Alzheimer's disease

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An estimated 24 million people worldwide have dementia, the majority of whom are thought to have Alzheimer's disease. Thus, Alzheimer's disease represents a major public health concern and has been identified as a research priority. Although there are licensed treatments that can alleviate symptoms of Alzheimer's disease, there is a pressing need to improve our understanding of pathogenesis to enable development of disease-modifying treatments. Methods for improving diagnosis are also moving forward, but a better consensus is needed for development of a panel of biological aneuroimaging biomarkers that support clinical diagnosis. There is now strong evidence of potential risk and protective factors for Alzheimer's disease, dementia, and cognitive decline, but further work is needed to understand these better and to establish whether interventions can substantially lower these risks. In this Seminar, we provide an overview of recent evidence regarding the epidemiology, pathogenesis, diagnosis, and treatment of Alzheimer's disease, and discuss potential ways to reduce the risk of developing the disease.

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Epidemiology

The cost of caring for the increasing number of people with dementia continues to rise and thus accurate estimates of dementia prevalence are needed. Recent systematic reviews of epidemiological studies have provided comprehensive estimates of dementia prevalence. A WHO report[1] estimated that dementia contributed 11·2% of years spent living with a disability in people over 60 years old—more than stroke, cardiovascular disease, and cancer. In 2005, Alzheimer's Disease International convened an international panel of dementia experts to undertake an evidence-based Delphi consensus on dementia prevalence worldwide. The Delphi study[2] estimated that there were 24·3 million people with dementia in the world in 2001, and predicted that this would rise to 42·3 million in 2020 and 81·1 million by 2040. The countries or regions with the largest number of affected individuals are China and the developing western Pacific, western Europe, and the USA (table 1). The quality of data on Alzheimer's disease prevalence varies between different regions, and important questions remain about whether differences in age-specific prevalence between regions are real or a result of different study methodologies. However, the advantage of the Delphi method is that it provides a rigorous consensus that takes into account a range of variables, including methodology, to estimate regional prevalence.

Pathogenesis

The two core pathological hallmarks of Alzheimer's disease are amyloid plaques and neurofibrillary tangles. The amyloid cascade hypothesis suggests that deposition of amyloid β (Aβ) triggers neuronal dysfunction and death in the brain (figure 1). In the original hypothesis, this neuronal dysfunction and death was thought to be a toxic effect of the total amyloid load. As knowledge of pathological changes in Alzheimer's disease increased, research focused on more specific alterations in Aβ processing, such as the cleavage of amyloid precursor protein (APP) into Aβ peptides ($A\beta_{1–40}$ and $A\beta_{1–42}$) and the importance of Aβ oligomers (small aggregates of two to 12 peptides). The $A\beta_{1–42}$ peptide aggregates more readily than $A\beta_{1–40}$, and the ratio of these two isoforms is influenced by the pattern of cleavage from APP by α, β, and γ secretases.[3] Small oligomers of Aβ can be more toxic than mature fibrils; Aβ56 seems to be a peptide of particular interest because it is negatively associated with cognitive decline in an APP mouse model and induces memory deficits when injected into

Search strategy and selection criteria

We searched the Cochrane library (1990–January, 2010), Medline (1990–January, 2010), and Embase (1990–January, 2010) for terms associated with the epidemiology, pathogenesis, diagnosis, treatment, and modifiable risk factors for Alzheimer's disease. For epidemiology we used the following terms: "prevalence OR incidence OR rates OR frequency" AND "dementia, Alzheimer's disease". In the first instance we preferred systematic reviews and Delphi consensus. For pathogenesis, we used the terms "genes OR genetic OR polymorphism OR haplotype, molecular biology OR proteomics OR protein OR amyloid OR tau" AND "dementia OR Alzheimer's disease". For diagnosis we searched using the terms "diagnosis OR diagnositic criteria OR neuropsychology OR biomarkers OR PET OR PIB OR SPECT OR CSF" AND "dementia OR Alzheimer's disease", and for treatment we used "Alzheimer OR dementia" AND "treatments OR pharmacotherapy OR non-pharmacologic/al treatments". Finally, for modifiable risk factors we used the following search terms: "risk OR prevention OR lifestyle OR vitamins OR diet OR alcohol OR cholesterol OR hypertension OR stimulation OR exercise" AND "Alzheimer OR dementia".

We mainly selected publications from the past 5 years and prioritised systematic reviews and meta-analyses. However, we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. In discussion of epidemiology, pathogenesis, diagnosis, treatment, and modifiable risk factors we gave more weight to randomised controlled trials and meta-analyses than, for example, to case series.

	WHO region	Dementia prevalence in people over 60 years old (%)	Number of people over 60 years old who have dementia (millions)		
			2000	2020	2040
Western Europe	EURO A	5·4	4·9	6·9	9·9
Eastern Europe low adult mortality	EURO B	3·8	1·0	1·6	2·8
Eastern Europe high adult mortality	EURO C	3·9	1·8	2·3	3·2
North America	AMRO A	6·4	3·4	5·1	9·2
Latin America	AMRO B/D	4·6	1·8	4·1	9·1
North Africa and middle eastern crescent	EMRO B/D	3·6	1·0	1·9	4·7
Developed western Pacific	WPRO A	4·3	1·5	2·9	4·3
China and the developing western Pacific	WPRO B/D	4·0	6·0	11·7	26·1
Indonesia, Thailand, and Sri Lanka	SEARO B	2·7	0·6	1·3	2·7
India and south Asia	SEARO D	1·9	1·8	3·6	7·5
Africa	AFRO D/E	1·6	0·5	0·9	1·6
Total		3·9	24·3	42·3	81·1

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Table 1: **Estimates of dementia prevalence worldwide according to the Delphi consensus study in 2005**

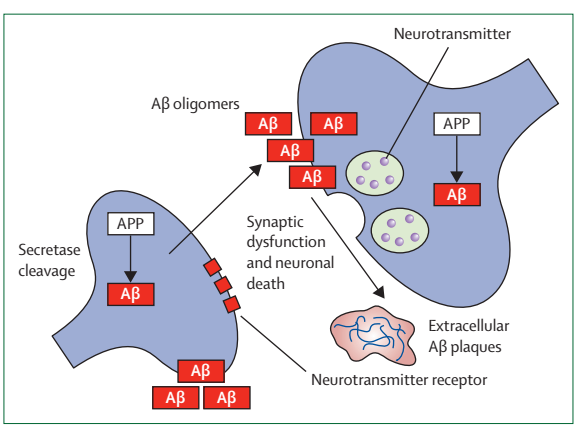

Figure 1: **Amyloid cascade hypothesis**
Aβ=amyloid β. APP=amyloid precursor protein. APP is processed into Aβ, which accumulates inside neuronal cells and extracellularly, where it aggregates into plaques. In the amyloid cascade hypothesis, these Aβ deposits are toxic and cause synaptic dysfunction and neuronal cell death.

rat brain.[4] The amyloid cascade hypothesis has also been more fundamentally challenged; for example, increases in Aβ might result from neuronal damage caused by another process.[5] Why Aβ aggregates into fibrils is unclear, but Aβ sequence, Aβ concentration, and conditions that destabilise Aβ[6] are thought to be important factors.

Tau, a microtubule-associated protein, is the major constituent of neurofibrillary tangles. The amyloid cascade hypothesis proposes that changes in tau and consequent neurofibrillary tangle formation are triggered by toxic concentrations of Aβ. The pathways linking Aβ and tau are not clearly understood, although several hypotheses have been proposed.[7] Tau is a soluble protein, but insoluble aggregates are produced during the formation of neurofibrillary tangles, which disrupt the structure and function of the neuron. Tau monomers first bind together to form oligomers, which then aggregate into a β sheet before forming neurofibrillary tangles. The tau in neurofibrillary tangles is hyperphosphorylated, but whether phosphorylation is involved in tau aggregation is unclear, although it seems to be important in reducing the affinity of tau for microtubules.[8] Once filamentous tau has formed, it can be transmitted to other brain regions. Injection of mutant pathological tau induces the formation of tau filaments in wild-type mice.[9] Many phosphokinases, including glycogen synthase kinase 3β (GSK3β), cyclin-dependent kinase 5 (CDK5), and extracellular signal-related kinase 2 (ERK2), have been investigated as potential treatment targets to reduce tau phosphorylation.[10] DYRK1A (dual specificity tyrosine-phosphorylation-regulated kinase 1A) primes tau molecules for further phosphorylation by GSK3β and might also be important in linking Aβ and tau.[11] However, post-mortem measurement of each of these classic pathological hallmarks only explains to a limited extent the expression of dementia in the population,[12] and numerous other potentially modifiable factors also contribute to the clinical presentation of dementia (see section on risk and protective factors for some examples).

The amount of risk of Alzheimer's disease that is attributable to genetics is estimated to be around 70%. Table 2 summarises genes known to be involved in Alzheimer's disease. Hardy and colleagues[26] have described the issues that have hampered the identification of Alzheimer's disease risk genes.[26–28] Identification of specific risk genes is problematic because the overall increase in risk conferred by a single gene is small. Additionally, not just individual genes but combinations of risk alleles need to be identified. Another complicating factor is the heterogeneity of the underlying pathological changes, particularly concurrent cerebrovascular disease.[29]

Established genetic causes of Alzheimer's disease include dominant mutations of the genes encoding amyloid precursor protein (*APP*) and presenilin 1 (*PSEN1*) and *PSEN2*.[13–15] These genes have been essential in our understanding of Alzheimer's disease mechanisms, although they are the cause of Alzheimer's disease in only 5% of patients, who usually have onset of clinical symptoms in midlife. *SORL1* has also been identified as an important genetic cause of late-onset Alzheimer's disease,[16] At least one further familial Alzheimer's disease gene is thought to exist, possibly located on chromosome 10.[30]

Several potential risk genes for Alzheimer's disease have also been identified. The most consistently associated risk gene is *ApoE*. Individuals with two *ApoE ε4* alleles have a more than seven times increased risk of developing Alzheimer's disease compared with those with *ApoE ε3* alleles.[17] Many candidate risk genes have been identified but not confirmed by initial studies. A meta-analysis website has helped to clarify the relative risks associated with each candidate gene. According to the Alzgene website, with the exception of *APOE*, the majority of the most commonly identified candidate genes have a relative risk of 1·2–1·5.

For the **meta-analysis website** see http://www.alzgene.org/

PSEN1 and *PSEN2* mutations affect concentrations of $A\beta_{1–42}$ because the presenilin proteins form part of γ secretase, which cleaves APP to produce Aβ.[31] *SORL1,* one of the VPS10 domain-containing receptor families of genes, reduces the interaction between APP and β secretase.[32] ApoE also seems to affect the rate of Aβ clearance.[33] Several other genes that affect Alzheimer's disease risk possibly have roles in the clearance or uptake of Aβ.

Tau mutations result in tauopathies, such as corticobasal degeneration and frontotemporal dementias, but not Alzheimer's disease.[34] However, tau is an important pathological substrate of Alzheimer's disease and is a potential treatment target because tau tangles are more closely associated with the severity of dementia than are Aβ plaques.[35] The relation between a tau haplotype and tauopathies has been studied. However, the relevance of the tau haplotype to Alzheimer's disease is not clear, but an interaction has been reported between the tau haplotype and a GSK3β haplotype.[18] Polymorphisms of phosphokinases, such as *DYRK1A,* might be associated with an increased risk of Alzheimer's disease and might have a role in explaining the link between Aβ and tau pathology because DYRK1A is upregulated by Aβ. The *TOMM40* gene is located in a region of chromosome 19 that is in linkage disequilibrium with *APOE,* and a repeat polymorphism in this gene affects the age of onset of late-onset Alzheimer's disease in patients with an *APOE* genotype.[36] Furthermore, recent genome-wide association studies in patients with Alzheimer's disease have identified mutations in genes such as *CLU* and *PICALM*,[37,38] but the associated risks were small (0·87) and large cohorts and replication cohorts are needed (>10 000 people). These genes do not markedly assist in predicting Alzheimer's disease risk,[39] but they might have important roles in identifying the pathways involved in the disorder and potential drug targets.

Diagnosis and biomarkers

An accurate diagnosis of dementia enables the detection of potentially treatable disorders that contribute to cognitive impairment, such as depression, vitamin deficiencies, and hypothyroidism, and allows patients and their families to plan their future life and finances, including advance directives and optimum treatment and care. With the prospect of development of disease-modifying drugs, early and accurate diagnosis and the ability to provide a prognosis is essential. Improvement of diagnosis in primary care is a high priority because most patients with dementia present to family doctors. Practical approaches, such as decision support software and practice-based workshops, can improve detection rates and diagnosis of dementia.[40]

	Role in Alzheimer's disease	Effect on risk of Alzheimer's disease
Familial genes		
APP	APP is a membrane protein cleaved by secretases. Cleavage of APP by secretases leads to both non-amyloidogenic processing and production of Aβ. Familial APP mutations result in preferential processing of *APP* through the amyloidogenic pathway[13]	NA
PSEN1	PSEN1 is a component of α secretase, which is involved in APP processing to Aβ. Familial *PSEN1* mutations can alter the production of $A\beta_{1-42}$ which forms plaques more readily than Aβ1–40[14]	NA
PSEN2	Processes APP into Aβ as part of the α-secretase complex. Familial mutations can alter the production of Aβ1-42, which forms plaques more readily than $A\beta_{1-40}$[15]	NA
SorL1	SorL1 interacts with APOE, affects APP trafficking, and overexpression of the protein results in reduced Aβ production. Binding of SorL1 to APP results in reduced Aβ production. SORL1 is a γ-secretase substrate. SorL1 concentrations are reduced in patients with Alzheimer's disease[16]	NA
Risk genes		
APOE	APOE is transported with cholesterol; *APOE* isoforms have differing transport efficiencies. APOE binds Aβ in an isoform-specific manner. APOE is involved in Aβ clearance through interaction with LRP. *APOE4* alleles are associated with increased amyloid burden and cholinergic dysfunction	3–10 times increased[17]
GSK3β	GSK3β phosphorylates tau, leading to tangle formation. *APP* cleavage products can activate *GSK3β*, leading to increased tau phosphorylation. GSK3β phosphorylates tau more effectively if tau has already been phosphorylated by other kinases, such as *cdk5*. GSK3β activity can also be promoted by *PSEN* complexes	1·7 times increased.[18,19] No Alzgene meta-analysis
DYRK1A	DYRK1A is located on chromosome 21. DYRK1A is involved in tau phosphorylation; its activity is upregulated by Aβ, therefore DYRK1A is a link between amyloid and tau pathologies. *DYRK1A* phosphorylates tau to prime the molecule for further phosphorylation by GSK3β. DYRK1A also phosphorylates septin 4, another tangle protein. DYKR1A is involved in *APP* phosphorylation, which leads to increased amyloidogenic processing through increased BACE interaction	T allele is less frequent in people with Alzheimer's disease. No Alzgene meta-analysis[20]
Tau	Tau is hyperphosphorylated in NFTs. Tau exists as six splice isoforms depending upon inclusion of N–terminal exons 2 and 3, and the exon 10 microtubule binding domain. Tau mutations can affect splicing and microtubule binding efficacy. The tau haplotype is associated with Alzheimer's disease, and affects expression levels of tau splice isoforms	H1C haplotype more frequent in Alzheimer's disease. No Alzgene meta-analysis of the haplotype[21,22]
TOMM40	TOMM40 is a translocase of outer mitochondrial membrane 40 homolog on the same chromosome as *APOE*. TOMM40 interacts with APP and is associated with the age of onset in late-onset Alzheimer's disease[23]	Alzgene odds ratio of 0·66 for rs8106922
CLU	Clusterin is a chaperone involved in Aβ formation and is associated with severity and progression of Alzheimer's disease[24]	Alzgene odds ratio of 0·87 for rs1113600
PICALM	Phosphatidylinositol binding clathrin assembly protein, present in endosomes which are enlarged in early Alzheimer's disease[25]	Alzgene odds ratio of 0·87 for rs541458

A full meta-analysis of risk genes can be found on the Alzgene website (http://www.alzgene.org/). NA=not applicable. Aβ=amyloid β. APP=amyloid precursor protein. APOE=apolipoprotein E. NFT=neurofibrillary tangle.

***Table 2*: Alzheimer's disease risk genes**

At present, Alzheimer's disease can only be definitively diagnosed post mortem, although earlier diagnosis may be possible with improved diagnostic techniques and criteria. Clinically, only probable diagnosis of Alzheimer's disease is possible at present. For a clinical diagnosis of Alzheimer's disease to be made, a detailed history of the type and course of symptoms is taken from the patient and another source (eg, partner or carer) to assess whether there is cognitive impairment and whether social, occupational, or other instrumental functions are affected, and a neuropsychological assessment is done. An operationalised clinical diagnosis with criteria such as the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) has good sensitivity and specificity (>80%) for distinguishing between patients with Alzheimer's disease and people without dementia, but the ability to distinguish between Alzheimer's disease and other dementias is less accurate (23–88%).[41]

Evidence-based recommendations are that CT or MRI should be used to detect intracranial lesions or diseases that might cause (eg, tumour, subdural hematomas, or hydrocephalus) or contribute to (eg, cerebrovascular disease) dementia syndromes.[42] Therefore, in general an operationalised clinical diagnosis of Alzheimer's disease is fairly accurate and can be augmented by investigations to rule out other major conditions that could result in cognitive impairment or dementia. However, more specific biomarkers are needed to improve the diagnostic accuracy for Alzheimer's disease in the earliest stages.

Isoforms of Aβ peptides and phosphorylation epitopes of the tau protein have been studied in cerebrospinal fluid (CSF). Meta-analyses suggest that Alzheimer's disease can be differentiated from other dementias by detection of lower concentrations of $A\beta_{1-42}$ and higher concentrations of total tau or tau hyperphosphorylated at threonine 231 and 181 than age-matched control individuals. These findings were confirmed in a multicentre study that had a-priori cutoffs with a sensitivity of 83% and specificity of 72%.[43] Additionally, findings from a longitudinal study showed that the combination of CSF total tau, hyperphosphorylated tau, and $A\beta_{1-42}$ at baseline yielded a sensitivity of 95% and a specificity of 83% for detection of early Alzheimer's disease in patients with mild cognitive impairment.[44] However, there is still a high degree of variability between CSF studies, and analytical techniques need to be standardised.[43]

Development of a panel of CSF biomarkers that could be used to create an Alzheimer's disease-suggestive biomarker profile would be very useful for early diagnosis of Alzheimer's disease. A combination of CSF biomarkers for $A\beta_{1-42}$, total tau, and phosphorylated tau with novel markers such as $A\beta_{1-38}$ has improved diagnostic accuracy.[45] Other potential candidate biomarkers include markers of inflammation and oxidative stress.[46]

Attempts to measure Aβ subtypes in blood have produced inconsistent results. Several biomarkers based on plasma proteins have been investigated with focused candidate multiplex or proteomics approaches. None have yet been tested in phase 3 trials, but promising findings, including replication by different groups and association with Alzheimer's-type pathology, have been reported for complement factor H, alpha-2-macroglobulin, and clusterin.[24,47]

Semi-quantitative structural MRI has been used successfully to identify differences in medial temporal lobe atrophy between patients with Alzheimer's disease and age-matched control individuals, with sensitivity and specificity greater than 85%,[42] and there is emerging evidence that measurement of medial temporal atrophy could also be used to identify patients with mild cognitive impairment that will eventually progress to Alzheimer's disease. However, differences in medial temporal atrophy between Alzheimer's disease and non-Alzheimer's disease dementias are less clear cut, and differences on imaging are probably too small for diagnostic purposes in individual patients.[48,49] Novel quantitative techniques, such as volumetric imaging, three-dimensional mapping of the hippocampus, and cortical thickness measurement are promising markers for Alzheimer's disease,[50] and are being investigated as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI) multicentre study.[51]

Functional neuroimaging techniques have also been developed for probable diagnosis of Alzheimer's disease. Radioisotopic scans can measure blood flow (99mTc-HMPAO or 133Xe) with single-photon emission CT (SPECT) and are available at most hospitals. However, a systematic review reported a clinical accuracy for patients with Alzheimer's disease versus control individuals of only 74%.[52] 99mTc-HMPAO SPECT is a useful neuroimaging technique for distinguishing Alzheimer's disease from frontotemporal dementia.[53] Ligands have also been developed that visualise specific neurotransmitter systems with SPECT. In particular, a large multicentre study has reported the utility of dopamine transporter imaging with ^{123}I-fluoropropylcarboxy-metoxynortropane in distinguishing dementia with Lewy bodies and Parkinson's disease dementia from Alzheimer's disease,[54] and this technique is now included as part of the diagnostic criteria for dementia with Lewy bodies.[55]

PET with fluorodeoxyglucose measures glucose metabolism and has shown good accuracy in distinguishing patients with probable Alzheimer's disease from both normal control individuals and patients with non-Alzheimer's disease dementias. This imaging method has been approved in the USA for diagnostic purposes and is sensitive and specific for detection of Alzheimer's disease in its early stages. A reduction of glucose metabolism in bilateral temporal parietal regions and in the posterior cingulate cortex is the most commonly described diagnostic criterion for Alzheimer's disease. A meta-analysis has reported a

sensitivity and specificity of 86% for diagnosis of Alzheimer's disease on PET imaging, although there were wide variations between studies.[56] Lower values have been reported for Alzheimer's disease versus non-Alzheimer's disease dementia.[56]

PET with Aβ ligands, such as ^{11}C-labelled Pittsburgh compound B (PIB) and an ^{18}F-labelled Aβ ligand, can be used to directly visualise Aβ in vivo (figure 2).[57] In a prospective multicentre study, increased retention of the PIB ligand identified 14 of 17 people who were clinically diagnosed with Alzheimer's disease during follow-up, whereas only one of 14 PIB-negative patients with mild cognitive impairment developed Alzheimer's disease.[58] Additional evidence suggests a significant association between PIB binding on PET and fibrillar Aβ at post mortem in most patients with Alzheimer's disease and significant correlations with CSF Aβ biomarkers.[59,60] Findings from PIB studies have also identified increased Aβ deposition before the onset of Alzheimer's disease, but there were so-called ceiling effects in longitudinal studies.[60] In a recent case study of a person with serial PIB there was a substantial relation between PIB retention in vivo and Aβ plaque distribution post mortem.[61] Although PIB imaging is promising, it needs to be assessed in larger multicentre studies. Findings from novel metabolic MRI technologies have also suggested a specific abnormality in Aβ clearance.[62]

One challenge for biomarker research is the substantial overlap of major brain pathologies. For example, 90% of people with dementia with Lewy bodies have substantial concurrent Alzheimer's disease pathology, and almost all patients with severe cerebrovascular disease also have substantial Aβ pathology, particularly those over 80 years old.[60] Conversely, 40% of patients with Alzheimer's disease have severe cerebrovascular disease.[29,63] Results from population studies of biomarkers in people with Alzheimer's disease are less variable than from people with Alzheimer's disease in usual clinical populations, and distinguishing between different dementias is challenging when the pattern of markers actually represents a combination of pathological changes. A better understanding of how combinations of pathologies affect changes in biomarkers is needed.

Techniques to measure brain volume and the volume of specific brain structures such as the hippocampus and to co-register images are being used successfully in patients with Alzheimer's disease, and those at risk of developing the disease, to measure progressive atrophy (figure 3),[64–66] to establish differences in rates of atrophy,[64] and to measure disease progression in clinical trials.[64] The increase in evidence of concordance between CSF and neuroimaging biomarkers led Jack and colleagues[67] to suggest an integrated biomarker approach to track disease course in Alzheimer's disease. They suggest that alterations in biomarkers associated with Aβ occur before the development of a full clinical dementia syndrome and in the early stages of Alzheimer's disease, with subsequent changes in biomarkers associated with tau pathology and neurodegeneration. This hypothesis is supported by findings from a recent longitudinal study that suggest that reduced CSF $A\beta_{1-42}$ in cognitively healthy people predicts substantial subsequent brain atrophy.[68] Although this approach has many advantages, there are a number of important caveats, including the selection of biomarkers and the building of valid and useful predictive models.[69] For example, the imprecise relation between the amount of Aβ and tau pathology and the presence of clinical dementia,[70] and the large overlap of Alzheimer's disease, synucleinopathies, and cerebrovascular pathologies are problematic when interpreting a biomarker profile in individual patients.

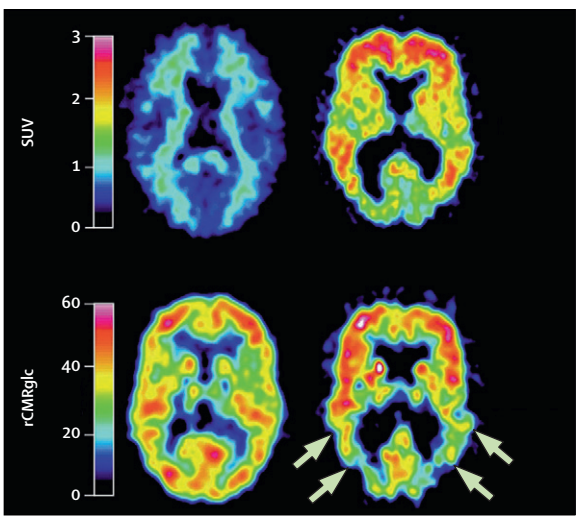

Figure 2: **Neuroimaging from a patient with Alzheimer's disease and a healthy person**
Carbon-11-labelled Pittsburgh compound B (^{11}C-PIB; top) standardised uptake value images from the brain of a 67-year-old healthy person (left) and a 79-year-old patient with Alzheimer's disease (right). ^{18}F-fluorodeoxyglucose (bottom) cerebral regional glucose metabolism (μmol/min/100 mL) images. There was high retention of PIB in the frontal and tempoparietal cortices of the patient with Alzheimer's disease and hypometabolism in cerebral regional glucose metabolism. There was an absence of PIB retention (top left) and normal cerebral regional glucose metabolism (bottom left) in the healthy person. Reproduced from Nordberg,[57] by permission of Elsevier.

An expert consensus group led by Dubois has proposed research criteria for Alzheimer's disease in an attempt to improve identification of people in the earliest stages of the disease, but also to refine diagnostic accuracy across the full spectrum of the illness (panel).[71] The research criteria are an attempt to incorporate knowledge of biomarkers into clinical practice. These new criteria are centred on early and substantial impairment in episodic memory, which is operationally defined within the criteria. They also stipulate that there must be at least one or more abnormal biomarker on structural neuroimaging with MRI, molecular neuroimaging with PET, and CSF analysis of Aβ or tau proteins. These criteria show that our understanding of neuroimaging and CSF biomarkers is improving, but, because of the present stage of knowledge,

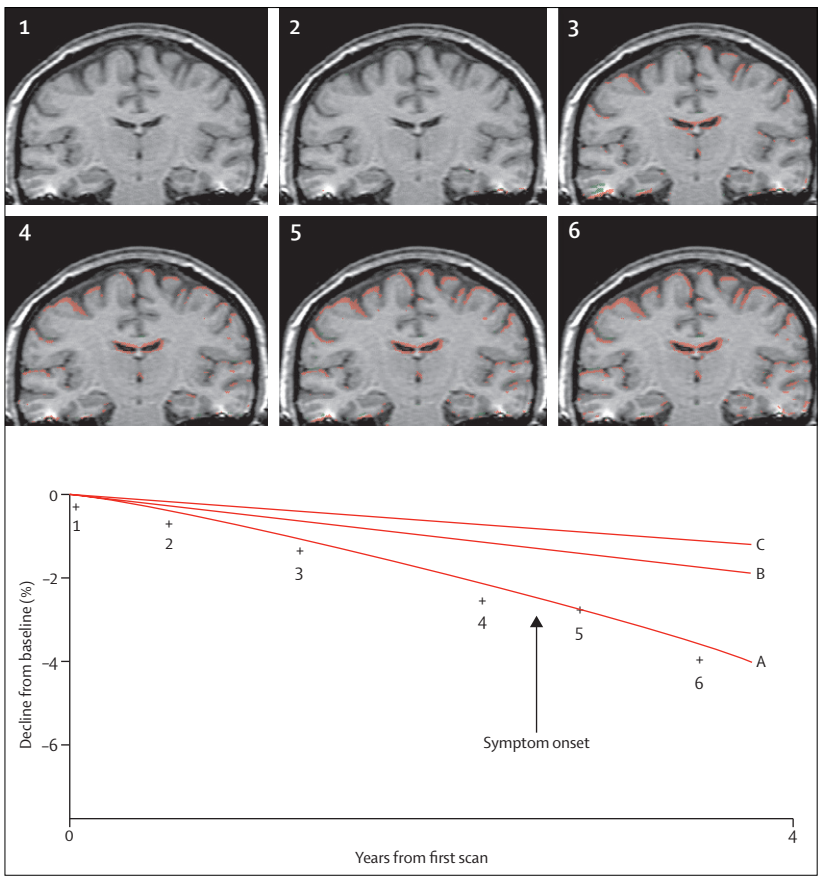

Figure 3: **Progressive atrophy in presymptomatic Alzheimer's disease**
Upper panel shows six serially acquired T1-weighted MRI scans from an initially asymptomatic patient who was destined to develop familial Alzheimer's disease. Scans were acquired over 4 years before criteria for dementia were met; the first symptoms were reported between scans 4 and 5 (arrow in lower panel). Each scan has been positionally matched (registered) to the baseline scan; red overlay represents tissue loss compared with baseline. Lower panel plots brain volumes, derived from registered scans in upper panel, relative to baseline (A); this gradual and accelerating loss, often difficult to see in unregistered scans, is qualitatively and quantitatively different from global brain atrophy in (B) normal ageing and (C) very healthy individuals with a mean age of 70 years. Reproduced from Fox and Schott,[65] by permission of Elsevier.

exact methods and thresholds for specific biomarkers are not set. The criteria represent a major step forward, but refinements, including more operationalised definitions of diagnostic thresholds for specific biomarkers, will probably need to be incorporated as prospective validation studies progress. The criteria might be less reliable in people over 80 years old, in whom the combinations of different pathologies are more common.[63] Additionally, the model needs to be validated and calibrated.[69]

Treatment

To effectively treat Alzheimer's disease, patients and families should be involved as soon as the diagnosis is made. The ability of patients to correctly use money, medications, transportation, and home appliances should be assessed, and information, services, and support should be provided to help patients and their families to live well with dementia. Concomitant medical conditions and polypharmacy can exacerbate cognitive decline and increase the risk of cerebrovascular disease and therefore should be used to best practice standards.

Table 3 summarises the main licensed treatments and examples of emerging pharmacological and immunotherapy treatments. Symptomatic treatments for Alzheimer's disease have been widely available since the mid-1990s. Cholinesterase inhibitors were thought to improve cognition and indirectly help function and behaviour in patients with Alzheimer's disease. Evidence from clinical trials and clinical practice is that the effect of cholinesterase inhibitors on cognition is moderate (1·5–2 points on the mini mental state examination over 6–12 months), with additional short-term (3–6 months)

Panel: Research diagnostic criteria for Alzheimer's disease

Probable Alzheimer's disease: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A Presence of an early and significant episodic memory impairment that includes the following features:
- 1 Gradual and progressive change in memory function reported by patients or informants over more than 6 months
- 2 Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
- 3 The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of Alzheimer's disease or as Alzheimer's disease advances

Supportive features

B Presence of medial temporal lobe atrophy: volume loss in the hippocampus, entorhinal cortex, or amygdala on MRI with qualitative ratings by visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C Abnormal cerebrospinal fluid biomarker: low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phosphotau concentrations, or combinations of the three; or abnormalities in other well-validated markers that will be discovered in the future

D Specific pattern of reduced glucose metabolism in bilateral temporal parietal regions on functional neuroimaging with PET or with other well validated ligands, such as Pittsburgh compound B or FDDNP (2-(1-(6-[(2-[^{18}F]fluoroethyl)(methyl)amino]-2-naphthyl) ethylidene)malononitrile)

E Proven Alzheimer's disease autosomal dominant mutation within the immediate family

Reproduced from Dubois et al,[71] by permission of Elsevier.

	Drugs	Status	Evidence
Symptomatic treatments			
Cholinesterase inhibitors	Donepezil, rivastigmine, galantamine	Licensed for mild-to-moderate Alzheimer's disease	More than 30 placebo-controlled randomised controlled trials, mainly of 6 months duration in patients with mild-to-moderate Alzheimer's disease (MMSE 10–26). Significant benefits in cognition, function, and global outcome, with MMSE gain of 1·5–2 points over 6–12 months. Several studies suggest similar benefit in severe Alzheimer's disease[72-75]
NMDA receptor antagonist	Memantine	Licensed for moderate-to-severe Alzheimer's disease	Significant benefit in cognition, function, global outcome, and neuropsychiatric symptoms over 6 months in three trials of moderate-to-severe Alzheimer's disease[76]
Treatments for neuropsychiatric symptoms			
Atypical antipsychotics	Risperidone, quetiapine, olanzapine, aripiprazole	Risperidone licensed for short-term treatment of severe aggression in Alzheimer's disease; other treatments are used off licence	Significant but modest efficacy for the treatment of aggression (SES 0·2–0·25) and psychosis (SES 0·15–0·2) over 6–12 weeks. Limited evidence of longer term benefits. Atypical antipsychotics associated with significant increase in stroke (RR 2·5–4·0) and death (RR 1·5–1·8)[77]
Antidepressants	Citalopram, sertraline	All antidepressants used off licence in Alzheimer's disease	Evidence not clear-cut. The largest trial with sertraline suggested no benefit for the treatment of depression in patients with Alzheimer's disease.[78] Severe depression should be treated, probably with a selective serotonin reuptake inhibitor
Anticonvulsants	Carbamazepine	Used off licence	There is preliminary evidence from small randomised controlled trials that carbamazepine might be an effective treatment for agitation or aggression in Alzheimer's disease[79]
Proposed disease-modifying treatments			
Immunotherapy	Bapineuzumab	In phase 3 clinical trials	Passive immunotherapy treatments show some benefit in animal models of Alzheimer's disease.[80] Bapineuzumab is in phase 3 clinical trials
Sectretase inhibitors	Tarenflurbil, semagacestat	In phase 3 trials	Tarenflurbil failed in phase 3 trials.[81] Semagacestat is in a phase 3 clinical trial programme at present
Amyloid aggregators	Tramiprosate	Discontinued	Failed in phase 3 trials[82]
Copper or zinc modulators	PBT2	Phase 2 clinical trials	PBT2 resulted in a decrease in cerebrospinal fluid amyloid and provided significant clinical benefit in a phase 2 clinical trial.[83,84] Phase 3 trials are awaited
Tau aggregation inhibitors	Methylthioninium chloride	Phase 2 clinical trial	A promising phase 2 trial suggested significant cognitive benefit over 52–78 months of follow-up, but there were major methodological limitations[85]
GSK3 inhibitors	Lithium	Early-phase clinical trials	The mood stabilising drug lithium inhibits the enzyme GSK3 and reduces the phosphorylation of tau in animal models.[86] Early-stage clinical trials are in progress
Natural products and vitamins	Vitamin E, ginkgo biloba, omega 3 fatty acids, and docosahexaenoic acid	Phase 2 and phase 3 clinical trials	Despite initial promise, a more recent randomised controlled trial in mild cognitive impairment did not report any benefit with vitamin E[87,88] A meta-analysis suggested ginkgo biloba might provide moderate benefit, but a large randomised trial did not show any advantage of ginkgo biloba compared with placebo[89,90] A large randomised controlled trial of omega 3 fatty acids did not report any benefit on function or cognition, but did suggest some possible benefit on neuropsychiatric symptoms in a post-hoc subgroup analysis.[91] A National Institute on Aging phase 3 trial of docosahexaenoic acid is in progress

MMSE=mini mental state examination. SES=socioeconomic status. RR=relative risk. GSK3=glycogen synthase kinase 3.

***Table 3*: Treatments for Alzheimer's disease**

improvement in cognition and global outcome and some stabilisation of function over this period. Moderate improvements in mood (particularly apathy) and social interaction have also been reported after treatment with cholinesterase inhibitors.[72–75] However, the outcome measures used in randomised clinical trials for the purpose of regulatory approval do not translate well into day-to-day practice. New approaches to measure outcome effects, such as goal attainment scaling, have reported beneficial effects of cholinesterase inhibitor therapy on individualised outcomes that are important to patients and their families.[92,93] Memantine improved cognitive performance and function over a 6-month period compared with placebo,[76,94] and preliminary evidence suggests that memantine might also be beneficial in the prevention and treatment of agitation and aggression.[95] There also seem to be additive benefits of combining a cholinesterase inhibitor and memantine.[96] Cognitive training in healthy older people and in patients in the early stages of Alzheimer's disease might also be helpful by improving specific aspects of cognitive ability associated with the type of training that is undertaken, with a recent meta-analysis and systematic review suggesting moderate benefit (standardised effect size 0·16) across a variety of training approaches.[97]

Antipsychotic drugs are commonly used to treat agitation, aggression, and psychosis in patients with dementia, but benefits are moderate, and serious adverse events include sedation, parkinsonism, chest infections, ankle oedema, and an increased risk of stroke and death.[77,98] Therefore, potential benefits and risks should be carefully balanced, other approaches used when possible, and long-term prescription avoided. Simple non-pharmacological treatments, such as social interaction, person-centred care training, and aromatherapy can be effective alternatives to drug treatment in patients with

Alzheimer's disease.[75–77,79,92–102] The benefit of antidepressant therapy has not been established, with a large trial reporting limited or no benefit.[78] Another large trial is in progress at present. Severe depression adds to impairment and disability in people with Alzheimer's disease and should be treated with antidepressants. Exercise and having an events schedule provide effective non-pharmacological alternatives for treatment of mild depression in patients with Alzheimer's disease.[103]

Several disease-modifying treatments for Alzheimer's disease have been proposed, most of which target Aβ. The immunotherapy approach is based mainly on the original Aβ cascade hypothesis. Active immunotherapy with fragments of the Aβ protein was effective at clearing Aβ and improving behaviour in transgenic mice.[104] However, results were mixed in a study in patients with Alzheimer's disease;[105] clearance of Aβ plaques occurred but some patients developed encephalitis, and the clinical benefit was less clear-cut than in the animal studies. Passive immunotherapy with antibodies to Aβ has shown some benefit in a transgenic mouse model of Alzheimer's disease,[80] and clinical trials in people with Alzheimer's disease are in progress. There is some scepticism about how this approach works, because only a small proportion of antibody crosses the blood–brain barrier. Other possible mechanisms of action have been proposed, such as the so-called peripheral sink hypothesis, which suggests that clearance of peripheral Aβ might lead to a diffusion gradient that promotes clearance of brain Aβ. Additionally, the absence of concordance between Aβ clearance and clinical benefit has generated debate regarding the direct pathogenic role of Aβ plaques in Alzheimer's disease.[105] Specific antibodies targeting oligomers or other toxic Aβ species have been suggested to more likely be effective for treatment of Alzheimer's disease than antibodies that target all or a broad range of amyloid subtypes.

Several potential therapies either inhibit β secretase or modulate γ secretase, with the goal of increasing the concentration of $Aβ_{1–40}$ and reducing $Aβ_{1–42}$. The development of specific inhibitors of β secretase is an obvious and attractive prospect to prevent production of Aβ because this is a key part of the production of Aβ from the cleavage of amyloid precursor protein. The nature of the active site of this enzyme is a challenge for therapeutic development because molecules that bind to this site do not tend to possess properties that enable them to easily cross the blood–brain barrier. One modulator of γ-secretase activity, tarenflurbil, seemed to be promising in phase 2 clinical trials, but did not show significant benefits in subsequent larger randomised controlled trials (eg, see trial of tarenflurbil[81]).

Several therapies have directly targeted the aggregation of Aβ or the disruption of preformed Aβ aggregates, or both. A clinical trial of an aggregation inhibitor, tramiprosate,[82] was negative, but other drugs that inhibit aggregation are being assessed in clinical trials. Several other factors influence the processing, aggregation, and clearance of Aβ and proteins in related pathways. One potential treatment target was identified from experimental evidence that suggested that both copper and zinc are involved in the precipitation of Aβ, are enriched in plaques, and modulate the response of the NMDA receptor.[106] These findings might explain the vulnerability of Aβ to abnormal interaction with these metal ions in the synaptic region. Findings from phase 2 studies of the ionopores clioquinol and PBT2 have reported clinical benefit and decreased CSF Aβ,[83,84] which provides some support for this hypothesis and offers encouragement for phase 3 trials.

Several promising drugs that target amyloid have failed in randomised controlled trials, and at present there is no drug with proven efficacy that directly acts on amyloid processing. This failure is mostly explained by expected attrition; in all medical specialties only a minority of drugs tested in clinical trials successfully become licensed treatments, which emphasises the urgent need for an increased number of clinical trials. A growing number of researchers also now believe that treatments that target amyloid might be more effective much earlier in the disease process than in late-stage disease, perhaps mainly in individuals identified by the Dubois research criteria. However, the complexity of normal and abnormal cellular interactions and the heterogeneity of pathological changes might mean that even this treatment approach is too simplistic, although it is a sensible next step.

A smaller number of therapies than have targeted Aβ have targeted tau phosphorylation or tau aggregation. A number of inhibitors of GSK3β have been developed over the past few years, and two well-known drugs, lithium and sodium valproate,[107] also inhibit this kinase to some extent. Lithium has shown some potential benefits in reducing tau pathology in animal models of Alzheimer's disease,[86] and a study of sodium valproate in man is in progress. Another approach to reduce tau pathology has been to try to directly inhibit tau aggregation; preliminary evidence suggests that methylthioninium chloride might have a substantial beneficial effect on this process.[85]

Risk and protective factors

At present, reduction of the risk of developing Alzheimer's disease depends mostly upon lifestyle changes and improved treatment or prevention of medical conditions that confer additional risk. A database of epidemiological reports that assess environmental risk factors for Alzheimer's disease is available online. There is a large amount of data about potential risk factors for Alzheimer's disease, including age,[2] genetics,[13] and head injury.[108] Here, we focus on modifiable risk factors. Table 4 summarises the evidence regarding modifiable risk factors for Alzheimer's disease.

Meta-analyses and systematic reviews provide robust evidence that cognitive reserve (a concept combining the benefits of education, occupation, and mental activities),[112]

For more on **reducing the risk of Alzheimer's disease** see http://www.alzheimers.org.uk/smartthinking

For the **database of epidemiological reports** see http://www.alzrisk.org/default.aspx

physical activity and exercise,[111] midlife obesity,[109] alcohol intake,[113] and smoking[110] are the most important modifiable risk factors for Alzheimer's disease. There is insufficient overall evidence from epidemiological studies to support any association between dietary or supplementary antioxidant or B vitamins and altered risk of incident dementia.[122,123] Data from several independent timepoints from a large Swedish epidemiological study suggest that better social networks and social activities might be associated with reduced incidence of Alzheimer's disease,[124] but this has not been examined systematically in large epidemiological cohorts.

Many treatable medical conditions are also associated with an increased risk of Alzheimer's disease, including stroke,[115] diabetes,[116] midlife hypertension,[114] and midlife hypercholesterolaemia.[118,120] Blood pressure and cholesterol both seem to be reduced in late life and in the prodrome to Alzheimer's disease;[114,118] thus, the difference between midlife and late life is an important distinction. There is probably an important relation between some of these conditions and the lifestyle factors mentioned previously, and interventions to promote healthy living will probably reduce the incidence of diabetes and stroke as well as having other, more direct, effects on dementia. There is limited evidence about the potential effect of management of diabetes or stroke on the risk of subsequent dementia, and more intervention trials on this topic are needed.

Randomised controlled trials have not consistently shown beneficial effects of statins and antihypertensive drugs on cognitive function or incident dementia.[119,120] This absence of effect might in part be explained by the design of the studies, which are difficult to interpret because they did not focus on the same age group as the longitudinal studies in which the association between statins and hypertensive drugs and dementia was first identified. Additionally, methodological issues, such as limited differences in blood pressure between treatment groups, might have contributed to the negative results in antihypertensive treatment studies. Specific biological mechanisms might confer additional benefits for certain classes of antihypertensive drugs—eg, diuretics and angiotensin receptor blockers[125]—but further clarification is needed.

	Description of study	Main outcomes
Lifestyle		
Obesity[109]	Meta-analysis of ten studies. All prospective studies with at least 2 years follow-up and participants over 40 years old	Dementia RR 1·42 (95% CI 0·93–2·16); Alzheimer's disease 1·80 (1·00–3·29)
Smoking[110]	Meta-analysis of four prospective studies with 2–25 years follow-up in over 17 000 people. In the four studies the dementia ORs were 3·17 (95% CI 1·37–7·35), 1·42 (1·07–1·89), 1·60 (1·00–2·57), and 1·63 (1·00–2·67)	Dementia RR 2·2 (1·3–3·6)
Physical activity[111]	13 prospective studies focusing on Alzheimer's disease, dementia, or both, with at least 150 000 participants	Dementia RR 0·72 (95% CI 0·60–0·86); Alzheimer's disease 0·55 (0·36–0·84)
Cognitive reserve (intelligence, occupation, and education)[112]	22 prospective studies with at least 29 000 participants followed up for a median of 7·1 years	Dementia OR 0·54 (95% CI 0·49–0·59)
Alcohol[113]	15 longitudinal studies with 2–8 years follow-up and at least 14 000 participants	Dementia RR 0·74 (95% CI 0·61–0·91); Alzheimer's disease 0·72 (0·61–0·86)
Medical conditions		
Midlife hypertension[114]	At least 15 years follow-up in most studies, with at least 16 000 participants	Four of five longitudinal studies focusing on midlife hypertension suggested that it is a significant risk factor for incident dementia (RR 1·24–2·8 in different studies) The biggest differences were reported in studies using 160/95 mm Hg as the threshold for hypertension
Stroke[115]	16 studies with at least 25 000 participants, mainly included patients aged 65 years and over	12 of 16 studies showed significant association between stroke and incident dementia, with overall doubling of incidence
Diabetes[116]	15 prospective cohort studies	Dementia RR 1·47 (95% CI 1·25–1·73); Alzheimer's disease 1·39 (1·16–1·66)
Midlife hypercholesterolaemia[117,118]	18 studies, but only five assessed high cholesterol specifically in midlife. All five midlife studies had over 15 years follow-up and a total of over 15 000 participants	Four of five longitudinal studies in midlife suggested a significant positive association between high total cholesterol and incident dementia. For overall difference the RR was 1·4–3·1
Intervention studies		
Hypertension[119]	12 091 participants between the three trials (SHEP, SYST-EUR, and SCOPE) with mean follow-up of 3·3 years. Only SYST-EUR reported significant benefit	OR 0·89 (95% CI 0·69–1·16) for incident dementia
Statins for prevention of dementia[120]	26 340 participants between the two trials (PROSPER and HPS), with follow-up of 3·2 and 5 years. Cognition was measured with different instruments at different timepoints and so a meta-analysis not possible	Neither of the two trials reported significant benefit of statin therapy
Vitamins B12 or folate[121]	Four trials in older people without existing cognitive impairment	Three trials showed no benefit. One trial (the only that selected participants based on increased homocysteine) reported benefit with respect to global function

RR=relative risk. OR=odds ratio. SHEP=Systolic Hypertension in the Elderly Program. SYST-EUR=Systolic Hypertension in Europe. SCOPE=Study on Cognition and Prognosis in the Elderly. PROSPER=PROspective Study of Pravastatin in the Elderly at Risk. HPS=Heart Protection Study.

***Table 4*: Meta-analyses or systematic reviews of risk factors for dementia and Alzheimer's disease**

From the available evidence, vitamin supplements do not seem to be effective,[121] but several cohort studies have reported the potential of a Mediterranean diet at reducing the risk of incident Alzheimer's disease.[126,127] There is no convincing evidence at present that specific interventions that focus on particular types of cognitive stimulation can reduce incident dementia. Although there is evidence of moderate benefits in specific aspects of cognitive functioning in older individuals,[128,129] brain training games do not confer benefit in people under 60 years old.[130] Many modifiable risk factors for Alzheimer's disease overlap; thus, the most promising approach to reducing prevalence of the disease is probably a more general intervention to promote healthy living, with a strong emphasis on exercise as an important component.

A recent independent consensus expert report commissioned by the Agency for Healthcare Research and Quality in the USA concluded that recommendations cannot be made for disease prevention because the available evidence is not robust enough for safe advice to be given. This is an important cautionary note and emphasises the need for further research into modifiable risk factors for Alzheimer's disease.[131]

Contributors

CBa planned the overall structure of the Seminar, took the lead of writing the pathogenesis and risk factors sections, and pulled together the different sections into the submitted manuscript. SG contributed to the overall manuscript and the final draft and took a lead in producing the first draft for the treatment section and table. AC did the literature review and wrote the epidemiology section, edited and formatted the Seminar, and produced the tables and figures. CBr contributed to the overall strategy of the seminar, led the BBC think SMART panel that underpinned the prevention section, co-wrote the prevention section with AC, and contributed to the final version of the manuscript. DA did the literature search and wrote the diagnosis section, and critically reviewed the Seminar. EJ contributed to the overall writing of the manuscript and the final draft and took a lead for the text and table relating to genetics studies and related molecular biology.

Conflicts of interest

CBa has received consultancy fees from Novartis, Lundbeck, Eisai, Acadia, and Bristol-Myers Squibb; honoraria from Lundbeck, Novartis, Eisai, and Acadia; payment for manuscript preparation from Bristol-Myers Squibb; and travel and accommodation expenses from Lundbeck, Acadia, Novartis, Eisai, and Bristol-Myers Squibb. CB's institution has received grants from Lundbeck and Acadia and grants from Lundbeck, Novartis, Eisai, and Acadia. SG has received payment for acting as a scientific adviser for Affris, AstraZeneca, Elan, ExonHit, GE Healthcare, Lundbeck, Merz, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Sonexa, and United Biosource; a speaker for Affris; chair of the data and safety monitoring board for Bristol-Myers Squibb; an investigator for Lundbeck, Eli Lilly, Novartis, Pfizer, and Sonexa; and a speaker for Affiris and Lundbeck. DA has received consultancy fees from Lundbeck, GE Healthcare, and Merck-Serono; grants from Lundbeck and Merck-Serono; honoraria from Merck-Serono, Lundbeck, Novartis, GE Healthcare, and GlaxoSmithKline; and payments for development of educational presentations from Lundbeck. AC, CB, and EJ declare that they have no conflicts of interest.

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