workplaces for brain health [25].

While education mostly takes place in childhood and young adolescence, a cognitively active lifestyle (e.g. with regard to leisure activities) is also important in midlife and beyond. Yates et al. [26] conducted a series of meta-analyses on this topic. Four out of five meta-analyses showed significant associations between participation in *cognitively demanding leisure activities* and reduced risk of cognitive impairment and dementia. The studies refer to a diverse set of activities with typical elements being reading, playing games (e.g. chess or card games), crossword puzzles and sometimes theater or artistic activities.

Diet

What we eat and drink has an impact on our health and wellbeing. With regard to dementia prevention, the so-called Mediterranean Diet (MeDi), a specific *dietary pattern*, is at the center of research interest. The MeDi is a balanced diet rich in fibers and fresh vegetables with unsaturated fats (olive oil), fish and little red meat. Recent meta-analyses show a consistent pattern of protective associations between a MeDi and AD [27] or dementia [28–30].

Furthermore, different *dietary components* were investigated in the identified meta-analyses. Results suggest a protective effect of unsaturated fats [14, 27], antioxidants and vitamin B [27], vitamins E and C, flavonoids, niacin and folate [28] as well as positive effects of coffee and tea [31]. Detrimental effects were reported for saturated fats [32] and low vitamin D. More research in this field is needed.

Alcohol and smoking

Excessive drinking increases dementia risk [33]. Nevertheless, there is evidence that mild consumption of alcohol may be protective against dementia [28, 33]. More research is needed to understand the non-linear, potentially J-shaped relationship between alcohol intake and dementia risk. Also, it is clear that excessive *alcohol consumption* is linked to multiple negative outcomes including addiction as well as specific forms of alcohol-related dementias [34].

Smoking bears a variety of serious health risks. A large evidence base suggests that smoking is also risk factor for dementia [14, 28] as well as for ACD, AD and VaD specifically [16, 27, 35]. Zhong et al. [35] suggest that dementia risk for former smokers reverts to approximately the same as for non-smokers. Although not yet firmly established, there may also be a link between passive smoking and risk for cognitive impairment or dementia [36].

(Treatable) chronic conditions as risk constellations for dementia

There are a number of, mainly chronic, disorders related to dementia risk, and their combination may even intensify the detrimental effects. *Hypertension* is a risk factor for dementia, especially when experienced during midlife [14], and antihypertensive treatment can reduce the risk for ACD [37] as well as AD and VaD [38]. In addition, diuretics were associated with reduced risk for dementia and AD [39]. Evidence suggests that *diabetes*, especially type 2 diabetes T2D, is a strong risk factor for dementia [14, 40], AD [41], VaD and non-VaD [40], and there is evidence that insulin sensitizers are connected to reduced dementia risk [42]. *Obesity* is common, and all reviewed meta-analyses [43, 44] and reviews [14, 45] show a clear connection between midlife obesity and dementia. More recently, the role of peripheral *hearing loss* as a common risk factor for dementia and AD was highlighted [6], but associations are inconsistent [46]. Whether this effect is mediated via impairment-related withdrawal from social interactions or could rather be conceptualized as a prodromal symptom remains unclear. Furthermore, *depression* is a well-known risk factor for dementia [14], ACD, AD and VaD [47]. As is the case with hearing impairment, depression, particularly later in life, could also be a prodrome of dementia [48].

Further risk factors and emerging fields for prevention

Traumatic brain injury (TBI) is primarily a consequence of traffic-related accidents and falls; however, sports injuries and indirect forces such as shock waves from battlefield explosions may also cause it. TBI is related to AD-risk [49, 50].

Although we did not identify any reviews or meta-analyses, there are reports on *anticholinergic drug use* and increased dementia risk in elderly individuals [51, 52]. This is important because a substantial proportion of the elderly uses anticholinergic drugs which are prescribed for various indications related to neurology, psychiatry and internal medicine. Table 1 gives an overview on systematic reviews and meta-analyses of dementia risk and protective factors.

Discussion

Compelling evidence from research synthesis of longitudinal observational studies

This meta-review is based on systematic reviews and meta-analyses of a large body of longitudinal observational studies. Results provide evidence for the protective effect of typical lifestyle factors such as physical activity, social interactions and a cognitively active lifestyle, as well as the Mediterranean Diet and non-smoking. There is also emerging evidence that mental demands at work matter. Heavy drinking is clearly risky, especially for brain health. We highlighted a number of potentially treatable chronic conditions which are clearly associated with increased dementia risk such as hypertension, type 2 diabetes, obesity and depression. Although the evidence base regarding the negative effects of hearing loss is still small, it clearly shows preventive potential. In addition, TBI is a risk factor for developing dementia. More research is needed on anticholinergic drug use.

For most of the mentioned associations, strength, consistency, temporality, plausibility and a dose–response relationship are established [53]. Information on plausibility comes

Table 1 Systematic reviews and meta-analyses of dementia risk and protective factors

Domain	Reference	MA	Search end date	Number of studies SR/MA	Outcome	Key findings
Physical activity	Beydoun et al. [16]	+	10/2012	28/8	AD	Protective effect of PA (pooled RR 0.58, 95% CI 0.49–0.70). Estimated PAR% of PA: 31.9 (95% CI 22.7–41.2)
	Blondell et al. [13]	+	12/2013	37/21	Dementia	Protective effect of higher vs. lower levels of PA (RR 0.86, 95% CI 0.76–0.97). After removal of one heavily weighted study, the effect of PA increased (RR 0.82; 95% CI 0.73–0.91)
	Deckers et al. [14]	–	12/2012	7/–	Dementia/cognitive decline	Reviewing abstracts with regard to PA and dementia/cognitive decline, the authors report: studies 7; higher risk/decline 5; lower risk/decline 0; no association 2; consistency of association 71%
	Guure et al. [18]	+	4/2016	–/45	ACD, AD, VaD	Protective effect of PA against ACD (OR 0.79, 95% CI 0.69–0.88) and AD (OR 0.62, 95% CI 0.49–0.75), but not on VaD (OR 0.92, 95% CI 0.62–1.30)
	Reiner et al. [15]	–	5/2012	6/–	Dementia/AD	PA was negatively related to the incidence of AD and dementia in healthy men and women
	Stephen et al. [17]	–	6/2015	24/–	AD	Leisure-time PA was protective against AD, but not work-related PA
Social activities	Kuiper et al. [21]	+	7/2012	19/5 size, 6 participation, 8 frequency, 3 loneliness, 4 satisfaction	Dementia	Low social participation (RR 1.41, 95% CI 1.13–1.75), less-frequent social contact (RR 1.57, 95% CI 1.32–1.85) and more loneliness (RR 1.58, 95% CI 1.19–2.09) were connected to a higher risk of incidence dementia, while associations between network size and dementia were inconsistent. There was no statistically significant effect of low network satisfaction on the onset of dementia (RR 1.25, 95% CI 0.96–1.62)
Education, mental demands at the workplace and a cognitively active lifestyle	Beydoun et al. [16]	+	10/2012	28/4	AD	Less than 8 years of education increased the risk of AD (pooled RR 1.99, 95% CI 1.30–3.04)
	Then et al. [24]	–	3/2011	9/–	Dementia	There was a protective effect of high job control and high work complexity with people/data against dementia
	Xu et al. [22]	+	11/2014	24/16	Dementia	Every year of education reduced dementia risk by 7% (RR 0.93; 95% CI 0.92–0.94). There was no statistically significant association between per year decrease in education and dementia (RR 1.03, 95% CI 0.96–1.10) or AD (RR 1.03, 95% CI 0.97–1.10). Low and high education showed a trend towards a dose–response relationship with risk of dementia and AD
	Yates et al. [26]	+	3/2014	19/7	Dementia	There was a significant association between participation in cognitive leisure activities and dementia risk (RR 0.61, 95% CI 0.42–0.90)

Table 1 (continued)

Domain	Reference	MA	Search end date	Number of studies SR/MA	Outcome	Key findings
Diet	Barnard et al. [32]	–	7/2012	4/–	Dementia/AD	In 3 of 4 studies, consumption of saturated fat was positively associated with AD-risk; the fourth suggested an inverse relationship. Saturated fat intake was positively associated with dementia in 1 of 2 studies
	Cao et al. [27]	+	9/2014	43/–	ACD/AD	The intake of unsaturated fatty acids (RR 0.84, 95% CI 0.74–0.95), antioxidants (RR 0.87, 95% CI 0.77–0.98), vitamin B (RR 0.72, 95% CI 0.54–0.96) and MeDi (RR 0.69, 95% CI 0.57–0.84) were related to a decrease of dementia, while low levels of vitamin D were associated with an increase in dementia (RR 1.52, 95% CI 1.17–1.98). Further investigation is needed with regard to the effects of fish (RR 0.79, 95% CI 0.59–1.06) and vegetables and fruits (RR 0.46, 95% CI 0.16–1.32)
	Deckers et al. [14]	–	12/2012	5/–	Dementia/cognitive decline	Reviewing abstracts with regard to high unsaturated fat intake and dementia/cognitive decline, the authors report: studies 5; higher risk/decline 1; lower risk/decline 4; no association 0; consistency of association 80%
	Di Marco et al. [28]	–	12/2013	26/–	Dementia	Authors find protective effects but also a lack of associations between dementia and vitamins E and C, flavonoids, niacin and folate as well as contradicting results for different fats. Evidence is in favor for MeDi and fish, but some studies show no association. Single studies report a protective effect of specific minerals—potassium, calcium and magnesium—and vegetables and fruits against ACD
	Lourida et al. [29]	–	1/2012	12/–	Dementia	Higher adherence to MeDi was associated with reduced risk of AD in 9 out of 12 studies
	Panza et al. [31]	–	1/2014	10/–	Dementia/AD	While some studies with brief follow-up periods indicated positive effects of coffee, tea and caffeine consumption against AD, some studies with baseline examination in midlife pointed to a lack of association
	Singh et al. [30]	+	11/2012	5/5	AD	Among cognitively healthy individuals, higher adherence to MeDi was associated with a reduced risk of AD (HR 0.64, 95% CI 0.46–0.89)
Alcohol	Cao et al. [27]	+	9/2014	43/–	ACD/AD	Further investigation is needed on the effects of alcohol (RR 0.74, 95% CI 0.55–1.01)
	Di Marco et al. [28]	–	12/2013	13/–	Dementia	Most studies suggest a protective effect of mild-to-moderate drinking, wine seems to be particularly protective
	Xu et al. [33]	+	10/2016	ACD: 11/10 AD: 5/4 VaD: 4/4	Dementia	Modest alcohol consumption ($\leq$12.5 g/day) is associated with reduced dementia risk—with the lowest risk at around 6 g/day, while excessive drinking ($\geq$38 g/day) may have the opposite effect. There was a nonlinear association between alcohol consumption and ACD-risk. The ACD-risk seemed to be elevated (around 10%) when the dose exceeded 23 drinks/week or 38 g/day. With regard to alcohol type, wine was seen as the most beneficial. The effect of alcohol may be greater in adults younger the 60 years

Table 1 (continued)

Domain	Reference	MA	Search end date	Number of studies SR/MA	Outcome	Key findings
Smoking	Beydoun et al. [16]	+	10/2012	36/9	AD	Current and previous smokers exhibited an increased risk for AD (RR 1.37, 95% CI 1.23–1.52). Estimated PAR%: 31.09 (95% CI 17.9–44.3)
	Cao et al. [27]	+	9/2014	43/–	ACD/AD	Smoking was related to an increase of dementia risk (RR 1.43, 95% CI 1.15–1.77)
	Deckers et al. [14]	–	12/2012	13/–	Dementia/cognitive decline	Reviewing abstracts with regard to smoking and dementia/cognitive decline, the authors report: studies 13; higher risk/decline 10; lower risk/decline 1; no association 2; consistency of association 77%
	Di Marco et al. [28]	–	12/2013	13/–	Dementia	The majority of studies find smoking to be a risk factor for dementia, while some research suggests that the risk of former smokers that quit is similar to that of non-smokers
	Zhong et al. [35]	+	3/2014	ACD: 27/27 AD: 22/22 VaD: 8/8	ACD/AD/VaD	Comparing current smokers with never-smokers, the authors find increased risks for ACD (RR 1.30, 95% CI 1.18–1.45), AD (RR 1.40, 95% CI 1.13–1.73) and VaD (RR 1.38, 95% CI 1.15–1.66). ACD-risk increased by 34% for every 20 cigarettes per day (RR 1.34, 95% CI 1.25–1.43). Former smokers did not show an increased risk of ACD (RR 1.01, 95% CI 0.96–1.06), AD (RR 1.04, 95% CI 0.96–1.13) or VaD (RR 0.97, 95% CI 0.83–1.13) Furthermore, significantly increased AD-risk from current smoking was seen only in apolipoprotein E ε4 non-carriers, and current smokers aged 65–75 years at baseline showed increased risk of ACD and AD compared to those aged younger or older
Hypertension	Deckers et al. [14]	–	12/2012	21/–	Dementia/cognitive decline	Reviewing abstracts with regard to hypertension (all/midlife/late life) and dementia/cognitive decline, the authors report: number of studies 21/8/16; higher risk/decline 16/7/12; lower risk/decline 2/0/2; no association 3/1/2; consistency of association 76/88/75%
	Levi Marpillat, et al. [37]	+	9/2010	11/11	Dementia	Antihypertensive treatment reduced the risk of ACD by 9% (HR 0.91, 95% CI 0.89–0.94)
	Rouch et al. [38]	–	3/2014	38/–	Dementia	Only 3 of 11 longitudinal studies did not find a significant protective effect of antihypertensive medication on incidence dementia. Medication could decrease the risk of AD and VaD. Two RCTs, SYST-EUR I and II, showed a 55% reduction in dementia risk due to antihypertensive medication (3.3 vs. 7.4 cases per 1000 patient years). Meta-analyses have sometimes produced conflicting results
	Tully et al. [39]	+	6/2015	15/15	Dementia	Diuretics were associated with reduced risk for dementia (HR 0.83, 95% CI 0.76–0.91) and AD (HR 0.82, 95% CI 0.71–0.94)

Table 1 (continued)

Domain	Reference	MA	Search end date	Number of studies SR/MA	Outcome	Key findings
Diabetes	Chatterjee et al. [40]	+	11/2014	Dementia: –/14 VaD: –/10 Non-VaD: –/11	Dementia/VaD/non-VaD	For women, diabetes was associated with increased risk of any dementia (pooled RR 1.62, 95% CI 1.45–1.80), VaD (RR 2.34, 95% CI 1.86–2.94) and non-vascular dementia (RR 1.53, 95% CI 1.35–1.73). For men, diabetes was connected to increased risk for any dementia (pooled RR 1.58, 95% CI 1.38–1.81), VaD (RR 1.73, 95% CI 1.61–1.85) and non-vascular dementia (RR 1.49, 95% CI 1.31–1.69). Overall, women with diabetes had a 19% greater risk for the development of VaD (multiple-adjusted RRR 1.19, 95% CI 1.08–1.30)
	Deckers et al. [14]	–	12/2012	19/–	Dementia/cognitive decline	Reviewing abstracts with regard to diabetes and dementia/cognitive decline, the authors report: number of studies 19; higher risk/decline 17; lower risk/decline 0; no association 2; consistency of association 89%
	Ye et al. [42]	+	12/2015	6/6	Dementia/AD	Insulin sensitizers were connected to reduced dementia risk (RR 0.78, 95% CI 0.64–0.95), $p = 0.015$
	Zhang et al. [41]	+	5/2016	17/17	AD	Diabetes increased AD-risk (RR 1.53, 95% CI 1.42–1.63). Risks were different in Western (RR 1.36, 1.18–1.53) vs. Eastern (RR 1.62, 1.49–1.75) populations
Adiposity	Albanese et al. [43]	+	10/2016	30/19	Dementia	Midlife obesity (BMI ≥ 30) increased dementia risk (RR 1.33, 95% CI 1.08–1.63), but not overweight (25 < BMI < 30) (RR 1.07, 95% CI 0.96–1.20)
	Deckers et al. [14]	–	12/2012	14/–	Dementia/cognitive decline	Reviewing abstracts with regard to obesity (all/midlife/late life) and dementia/cognitive decline, the authors report: studies 14/6/8; higher risk/decline 7/4/3; lower risk/decline 2/0/2; no association 5/2/3; consistency of association 50/67/38%
	Emmerzaal et al. [45]	–	12/2013	28/–	Dementia	Generally, there was an increased risk among adults that were overweight and obese during midlife, while elevated BMI was associated with lower risk in late life
	Pedditizi et al. [44]	+	9/2014	21/13	Dementia	Being obese below the age of 65 years was positively associated with dementia (RR 1.41, 95% CI 1.20–1.66), but not for those aged 65 and over (RR 0.83, 95% CI 0.74–0.94)
Depression	Cherbuin et al. [47]	+	2/2014	Total: –/36 ACD: –/28 AD: –/28 VaD: –/10	ACD/AD/VaD	The increased risk associated with depression did not significantly differ by type of dementia and ranged from 83 to 104%
	Deckers et al. [14]	–	12/2012	21/–	Dementia/cognitive decline	Reviewing abstracts with regard to depression and dementia/cognitive decline, the authors report: number of studies 21; higher risk/decline 19; lower risk/decline 0; no association 2; consistency of association 90%
Hearing impairment	Livingston et al. [6]	+	-	–/3	Dementia	Midlife hearing loss was associated with increased dementia risk (RR 1.9, 95% CI 1.38–2.73). Weighted PAF: 9.1%
	Zheng et al. [46]	+	1/2016	4/4	AD	Hearing impairment increased the risk of developing AD (RR 4.87, 95% CI 0.90–26.35)

Table 1 (continued)

Domain	Reference	MA	Search end date	Number of studies SR/MA	Outcome	Key findings
TBI	Julien et al. [49]	–	5/2016	18/–	AD	About 55.5% of TBI patients may show deteriorated condition, from cognitive deficits to then meeting diagnostic criteria for AD. Whether TBI is a risk factor for AD remains elusive
	Perry et al. [50]	+	2/2012	–/57	AD	There was a positive association between prior TBI and AD (OR 1.40, 95% CI 1.02–1.90)

MA meta-analysis, – not applicable/no information, *ACD* all-cause dementia, *AD* Alzheimer's disease, *VaD* vascular dementia, *TBI* traumatic brain injury, *PA* physical activity, *MeDi* Mediterranean diet, *OR* odds ratio, *PAF* population attributable fraction, *PAR%* population attributable risk percentage, *RR* relative risk

from research examining mechanisms underlying each of the associations. Three broad mechanisms are discussed: (1) the increase of cognitive reserve (e.g. via education or mental demands at work); (2) the reduction of brain inflammation (e.g. via MeDi); and (3) the reduction of brain damage from vascular, neurotoxic or oxidative stress (e.g. by quitting smoking or treating diabetes). Risk/protective factors can have an impact via one main mechanism (e.g. education increases cognitive reserve), or via more than one mechanism (e.g. physical activity) [6].

Findings from longitudinal observational population-based studies often investigating the lifestyle of individuals over decades in real life scenarios provide a solid foundation for proposing prevention strategies. That many of the risk factors are interrelated and potential effects need to be separated to avoid confounding is often cited as limitation for such studies. Confounding is usually dealt with by statistical adjustment; however, this approach could be incomplete and may become more difficult as the magnitude of risk factors becomes smaller. In addition, more research is needed to gain insight into the effects of interactions between factors that often co-occur (ExE), and between modifiable and non-modifiable risk factors (ExG). This is important because non-modifiable factors may to some extent have an impact on the effects of lifestyle factors. For example, the presence of apolipoprotein E ε4 may moderate the relationship between smoking and AD [35]. In a large German cohort study, Luck et al. [54] showed that physical activity even in late life reduced conversion to dementia and AD or in delays in the onset of clinical manifestations. Indices of interaction indicated no significant interaction between low physical activity and the APOE ε4 allele for general dementia risk, but a possible additive interaction for AD-risk. Although highly valuable, to mention each interaction is beyond the scope of this paper.

Limited results from randomized controlled prevention trials (RCTs)

Following the principles of evidence-based medicine [55, 56], it would be ideal to report evidence from randomized controlled trials (RCTs) for each risk or protective factor mentioned above. Evidence-based medicine classifies studies according to grades of evidence on the basis of the research design, using internal validity. The highest grade is reserved for RCTs and the lowest grade is applied to case series and expert opinion. Observational studies fall at intermediate levels [57]. Andrieu et al. [58] reviewed *single-domain lifestyle interventions* (RCTs) addressing individuals with or without risk factors for AD over the past three decades. In general, evidence was inconclusive, although several trials on physical activity, cognitive training, or antihypertensive interventions showed some evidence of efficacy. Small and

Table 2 Public brain health agenda: ten key actions and recommendations

Key action	Recommendation
Increase physical activity	Regular physical activity and exercise is recommended at all ages. An active lifestyle should be established from an early age and be integrated into daily living
Foster social integration	Social integration is key at any age. Especially in older individuals, the promotion of social interaction and the reduction of loneliness gain importance because they often experience losses on many levels (e.g. when leaving the workforce or the death of loved ones)
Improve education and foster lifelong learning	Provide and foster formal and informal learning throughout life, from pre-school to post-retirement, to promote the continuous development and improvement of knowledge and skills [78]. A comprehensive formal education is an important basis for continuing lifelong learning
Provide mentally stimulating workplaces	Promote mentally stimulating workplaces by increasing complexity, variety and autonomy, for example, via job enrichment or job enlargement
Promote a cognitively active lifestyle	Foster a cognitively active lifestyle throughout the life span, such as by facilitating mobility for older individuals to improve access to cultural events and institutions in remote areas
Mediterranean-like diet	A diet that is high in legumes, unrefined cereals, fruits, and vegetables with unsaturated fats (olive oil) and moderate to high consumption of fish, moderate consumption of dairy products (mostly as cheese and yogurt) and low consumption of meat products is recommended [79]
Reduce alcohol consumption	Considering the complex risk profile of alcohol, consumption should be reduced
Stop smoking	Prevent youth from starting smoking and support smokers that are willing to quit
Prevent, diagnose and treat chronic conditions	Facilitate prevention, diagnosis and treatment of hypertension, diabetes, depression, obesity and hearing loss. Increase awareness for the negative consequences related to brain health in the population and among health professionals
Reduce anticholinergic medication in the elderly	Anticholinergic medication should be used with caution in the elderly. Increase awareness for the negative consequences of these medications related to brain health in the population and among health professionals

selected samples, inappropriate timing of the intervention, short duration of intervention and follow-up were the most important shortcomings of these trials [59, 60]. It is important to keep in mind that in the last decade our perspective on timing in dementia has substantially changed. While dementia was previously viewed as a disease of old age, there has been a paradigm shift towards recognizing that the disease starts much earlier and has a long preclinical phase. This shift is also reflected in newer diagnostic criteria including milder forms of cognitive impairment, an additional focus on non-memory impairments and criteria related to biomarkers [7, 61–63]. Shifting diagnostic criteria towards earlier manifestations has an impact on how we think about prevention in terms of primary and secondary prevention [64]; it also clearly suggests a life span perspective. Furthermore, successfully tackling lifestyle changes in short-duration single-domain interventions is challenging, as lifestyle is usually rooted in a broader context and shows a certain degree of stability over longer time periods [65]. That said, the results from these short-duration single-domain interventions with limited follow-up periods are not surprising.

Based on these observations, the fact that multiple modifiable risk factors operate jointly and that there are age-dependent and combined effects of the risk factors (GxE, ExE), researchers have progressed to *multi-domain interventions* which address multiple risk factors at once in large groups of individuals with reasonable follow-up periods. The prototype for such studies is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability FINGER [66, 67]. This study investigated four intensive lifestyle-based strategies—diet, exercise, cognitive training, and vascular risk management—over 2 years in more than 1200 individuals aged 60–77 years who are at risk of dementia according to the CAIDE risk score. The intervention showed small but positive effects on cognition in high-risk individuals. However, it must be noted that small individual effects may have a substantial impact on brain health on the population level [68]. Similar interventions which were not initially targeted to high-risk groups have failed to show positive results [58, 69]. Multi-domain intervention trials making use of new technology such as the "Healthy Aging through Internet Counseling in Elderly" (HATICE) program are under way [70]. AgeWell.de, a recently initiated German multi-domain intervention study in high-risk individuals, is focused on the primary care setting. Although multi-domain interventions seem promising for selected prevention in high-risk individuals, questions remain regarding the dose needed to change behavior, the optimal timing of the intervention during the life course, target groups, modes of delivery, and implementation settings.

The classical research chain of identifying a single risk factor to proof from concept studies, and small and large

RCTs to broad implementation studies might not be the ideal framework for investigating lifestyle factors for brain health and the prevention of dementia. Immediately investigating multi-domain interventions in large RCTs seems promising in high-risk individuals, paving the way for selected primary intervention strategies. However, this line of research is still in its early phases.

Is it too early for a public brain health agenda?

The histories of epidemiology and public health have many examples of when pure observation informed successful preventive efforts. It started with John Snow, considered as one of the fathers of modern epidemiology. He identified a public water pump on Broad Street in London as the source of the cholera outbreak in 1854 and persuaded the local council to disable the pump by removing its handle. This has been credited as ending the outbreak. Many other examples followed. Similar to infectious diseases in former centuries, non-communicable diseases such as dementia are currently a huge challenge for health and social systems. Despite the limited evidence from prevention trials so far, we argue that it is time to discuss a public brain health agenda consisting of risk reduction strategies. Although these suggestions are mainly based on dementia risk factor knowledge from a large body of well-conducted longitudinal observational studies, this available knowledge can be used. Some protective factors such as education and lifelong learning cannot be investigated in trials, while other common constellations such as obesity reduction in midlife and late life dementia would require follow-up time-frames exceeding a researcher's life. The recently observed reduced incidence rates in later-born cohorts in some Western countries suggest that changes in risk factors drive dementia incidence and that risk reduction may have a substantial public health impact [8–11]. The changes in risk factors responsible for currently declining age-specific incidence rates in the western world may include improvements in living conditions, education and better healthcare, particularly an improved management of cardiovascular risk factors [71]. Furthermore, lifestyle recommendations such as promoting a physically active lifestyle, social integration and a healthy diet are safe and confer many additional health benefits. Considered together, the time seems right for the establishment of a public brain health agenda.

Multiple projections addressed the potential for the prevention of risk and estimated the brain health impact [72]. Norton et al. 2014 estimated the total impact of a set of risk factors—diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment—on the reduction of worldwide AD prevalence to be 28.2%, or 9.6 million attributable cases [72]. According to population projections, 30.5% of current AD cases in Germany (305,000 cases) could be attributable to the risk factors considered. Therefore, a 10–50% reduction of all seven risk factors could have potentially prevented 23,000–130,000 of the current AD cases in Germany [73].

Based on the results regarding risk and protective factors for dementia, we suggest corresponding key actions. Table 2 shows ten suggested key actions and recommendations for a brain health agenda: (1) increase physical activity, (2) foster social integration, (3) improve education and foster lifelong learning, (4) provide mentally stimulating workplaces, (5) foster a cognitively active lifestyle, (6) propose a healthy Mediterranean-like diet, (7) reduce alcohol consumption, (8) stop smoking, (9) prevent, diagnose and treat chronic conditions, (10) reduce anticholinergic medication in the elderly. In a further step, these key actions should be translated into more specific public health initiatives. For example, to promote physical activity, activities may range from fostering individual exercise programs to increasing school-based physical education and walkability promoting land-use policies [74]. Different initiatives could be systematically developed from social ecological models (SEMs) that describe the interactive characteristics of individuals and environments underlying health outcomes. SEMs recognize individuals as embedded within larger social systems and have long been recommended to guide public health practice. Based on earlier work, McLeroy et al. [75] offered five SEM levels specifically related to health behaviors: intrapersonal factors, interpersonal processes and primary groups, institutional factors, community factors and public policy [75–77]. Therefore, key actions should be further elaborated and broken down to initiatives related to each of the SEM levels. This will also shift attention from the individual to the importance of social and political environments to prevent dementia and improve brain health. Although the majority of key actions may read as individual actions associated with behavior change, one can think of various environmental changes to support such a public health agenda. For instance, increased walkability of cities and improved infrastructure for biking may contribute to more physical activity. Also, neighbourhood centres and multigenerational housing projects could support social integration. Additionally, measures to increase school education and free, online university courses can support lifelong learning, and subsidized access to cultural events may help facilitate a cognitively active lifestyle within vulnerable populations. Food labelling could help consumers to make healthier food choices. Furthermore, environmental changes could address the creation of cognitively stimulating workplaces and support mobility in old age. Returning to George Snow, he could have educated London residents not to drink the water from the pump on Broad Street to change individuals' behavior. We know, however, that he did

something more powerful: he tackled the environment and persuaded the local council to disable the pump.

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Compliance with ethical standards

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

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