

Towards Primary Prevention of Alzheimer's Disease

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Abstract

The incidence of Alzheimer's disease is predicted to rise as life expectation grows across populations. The cause of the disease is unknown, and very likely multifactorial. Pharmacological attempts at curing, stopping or modifying it have, by and large, been unsuccessful, and no breakthrough is in sight. However, a lot of elements that seem to contribute to the disease as risk factors have been identified, mainly from epidemiological and basic research studies. Many of these are amenable to lifestyle modification. We describe what we see as important elements here, along with the supporting evidence. We propose that the following elements would be crucial pillars for a primary prevention program:

- a) the avoidance and removal of toxins
- b) a healthy diet
- c) culture of consciousness with an emphasis on constructive use of cognitive capacities and information load, along with the practice of some mindfulness based exercise on a regular basis to implement stress control
- d) physical exercise and an active lifestyle
- e) supportive social relationships.

While all these elements are being researched in single fashion or in various combinations, to our knowledge there is no program that combines them all. While most lifestyle intervention studies have used a rather strict formula, we advocate individual adaptation and counselling to find ways of implementing necessary changes in ways that are sustainable. These would then need to be followed up by implementation studies and studies on long term effects.

1. Introduction

Alzheimer's disease is on the rise. In 2010, 35.6 million people worldwide suffered from dementia, with 60-80% of all cases being Alzheimer's type dementias. In 2050 it is estimated that figures will rise to 115 million, a 225% increase (International 2010). In 2007 associated costs have been estimated at 189 billion Euro in Europe (Luengo-Fernandez, Leal et al. 2011), and worldwide costs are estimated at US-\$604 billion every year. Currently between six and nine percent of the population at age 60 and beyond suffers from dementia, and costs for treatment and care per

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person per year are currently US-\$32,000 in Europe (International 2010). These figures can be expected to rise further with continuing growth in the world's population and longer life expectancy. It is quite conceivable that the financial and psychological burden of care for demented people will soon significantly impact the well-being and economical welfare of societies and younger people. Hence, action is urgently needed.

To date, therapeutic attempts have been largely unsuccessful. Decades of development of pharmacological agents have yielded but a few agents that can slow, only for small amounts of time, disease progression. These come with high costs and considerable side-effects. No magic-bullet breakthrough has been achieved, as was originally hoped for (Roberson and Mucke 2006; Mangialasche, Solomon et al. 2011). Some recent advances provide only small effect sizes and no durable change or reversal of the disease (Howard, McShane et al. 2012). One of the reasons for this dire state of affairs might be the fact that most attempts at targeting the disease therapeutically have used mono-causal hypotheses with only limited empirical support (De la Torre 2011). Although abnormal production rates of amyloid-beta are surely a pathological sign of the disease, which has triggered the amyloid hypothesis, it is still unclear, whether this high anomalous production rate is a result of the disease process, its cause, or just an accompanying feature. The same is true for hyperphosphorylated tau and the destruction of the microtubule skeleton of neurons that is also observed with Alzheimer's disease (AD), which leads to neuronal cell death and the fibrillar tangles that can be found post-mortem. However, post-mortem studies with victims of traffic accidents have shown that these purported pathognomic signs of AD are also present in some young people who did not have clinical signs of dementia (Braak and Del Tredici 2011). Furthermore, in old people most of these signs can be observed without the clinical specificity of AD (Snowdon 1997). Thus we have a situation where, although to some extent plausible, the amyloid hypothesis of AD, to name just one example, has been fruitful in the development of therapeutic strategies, but anti-amyloid vaccines, although effective in animal models (Janus, Pearson et al. 2000), have shown no clinical efficacy so far (Morgan 2011). The same is true for the cholinergic hypothesis. Starting from an earlier observation, the hypothesis that AD is due to the gradual destruction of cholinergic neurons in the basal forebrain was proposed as early as 1982 (Bartus, Dean III et al. 1982). This system has an important function in that it is necessary for the typical lateral inhibition, among others, crucial for focusing, memory building and retrieval processes (Hasselmo and McGuaghly 2004). While a loss of cholinergic neurons and fibres concomitant with AD progression is certainly well documented by now (Schliebs and Arendt 2011), it is by no means clear whether this is a process specific for AD, as it can also be seen in other diseases: It is also not clear, whether this loss of cholinergic neurons is the cause or the result of the disease process, or, again, just an accompanying feature (Contestabile 2011). At any rate, if the destruction of cholinergic neurons were the sole cause, then pharmacological interventions targeting this process, either by providing more acetylcholine or mitigating the effects of a lack of this neurotransmitter by boosting NMDA-receptors (Nyakas, Granic et al. 2011), should be expected to show larger effect sizes than they have recently done (Howard, McShane et al. 2012). These are only two examples, cursorily touched upon, of how monocausal hypotheses of AD have not been very successful.

There is growing evidence that the pathological process leading to AD starts early, before any clinical signs of memory loss or dementia start to become obvious (Braak, Thal et al. 2011). However, since biomarkers that might allow earlier diagnosis are either invasive (Dubois, Feldman et al. 2010; Hampel, Frank et al. 2010; Albert, DeKosky et al. 2011; Wagner, Wolf et al. 2012), or require some clinical sign of memory impairment to be present for non-invasive testing (Kaschel,

Logie et al. 2009; Foley, Kaschel et al. 2011), an earlier targeting of the disease seems to be out of the question for the time being and for as long as early-onset signs are not known. Although some genetic markers, such as the apolipoprotein ϵ -4 allele, have been identified as risk factors (Farrer, Cupples et al. 1997; Wisdom, Callahan et al. 2009), their explanatory and predictive values are far from sufficient.

Thus we are facing an impasse: We know that the disease starts long before symptoms manifest, but we do not know what causes it. We know that incidence figures are going to rise and that we cannot expect benign developments, but we do not know how to counteract this. A lot of efforts have been invested into basic research trying to disentangle potential causes, and into pharmacological research trying to find pharmaceutical cures. These efforts in tandem have produced some fruitful ideas and many single insights, but no clear cut, comprehensive strategy of treatment.

The evidence of an association between lifestyle factors and the risk of AD has increased during the last decade. The scientific opinions regarding the prevention of AD are controversial. Whereas an expert conference of the National Institutes of Health has concluded that there is not enough evidence for promoting prevention (Daviglius, Plassman et al. 2011), a number of research groups and Alzheimer's associations have contradicted this conclusion (Woodward 2007; Middleton and Yaffe 2010; Mangialasche, Kivipelto et al. 2012).

We aim to complement the current research: First by including both common factors such as non-smoking and less popular potential risk factors, and second by trying to address lifestyle as dependent on the complex individual life situation. Thus, based on some well researched facts and emerging knowledge, we present some plausible hypotheses for consideration in the development of potential prevention strategies.

Growing interest has been directed towards the neuronal redox system, since neuroinflammation is an important component in the pathological cascade, stemming from an imbalance between pro- and anti-inflammatory processes. Thus, strategies that rebalance the redox system should also be useful. These fall within the domain of lifestyle factors such as diet.

It seems to be a well-established fact that members of populations with a lower risk of AD, such as Japanese people, increase their risk of AD when they move to the US (Graves, Rajaram et al. 1999). This seems to point to the importance of lifestyle and food. We know that a lot of the brain areas suffering damage in AD are the same as those comprising the so called default mode network, a network of brain areas that produce the baseline activities of the brain (Roberson and Mucke 2006). Thus, this network seems to be especially vulnerable in AD patients, perhaps because of a basic hyperactivity. Hence, activities targeting this network, such as relaxation and meditation exercises, might be useful. The role of omega-3 fatty acids for neuronal repair and growth processes has long been known. It is also known that the ratio of omega-3 to omega-6 fatty acids in the Western diet has dramatically changed over the last century (Simopoulos 2011), while the load of environmentally produced toxic substances has also increased.

These thoughts have prompted a couple of research groups to tackle the issue from another point of view: AD is obviously a multi-factorial disease, with many potential causes which, perhaps, interact with each other and potentize each other's effect. Although its clinical manifestation is late in life,

the pathological changes might start much earlier. Hence an analysis and potential modification of lifestyle factors which might be potential contributors to the disease before it even starts manifesting should be a more fruitful approach than waiting for it to happen and then trying to cure it (Hofman, de Jong et al. 2006).

Supporting, emphasizing the timeliness and complementing attempts at testing lifestyle based prevention programs that are already ongoing, we present here the most pertinent findings from our literature reviews, together with some more speculative ideas and hypotheses for further scrutiny. We describe elements of life-style interventions that are aimed at modifying those aspects that are most important according to our reviews. Not very surprisingly, the resulting program sounds rather generic, since a primary prevention program for most chronic diseases will contain most of these elements. The specificity, however, lies in some single components and its innovative feature is the idea to not use it like a medication, given to everyone in the same dosage, but to adapt it individually to specific situations and to find individually suitable modifications that are sustainable over the life span.

2. Elements of a Primary Prevention Program

The proposed modules of our prevention program consist of

- a) avoidance of smoking and toxins, such as lead, mercury, aluminium, and reducing intake of potentially harmful trace elements such as iron and copper
- b) the adaptation of nutrition: micronutrients such as omega-3 fatty acids, but also the provision of phytochemicals that serve as free radical scavengers (derived from fresh vegetables and fruit), combined with a restriction of calorie intake in order to prevent insulin resistance of neurons and to prevent a pro-inflammatory cascade
- c) the adoption of a practice of "culture of consciousness" that targets the hyperactivity of the default mode network and helps balance stress
- d) physical exercise and an active lifestyle
- e) participatory activities and social inclusion in networks, and social relationships that are supportive and fulfilling.

The supporting evidence for these elements varies in quality, but where evidence is lacking, reason might be invoked to guide future research towards a direction where it is needed. Methodologically, we have opted for interdisciplinary reviews to compile the evidence. We have amalgamated, where applicable, evidence from basic research with epidemiological and clinical trial evidence to arrive at a comprehensive picture. In some areas our evidence picture is still incomplete, but current research should soon complete it

2.1 Avoidance of Toxins

Over the years a lot of single substances have been implicated as a potential cause of AD. As a rule, this monocausal type of thinking was misguided, and there is no single toxin that can be pinpointed as a typical cause for AD. Causal agency that can be demonstrated for some agents in basic research systems, such as cell systems, enzymatic systems or animal models, cannot be translated to humans, as the complexity of human physiology and its non-linearity as a resulting property makes predictions next to impossible and allows for an extremely wide range of ways in which humans respond to one and the same agent (del Sol., Balling et al. 2010; Pincus and Metten 2010; Barabasi, Gulbahce et al. 2011). Only with very massive doses and in rare cases can the causal agency of

toxins be proven. More important are the cases where toxins act in very small doses over large time spans. Here, the system might initially be able to counteract, compensate, and rebalance, and only after a long time of challenge, perhaps combined with an additional co-factor, may the toxin then become causal, thus hiding its potential for damage.

Mercury

One such substance is mercury, especially metallic mercury. In a systematic and interdisciplinary review, we found that while mercury can produce all the signs of AD in cell cultures and animal models, the association between mercury exposure and AD in clinical cases was loose and often counterintuitive (Mutter, Curth et al. 2010). There is a clear, albeit weak, relationship between mercury exposure and memory and attention function in workers continually exposed to low-levels of mercury, and cases of mercury poisoning with massive doses clearly point to the toxic potential of this neurotoxin, which is one of the most toxic natural substance. There has been a steady influx of mercury, both inorganic and organic, into the natural environment from the middle of the 19th century onwards, as a consequence of industrial production, usage in dental amalgams, as a preservative, and in various domestic uses, including energy saving light bulbs. Its main potential as a promoter of AD might be the fact that in the human brain, mercury binds to selenium, which is one of the body's principal detoxification mechanisms against mercury intoxication. Since selenium is also one of the most important elements in the brain's redox balance, buffering oxidative stress, it is a very reasonable scenario that an organism either challenged with low doses of mercury over a long period or with various short term high-dosages, can buffer these with selenium only for a limited period, and once a threshold is reached, a cascade of inflammatory processes is started due to rising oxidative stress. Triggers for such processes might be additional stress, a continually low provision of selenium, an additional challenge with the toxin, or a combination thereof. Indeed, in another systematic review on the relationship between selenium and AD we saw that, again in basic research models, selenium seems to be a beneficial protective factor, while in human studies, especially supplementation studies, the benefit of long-term supplementation with selenium is less clear (Loef, Schrauzer et al. 2011).

Thus, the avoidance of mercury is one useful element for a generic prevention program for AD. This affects various aspects of public health, such as political measures to restrict the circulation of and subsequent environmental pollution with mercury, and the gradual fading out of this toxic metal from dental repair work. Where repair work is required, alternative materials should be considered, and selenium supplementation might be considered as a temporary measure to buffer overload with mercury during such procedures.

Lead

Another potentially dangerous substance with a well known neurotoxic profile for which we found some evidence of relationship with AD, especially in basic research models but also in studies with elderly people, is lead (Loef, Mendoza et al. 2011). Lead used to feature as an additive in gasoline, now no longer used. It still plays some role, however, in piping in old buildings. This should be considered and replaced when refurbishing homes.

Tobacco and Coffee

There is no doubt that smoking harms human health. In relation to AD, however, early studies suggested that smoking might have a protective function (Katzman, Aronson et al. 1989). Later evidence was highly heterogeneous and did not, in most cases, differentiate for the amount of daily

consumed cigarettes. A systematic review and meta-analysis that includes studies up to 2007 found that current smokers had a 50% higher risk of suffering from AD than a non- or never-smoker (Peters, Poulter et al. 2008).¹ Most recently, Rusanen et al. (2011), analyzed the effects of smoking in relation to the packs smoked per day (Rusanen, Kivipelto et al. 2011). They found a dose-dependent effect, with the risk of AD almost doubling for persons smoking more than 2 packs per day. Importantly, there is no difference between those who never smoked and those who stopped smoking up to approximately ten years on average before the study began.

Similar to smoking, coffee consumption elevates blood pressure (Freestone and Ramsay 1982), but in contrast to the consumption of tobacco, caffeine has no negative impact on AD or cognitive performance.

A recent meta-analysis, including nine cohort studies and two case-control studies, found that caffeine intake is associated with different measures of cognitive performance (Santos, Costa et al. 2010). The relative risk was RR=0.84 (CI 95% 0.72-0.99). One study analyzed the association for genetic subgroups and reported a particular strong effect of caffeine in APOE ε4 carriers (Eskelinen, Ngandu et al. 2009). Although this indicates a protective effect of coffee consumption on cognitive decline, there was a large heterogeneity between the studies, and further evidence is necessary to ascertain more definite answers.

2.2 Nutrition and Micronutrients

Plant Derived Antioxidants

While some of the nutritional advice we found evidence for is very generic, other suggestions are specific. A very reasonable and generic suggestion that is well supported by epidemiological studies, is the ample provision of food containing phytochemicals with antioxidant capacity. We know today that plants, especially fresh and colourful ones, with dark green and red colours, contain hundreds of such substances, only few of which have been researched so far. Knowing that one of the pathological mechanisms not only of AD, but also of many other chronic diseases, is a shift of balance in the pro- and anti-inflammatory status towards inflammation, and that this shift increases oxidative stress and oxidative damage, increasing the provision with antioxidants is a natural step. However, quite a few intervention studies have now shown that a simple supplementation of food with single element vitamins and antioxidants does not have the desired effect (Tabet, Birks et al. 2008). This is likely due to the fact that in natural sources the synergistic effect of hundreds of such substances is active, while single substances, such as vitamin C, only play a minor role. Thus the logical advice would be to increase the intake of natural sources of such antioxidants. According to the published epidemiological evidence, vegetables, and in this case, green leafy vegetables in particular, seem to be more important than fruit (Loeff and Walach 2012). This might be due to the fact that fruit is often a considerable source of sugars, increasing the levels beyond the usually high intake of carbohydrates in Western societies. Another reason might be that vegetables are often eaten or prepared with fat, which allows the body to absorb lipophilic vitamins and antioxidants, such as vitamin E.

In addition to well researched sources of antioxidants, such as green tea (Dragicevic, Smith et al. 2011) or red wine (Orgogozo, Dartigues et al. 1997), are those which are completely under-researched, such as mustard, almonds and other nuts. These might show some promise, but

¹ This is confirmed by our own meta-analysis that included studies up to 2011, as yet unpublished.

thorough research is needed. Additionally, whole fruit and vegetable extracts as food supplements might be considered (Roll, Nocon et al. 2010).

Omega-3 to Omega-6 Essential Fatty Acid Balance and Fat Intake

Fats have received a bad press, mainly through prevention campaigns against cardiovascular disease. Thereby a couple of things have been overlooked: Not only the quantity of fatty acid intake is important, but also the quality of what is ingested and the balance between different types. Thus, the crude formula of "less fat is healthy" is erroneous in its simplicity, and the collective lowering of lipids through lipid lowering drugs on a grand scale needs to be reconsidered with care, especially in the light of the fact that the effect sizes of the preventive effect of such action is very small (Penston 2003; de Lorgeril, Salen et al. 2010).

When considering the issues from the point of neurological health, two things stand out: there are fatty acids that are essential for the body in general, because we cannot synthesise them and hence have to ingest them, and the balance between the two main types of essential polyunsaturated fatty acids (PUFAs), the omega-3 and omega-6 PUFAs, might be crucial. Neuronal membranes, axons and cell organelles contain a high amount of phospholipids of which omega-3 and omega-6 PUFAs are important components, and all neuronal recovery processes, neurogenesis and processes of plasticity with branching of axons and the growth of dendrites are crucially dependent on the availability of omega-3 PUFAs (Lerman 2006; Cole, Ma et al. 2009).

Apart from their role in providing the building blocks for membranes in neurons and elsewhere, omega-3 PUFAs are also precursors of signalling molecules that affect many elements in the immune system. Omega-6 PUFA are converted to prostaglandins, leukotrienes and further products that have atherogenic, inflammatory, and prothrombic effects (Schmitz and Ecker 2008). In contrast, omega-3 PUFAs, such as docosahexaenoic acid, and their eicosanoic derivatives, are competitive for the enzymes that catalyze the metabolism of omega-6 PUFAs, and have anti-inflammatory functions. While also essential for a healthy functioning of the immune system, a point of note here is that the balance of intake between omega-3 and omega-6 PUFAs in the Western diet has shifted over the last century. While it was around 1:1 for a very long time, likely since prehistoric times, in the decades after World War II it has shifted to a ratio of 1:15 in Europe and 1:20 in the US (Moffett, Ives et al. 2009). This is of relevance, because both PUFA types compete for rate limiting enzymes in the elongation and desaturation cascade, as well as for the cyclooxygenase and 5-lipoxygenase which participate in the synthesis of anti- and pro-inflammatory eicosanoids such as leukotrienes and prostaglandins from omega-3 or omega-6 PUFA, respectively (Lewis, Austen et al. 1990; Dubois, Abramson et al. 1998). The result of an imbalance leads to a long term increase of pro-inflammatory cytokines, thus making pro-inflammatory responses more likely and down-regulation of inflammatory processes more difficult. Furthermore, a lack of omega-3 PUFAs also means that neuronal repair and growth processes are hampered. This is the reason why omega-3 PUFAs, and, increasingly, the ratio of intake between omega-3 and omega-6 PUFAs, has become the focus of attention, especially for neurological disorders.

Indeed, our review found that high consumption of fish, one of the major sources of omega-3 PUFAs, is associated with a lower incidence of dementia (Loeff and Walach 2012). While, again, clinical trial evidence of supplementation is equivocal, the epidemiological record and basic research evidence is clear cut. In models of AD, Omega-3 PUFAs protect neurons and animals from

damage, and can even repair it, and in most epidemiological studies a higher intake of omega-3 PUFAs through fish is associated with less cognitive decline and dementia incidence.

The important thing to note here is that the epidemiological studies provide only very crude measures of PUFA-differentiation, as they mainly operate with coarse grained questionnaires. Although it is true that omega-3 PUFAs are mainly derived from fish, they stem, in fact, from alpha-linolenic acid, which is enriched in the chloroplasts of green leafy vegetables (Simopoulos 1991) such as algae, herbs, and salads such as rocket or mache. Thus eggs from free range chickens that feed on such dark leaves will contain omega-3, while eggs from chickens in cages fed on a diet of grain and corn, won't. Likewise, cheese from cows grazing in areas where they can accumulate omega-3 PUFAs, such as Alpine cheese, will contain a lot of omega-3, while cheese from industrial production won't (Hauswirth, Scheeder et al. 2004). These are only two examples of the complexity of the issue. In addition, there are always two ways of improving the balance. First, omega-3 intake can be increased. Some lifestyle modification programs achieve this with supplementation of up to 3 grams of omega-3 per day (Ornish, Weidner et al. 2005). Second, omega-6 intake can be decreased. This can be achieved by reducing fat from animal sources, especially if the animals have not been kept in their natural environments, by reducing some plant oils such as olive, sunflower, peanut, pumpkin, corn, thistle or wheat germ oils which contain mainly omega-6 PUFAs, and by increasing flax, granola and walnut oil, which contain more omega-3 PUFAs. A lot remains to be clarified in this area, but one lifestyle advice seems to be quite well founded: increase the intake of omega-3 PUFAs relative to omega-6, and decrease omega-6. A target of 1:4 ratio of omega-3 to omega-6 PUFAs is being discussed as both necessary and realistic (Simopoulos 2006).

What has emerged across disciplines as a hazard generally, are trans-unsaturated fatty acids. These also apply to AD, as trans-fat consumption seems to be associated with an increased relative risk of AD, particularly in people with low PUFA intake (Morris, Evans et al. 2003).

In nature, nearly all unsaturated fatty acids contain the cis-configuration which is modified by partial hydrogenation to saturated fats or to those with trans-configuration (Emken 1984). Consumption of hydrogenated fats in particular has increased continuously over the last century, importing a number of negative health effects without any known nutritional benefits (Ascherio and Willett 1997). For instance, trans-unsaturated fats increase low-density lipoproteins levels and decrease the levels of high-density lipoproteins.

Thus food that is fried in the wrong type of fat, or in fats that are overheated, is problematic, as are certain types of margarine or purportedly healthy fat replacements containing dehydrogenated fats. As using PUFAs for frying creates trans-fats, it is recommended that short- or middle-chain fats, such as palm or coconut fat, be used for frying.

Carbohydrates and Diet Restriction

A rather new development is the insight that AD might be a form of diabetes, where neurons become insulin resistant (de la Monte and Wands 2005; de la Monte and Wands 2008; Grosman and Picot 2009). Of note, insulin also increases the production of amyloid beta and triggers pro-inflammatory processes, while the hippocampus expresses many insulin receptors, testifying to the importance of insulin also in the brain (Marks, Porte et al. 1990). Thus, growing insulin resistance of neurons correlates with a lot of the features observed in AD, such as hyperphosphorylation of tau, increased production of amyloid beta, and an increase in oxidative stress as a result of mitochondrial dysfunction (Neumann, Rojo et al. 2008).

That insulin resistance plays a role is supported by the observation that diabetes type 2 increases the risk for AD, and treatment of such diabetes type 2 decreases it (Hsu, Wahlqvist et al. 2011). Recent evidence shows that there is a Warburg effect also in the brain (Newington, Pitts et al. 2011). As early as 1924, Otto Warburg famously made an observation which won him the Nobel Prize (Warburg, Posener et al. 1924): Tumour cells can generate energy by switching their metabolism from oxidation to glycolysis. As this is done in the presence of oxygen it is called aerobic glycolysis. Warburg originally thought this was typical for tumour cells only. This turned out to be not the case. Apart from tumour cells, retina cells, neurons and some other cell types can activate this process. Apparently one can see this as an alternative, albeit ineffective, way of providing the cell with energy. The benefit of this process is that no free radicals are produced and thus the cells can protect themselves from oxidative stress. This is supposed to be one of the mechanisms with which cancer cells protect themselves. But this is now also proven for neurons as a potential mechanism. Since neurons, apart from activating glycolysis, can also generate energy from ketone bodies, one long-term prevention strategy and alternative treatment strategy for AD might be to restrict carbohydrate and sugar intake to prevent insulin resistance of neurons, and to trigger the generation of energy from ketone bodies. Here, middle-chain fatty acids, such as are contained in coconut products and in butter, might play a role. To our knowledge, this has not been researched to date.

Apart from the fact that restriction of caloric intake is, if moderate, a good preventive health measure in general (Fontana and Klein 2007), there is also evidence specifically supporting its role in the prevention of cognitive decline (Martin, Mattson et al. 2006; Witte, Fobker et al. 2009). Thus a very simple and generic lifestyle advice would be to be mindful of calorie intake in general and of the intake of easily degradable carbohydrates in particular. This is, of course, generic advice that has already been issued for cardiovascular treatment and prevention programs, and for cancer prevention programs (Ornish, Scherwitz et al. 1998; Ornish, Weidner et al. 2005; Ornish 2009). A shift of energy intake from carbohydrates and sugar towards wholesome fats is advisable in the light of these findings, but would also need further elucidation.

Obesity and diabetes

Obesity is associated with dementia (Loef and Walach 2012). In a systematic review, we identified thirteen relevant studies, of which four had not been included in an earlier review (Anstey, Cherbuin et al. 2011). Compared to a normal BMI (20-25), underweight (BMI<20) was not significantly associated with AD (RR=1.39 (CI 95% 0.66-2.91)), as reported earlier. In addition, obesity in later life (BMI > 25) appeared to be inversely associated with dementia compared to normal BMI (20-25) (RR=0.79 (0.69-0.9)).

In consequence, the relationship between midlife BMI and dementia risk is J-shaped from the perspective of the most current evidence. In later life (age > 60 years), overweight persons have a lower risk of dementia than those with normal weight. However, with respect to the still very limited number of studies in the meta-analysis, further improvements in precision are likely in the near future.

Moreover, a recent work compared prediction models for AD prevalence which include and neglect the rising prevalence of obesity as a risk factor of AD (Loef and Walach 2012). We found that the

inclusion of obesity may result in up to 20% higher prevalence rates in 2050 than predicted by forecast models that are based solely on the demographic change.

Of note, obesity is also a risk factor of diabetes (Hartz 1983) which may aggravate the effects of a high carbohydrate diet, as outlined above. Numerous epidemiological studies substantiate the relationship between diabetes and AD (for a recent review see Luchsinger, 2010)

Other Micronutrients

Selenium was previously mentioned as a trace element essential for guaranteeing the brain's redox-buffering capacity. It is therapeutic within a small range, and if taken in too high a dose over too long a time it can be toxic. However, this danger would not occur under natural circumstances, as there are very few natural foods that contain such high amounts of selenium, Brazil nuts being those with the highest amount. But the naturally supportive range is considered by many to be difficult to reach in our current diet, as natural soils in certain areas of Europe, China and the US are poor in selenium, and, apart from fish, grains are the main source for naturally derived selenium. Although our systematic review found conflicting evidence regarding the supplementation of selenium, there can be no doubt from fundamental research that selenium is crucial for maintaining antioxidant capacity in the brain (Loef, Schrauzer et al. 2011), especially in the light of a potential load with mercury (Mutter, Curth et al. 2010). Hence, particularly in older age, occasional supplementation with selenium might be useful.

There are other essential trace elements whose dietary intake might be relevant for AD. The homeostasis of iron, copper and zinc are crucial for normal neuronal functioning, but only within small windows; Too much can be as unhealthy as too little (Frederickson, Suh et al. 2000; Zatta, Drago et al. 2009).

As a supplement, iron should play only a minor role in defined situations, such as anemia, and not become a general-usage substance. Avoiding substances that contain a large amount of iron would be an obvious measure. Iron is contained in large amounts in red meats, and a logical consequence would be to restrict one's intake of red meats, a preventive action that is also wise in the light of epidemiological data pointing to its role in cardiovascular risk, and in terms of general ecological sustainability of global food production (Sinha, Cross et al. 2009). Copper is another substance often contained in multi-substance formulae of food supplements which, in the light of our review (Loef and Walach 2012), might be damaging rather than helping in respect to AD. In the case of zinc, it might be speculated that a subclinical deficiency increases the risk for AD (Loef, von Stillfried et al. 2012). With the exception of iron, the evidence remains inconclusive.

The role of a number of vitamins in lowering the risk of AD are under discussion. In particular, calciferol (Annweiler, Allali et al. 2009), tocopherol (Isaac, Quinn R et al. 2008) and the B vitamins (Dangour, Whitehouse et al. 2010).

Let us give more details for one example: Homocysteine, a waste product of human metabolism, is normally recycled into methionine or converted to cysteine during the activated methyl cycle. If that methylation process is ineffective or compromised, homocysteine levels rise. Since homocysteine is also neurotoxic, it was implicated as a potential causative agent (Mulder, Schoonenboom et al. 2005) and has indeed been found to be raised in a longitudinal study of Alzheimer cases. Vitamin B12 and folate contribute to activating the methyl cycle and thus reduce homocysteine (Clarke, Smith et al. 1998). Homocysteine can also lead to an increase of amyloid

beta and tau (Sontag, Nunbhakdi-Craig et al. 2007). Indeed, one systematic review showed that Alzheimer patients had higher levels of homocysteine and lower levels of B-vitamins (van Dam and van Gool 2009). The longitudinal study of the Oxford OPTIMA cohort showed a clear relationship between baseline homocysteine level and cognitive decline, an effect that was also seen in the Rotterdam study's imaging component, where high homocysteine level and hippocampal atrophy was related (den Heijer, Vermeer et al. 2003). While supplementation of folic acid leads to a reduction in homocysteine (Luchsinger and Mayeux 2004; Trialist-Collaboration 2005), this was not always accompanied by improvements in cognitive performance (McMahon, Green et al. 2006; van Dam and van Gool 2009). Again, this might be a function of treatment onset: if used as a therapeutic treatment, homocysteine lowering might not be able to reverse pathological processes that have already started earlier on. But as a preventive treatment it might be useful. However, as such, it has not been studied to date (Coley, Andrieu et al. 2008). In the light of these findings, however, supplementation of vitamin B12 and folate might be wise, especially if homocysteine levels are high.

In addition to single nutrients, nutritional patterns such as the Mediterranean diet have been reported to be associated with a decreased risk of dementia or mild cognitive decline (Feart, Samieri et al. 2009; Scarmeas, Stern et al. 2009), thus supporting an integrative dietary change rather than the preventive supplementation of selected nutrients.

2.3 Culture of Consciousness, Stress Management

When observing some business cultures, the phenomenological parallelism with AD symptomatology on a collective-cultural level seems obvious: the overload of information through multiple incoming channels – mobile phones, emails, SMS, internet, radio and TV -, the speeding up of information processing because of high through-put demands, and the assumed demand of multi-tasking, lead to an inability to focus, to burn-out and a loss of memory function and cognitive underperformance. The hypothesis seems warranted that AD is not only a medical problem of our time, but also a cultural problem that finds a medical expression later in life. While younger people are able to cope with the high demands on their cognitive capacity, somewhere down the line this capacity is ever more challenged and then breaks down. Perhaps we could benefit from viewing AD also as a medical signature for a time and a culture that has speeded up all processes and is cognitively overloading its members, who, in turn, have not learned to cope with this demand. A result of this situation is rising stress levels and burnout, which, typically, also shows itself in memory problems. It has been long known that the hippocampus is one of the brain structures with glucocorticoid receptors. Hence our common experience that when under stress it is much more difficult to remember and memorise content and context. If cortisol levels are too high, atrophy in the hippocampus can be observed, which is relevant for various psychiatric diseases such as depression (Bremner, Vythilingam et al. 2004; van Praag, de Kloet et al. 2004; Kudielka and Kirschbaum 2007; Mössner, Mikova et al. 2007; Hains and Arnsten 2008; Pütz 2008), and might also be relevant for AD. Indeed stress across the life-span is associated with AD with a hazard ratio of 1.6, such that with three episodes of long term stress the hazard ratio rose to 2.51 (Johansson, Guo et al. 2010).

Thus the hypothesis is quite plausible that learning to manage stress and deal constructively with the cognitive overload that our culture provides us with is a useful measure within a multimodal package to prevent AD. One way of instituting such a “culture of consciousness” (Metzinger 2006) is to teach people a mindfulness or meditation program, providing training in directing attention,

relaxing the body and the mind, and carefully observing one's own reactions. Why meditation, and not just relaxation, might be important, is supported by three further observations:

1) The basal fore-brain, the structure implicated in the early stages of AD (Teipel, Flatz et al. 2005; Grothe, Zaborsky et al. 2010), non-specifically provides all those brain centres that are active with an enhancement of activity, while it decreases the activities of neighbouring centres (Hasselmo and McGuaghy 2004). This is the neurobiological equivalent to focusing on an action, providing centres of activity with lateral inhibition and thus enhancing their effectiveness. Phenomenologically speaking, this capacity to focus and thus relegating intended content to short term memory, work-space memory and then long term memory is what is compromised in AD. Hence a training of this capacity to focus should, hypothetically and theoretically, also be an antidote, at least on the phenomenological level, against this decline of cognitive focusing and memory abilities that we observe in AD. Of note, a recent imaging study with Zen practitioners and age matched controls has shown that both the cognitive decline over time and the deficit in attending common in older participants are not visible in Zen practitioners (Pagnoni and Cekic 2007). Other morphometric imaging studies have shown that in participants with mindfulness training, hippocampal volume is larger compared with age matched controls (Lazar, Bush et al. 2000; Hölzel, Ott et al. 2007; Hölzel, Ott et al. 2007; Ott, Hölzel et al. 2011). This is not just incidental correlation, but has also been shown in a longitudinal study (Hölzel, Carmody et al. 2009).

2) One way of considering meditation is as a method of reducing the activity of the default mode network (Gusnard and Raichle 2001; Raichle and al. 2001; Mason, Norton et al. 2007). This has been shown in an imaging study (Pagnoni, Cekic et al. 2008). The activity of the default mode network is likely the neural correlate of mind-wandering (Smallwood and Schooler 2006). Meditation, it is hypothesised, acts on this mind-wandering phenomenon and helps monitoring it, thus improving affect. From a neurobiological viewpoint, it does this by reducing default-mode network activity. It is interesting to observe that the structures implicated in AD largely overlap with the default mode network, and it has been suggested that AD, among others, is a result of the hyperactivity of the default mode network (Roberson and Mucke 2006). If that hypothesis is warranted, then learning to meditate would help by cultivating consciousness and preserving cognitive capacities.

3) Through meditation, not only is the capacity to focus being developed and some physical relaxation induced, but also what is called "meta-cognitive awareness" is being installed (Smallwood and Schooler 2006). Such meta-cognitive awareness is not just a strategy; It is a durable capacity to discover, early on, situations that are unwholesome and need changing. Thus it equips people with the tool to anticipate situations that are prone to produce stress and burnout before they can become dangerous. In this way it can help in installing a culture that is conducive to health in a general sense.

Taking all of these points into consideration, we would consider a comprehensive culture of consciousness, involving a set of practices, the prime tool of which would be a meditation practice, as an important component in a preventive program. While there is a lot of evidence for the clinical efficacy of mindfulness based programs in general for the treatment of some psychological and physical diseases (Grossman, Schmidt et al. 2004; Fjorback, M. et al. 2011; Keng, Smoski et al. 2011; Fjorback and Walach 2012), there are no reliable data existing, to our knowledge, that document

the effect of meditation in the prevention of cognitive decline. Nevertheless, for the reasons mentioned above, it would be worthwhile to start some research in that direction.

2.4. Exercise

Exercise is among the lifestyle elements whose positive benefits are best supported by evidence. Whatever disease one is looking at, being active and exercising is therapeutic and preventive (Thompson, Buchner et al. 2003; Shaw, Gennat et al. 2006; Thomas, Elliott et al. 2006; Warburton, Nicol et al. 2006). In our systematic review and meta-analysis of 16 prospective studies with 30,774 patients (in prep.) we updated and extended an earlier work (Hamer and Chida 2009). We found that exercise also reduces the risk of dementia and AD by approximately 30% when the highest quintile is compared to the lowest. While an active lifestyle in general is helpful, it seems that moderate to intensive activity conducted several times a week is most effective in the prevention of dementia. Although daily walking of a mile or more also has some effect, there is a clear dose-effect. This supports the general recommendations of the WHO which includes at least 150 min of moderate physical activity per week for the elderly, ideally 300 min (WHO 2011).

Thus one should not only encourage everyday activities, but also the inclusion of participation in a sport as a hobby, performing moderate physical activity on a regular basis. It seems more important to install regular periods of activity than to merely conduct everyday activities such as cooking or climbing stairs.

2.5 Social Inclusion and Relationships

Psychosomatic researchers have observed that in Alzheimer cases, compared with other forms of dementia, many of those who developed the disease lived in social situations that deprived them of healthy participation, shared decision making and supportive relationships (Bauer, Qualmann et al. 1998; Bauer 2002). These included, for example, work environments that were threatening and unsupportive, or unhealthy intimate relationships or partnerships, with subsequent withdrawal. The data regarding these issues are old, as this research has not been taken further, but it seems relevant nevertheless. In addition, living with a partner in midlife protects against cognitive impairments in later life (Håkansson, Rovio et al. 2009) and people who engage in social activities during midlife have a lower risk of dementia (Saczynski, Pfeifer et al. 2006).

Hence we suggest making including social inclusion part of a comprehensive prevention program for AD, especially considering that the importance of social relationships and interpersonal resources are being highlighted in other areas of medicine (Cohen 2004).

2.6 Multiple Lifestyle Intervention Trials

While the evidence from observational studies supports preventive measures of AD, there are only a few randomized controlled trials which investigate how lifestyle modifications impact the cognitive performance in elderly people. Of these, only three ongoing studies address multiple lifestyle dimensions although the current evidence supports such an intervention: the Prevention of Dementia by Intensive Vascular Care study (PreDIVA, ISRCTN29711771), the Multidomain Alzheimer Preventive Trial (MAPT, NCT00672685), and the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER, NCT01041989). In all of these studies the participants are aged 60 years or above - in two studies at least 70 years -, and are at increased risk of dementia. They will be followed for up to seven years. The MAPT-study compares omega-3-supplementation with or without multiple lifestyle intervention (cognitive training, physical

exercise, social activities, nutritional guidance) to placebo. In the FINGER study, the control arm receives standard health counseling, and the interventional one a combination of nutritional advice, aerobic exercise, and cognitive training. The PreDIVA, as its full title suggests, investigates the effects of vascular care in the elderly by nurses.

Table 1: Substances and actions implicated in the prevention of AD, the main sources and actions to take.

Substance Implicated	Main Sources	Action	Evidence
Inorganic mercury	dental amalgams, energy saving light bulbs, old thermometers	Avoid, carefully fade out	(Mutter, Curth et al. 2010)
Organic mercury	Fish	Choose fish wisely, avoid fish that are known to contain more mercury, such as tuna and swordfish	(Levenson and Axelrad 2006; Levitan, Wolk et al. 2009)
Lead	Pipes, gasoline	Avoid and refurbish	(Loef, Mendoza et al. 2011)
Aluminium	Cooking pots	Replace	(Flaten 2001)
Iron	Supplements, red meats	Drop supplement, restrict red meat intake in people that are not at risk of a deficiency	(Loef and Walach 2012)
Copper	Supplements, pipes, oyster	Drop supplement, replace pipes	(Loef and Walach 2012)
Antioxidants	Green, leafy and coloured vegetables and ripe fruit, green tea, red wine, seeds such as mustard and almonds	Increase intake, prefer ripe and fresh produce, in times of allostatic overload consider whole-extract supplements	(Devore, Grodstein et al. 2010; Loef and Walach 2012)
Omega-3 PUFAs; Omega-3 to 6 ratio	Fatty fish, algae and dark green herbs, flax oil, walnut (oil), almonds, granola oil	Increase intake, only in specific cases: consider supplements;	(Issa, Mojica et al. 2006; Lim, Gammack et al. 2006; Fotuhi, Mohassel et al. 2009)
Omega-6 PUFAs; Omega-3 to 6 ratio	Animal fats, milk products unless from free range, plant oils (olive, sunflower, peanut, thistle, corn)	Decrease intake	(Loef and Walach 2012)
Carbohydrates and refined sugars	White and refined flour and baking, sugar and soft drinks	Avoid and replace with wholemeal wheat products, increase fat intake and reduce	(Fontana and Klein 2007)

		carbohydrates, drop the occasional meal and increase fasting periods	
Selenium	Wheat, fish, Brazil nuts	If mercury load is anticipated or present, supplement, else watch intake	(Loef, Schrauzer et al. 2011)
Folate and Vitamin B12	All leafy vegetables, wheat and milk, nuts, liver	If homocysteine is high, supplement	(Oulhaj, Refsum et al. 2009; van Dam and van Gool 2009)
Culture of consciousness	Meditation, mindfulness	Start learning and practicing regularly	(Pagnoni and Cekic 2007)
Exercise	sports activities, biking, hiking, walking	at least 150 min per week of moderate to intensive activity	(Hamer and Chida 2009; Graff-Radford 2011)
Social inclusion	Close relationships	Foster supportive relationships	(Saczynski, Pfeifer et al. 2006)
Overweight		Target a BMI of 18.5-25	(Anstey, Cherbuin et al. 2011; Siervo, Arnold et al. 2011)

3. Evidence from cell and animal studies

The epidemiological findings outlined above are supported by animal studies showing that the pathophysiology of AD covers multiple biochemical pathways that interact in a highly complex manner (Frautschy and Cole 2010).

For example, the predominant histological features of the AD are amyloid plaques and neurofibrillary tangles. The plaques consist of deposits of the amyloid beta (A β) protein which is a cleavage product of the amyloid precursor protein (APP) (Esch, Keim et al. 1990).

Experiments with transgenic mice overexpressing the APP showed clear indications for the interaction between AD pathology and lifestyle behaviors. If these mice are exposed to a cognitively stimulating environment, the burden of amyloid plaques is significantly reduced and the cognitive function is improved (Ambrée, Leimer et al. 2006; Costa, Cracchiolo et al. 2007). In the same vein, voluntary exercise and dietary restriction reduce the number of amyloid plaques in the brain of Alzheimer mouse models (Adlard, Perreau et al. 2005; Wang, Ho et al. 2005).

Supplementation of vitamins such as vitamin E (Lloret, Badía et al. 2009) and the consumption of ω -3 poly-unsaturated fatty acids (Huang 2010) may reduce the risk of AD by decreasing the oxidative damage that was found in brain tissue samples of AD patients (Markesbery 1997).

Different lines of evidence support the importance of mitochondrial dysfunction in the etiology of AD (see (Swerdlow 2011) for a review). Mitochondria are cellular organelles which facilitate the production of ATP (Benard, Bellance et al. 2007). In AD brain tissue samples, the number of mitochondria is reduced, mitochondrial DNA shows a higher mutation frequency, the activity of the cytochrome c oxidase and other enzymes is lower than in control samples (Swerdlow 2011) (Lin

and Beal 2006). The mitochondrial damage has been shown to be associated with A β toxicity (Lustbader, Cirilli et al. 2004). Synaptic mitochondria show a particularly early and high degree of sensitivity to A β toxicity resulting in high A β accumulation and pathological alterations as compared to non-synaptic mitochondria (Du 2010). This occurs even before the symptomatic onset of the disease, highlighting the importance of the mitochondrial dysfunction in the pathological cascade of AD.

These findings imply preventive and therapeutic approaches (Du, Guo et al. 2011; Toledo, Watkins et al. 2006). For instance, Du et al. (2011) demonstrated that the abrogation of cyclophilin D (a crucial component of the mitochondrial permeability transition pore) results in a protection against A β mitochondrial toxicity (Du, Guo et al. 2011).

Although the evidence from molecular biology enables a better understanding of how lifestyle modifications may reduce the risk of AD, it can only be used in combination with observational and interventional studies to conclude behavioral recommendations.

4. What does lifestyle mean?

None of the many articles that have raised the question whether and how prevention of AD is associated with lifestyle have discussed what healthy lifestyle actually means, what parameters it depends on, and why this is crucial for the implementation of preventive measures. Implicitly, the term is often used as a pool of behaviors that each can be unconditionally adopted if the individual chooses to. Considering the great obstacles that have been experienced when trying to make people adhere to lifestyle changes with various indications, one might question the concept. Medical sociologists have defined a healthy lifestyle as patterns of behavior based on decisions which depend on multiple factors such as socio-economic status, age, gender, health literacy, ethnicity, the wealth of the state one is living in and many more (Cockerham 2007). Thus lifestyle is determined by much more than one's own choice and based on an individual set of parameters that need to be taken into account in prevention projects. To give an example, the association between a healthy lifestyle and socio-economic status (SES) may, at least in parts, explain why the incidence of AD is higher in people with a low SES (Karp, Kåreholt et al. 2004). In modernity, many different lifestyles have evolved that mean more to the individuals than a random scheme of habits, as they allow one to position and identify oneself in society (Giddens 1991). This pluralism of lifestyles might counteract the strategies to randomize groups to standardized lifestyle interventions, simultaneously challenging public health endeavors to promote standardized behaviors.

5. Discussion: Future Directions

Based on the information above, we propose to implement and study an individualised lifestyle based prevention program of AD, the components of which comprise avoidance of toxins, nutrition, culture of consciousness, exercise and the cultivation of wholesome social relationships (see Table 1). However, rather than prescribing a single lifestyle for everyone, we would advocate individual titration and adaptation through a counselling process, which is normally more effective than just teaching or prescribing lifestyle changes (Appel, Clark et al. 2011). Lifestyle interventions have, in general, produced rather disappointing results in the field of cardiovascular prevention (Angermayr, Melchart et al. 2010). We suppose that this is due to the fact that such programs normally try to produce a one-fit-all prescription. But lifestyles, being the expression of individual

choices, predilections, and perhaps even genetic diversity, are as individual as people's faces. Thus the challenge will be to develop individualised programs that, via coaching, perhaps over the internet, will help individuals to adapt their personal lifestyle in such a way that as many elements as possible can be integrated. For instance, a reduction of carbohydrate intake can be achieved in various ways: one can eat less in one meal; one can eat less meals; one can eat normally over a period and then install a short period of fasting; one can drop certain types of carbohydrates and replace them with other types; some of the calories normally ingested through carbohydrates can be replaced by other sources. A multitude of options exist, but in order to make a lifestyle change and choice durable, the choices need to be heartfelt, consciously chosen and practical. To quote another example: It is likely that a good provision with omega-3 PUFAs is an essential element of a good preventive diet. This can be achieved through regular consumption of fish, about twice a week. But what about people who do not like fish, or strict vegetarians? In these cases, they could then opt for supplements from algae, or change from the oils they are using to flax-oil and walnut oil. They could prefer certain types of cheeses over others. Alternatively, people could just reduce omega-6 intake in order to lower the omega-6/omega-3 ratio. Again, the best choice for the individual will need to be tried out and discussed, involving the individual themselves in the process.

Hence, such a comprehensive lifestyle program needs to be supported by counselling and implementation activities. Perhaps one of the first steps would be to find out what certain parts of the population are willing to try and to do. Implementation studies with a strong qualitative backbone – focus groups, interviews, observational studies with documentation of behaviour – are required to establish this. Counselling should be provided. Whether this should be through personal contact or an interactive expert system would need to be clarified, but in the light of the data of other studies (Appel, Clark et al. 2011), internet coaching would likely suffice.

Another way of testing the potential benefit of such a program would be to use it, perhaps in a stronger “dose”, also as a treatment program for people with mild cognitive impairment and to observe whether one can change conversion rates or cognitive decline. This is currently done by the three European trials FINGER, MAPT, and PreDIVA, with different combinations of lifestyle factors. It is plausible to assume that if our, or other, programs and their components are useful in prevention, they should also be effective in treating very early symptoms of cognitive decline such as occasional failure of memory or mild cognitive impairment.

At any rate, we suggest that it is time to start researching lifestyle components as elements to prevent and, potentially, even treat – as early interventions – AD and cognitive decline. Most of the components we have mentioned - avoidance of smoking and the toxins mercury, lead, aluminium, a healthy diet; meditation and a culture of consciousness, as well as exercise and inclusive social relationships – have at least some evidence to support them, and those that have no direct evidence for them, such as meditation or inclusive social relationships, have some compelling indirect evidence that recommends them. Although we have here treated such lifestyle changes as preventive measures against AD and cognitive decline, they are rather generic.

This we consider a strength rather than a weakness, as they are very likely preventive against quite a few other chronic diseases, such as cardiovascular disease, cancer, metabolic syndrome and diabetes. In order to increase the adherence to a healthy lifestyle, it may therefore be of general interest to better understand the dependence of health behaviours on its multiple determinants.

It is time that charitable trusts and public funding bodies take such interventions into consideration when issuing calls for proposals and making funding decisions.

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