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Abstract:	\<h6 style="margin: 2pt 0cm 0.0001pt; break-after: avoid; font-size: 12pt; font-family: Cambria, serif; color: rgb(36, 63, 96);"\>\<span lang="EN-US" style="color: black;"\>In this seminar the main developments in the field of Alzheimer’s Disease (AD) are highlighted. Most recent data estimate a doubling of dementia prevalence in Europe by 2050. When prevalence estimates of AD are made on a biological, rather than a clinical definition of AD, the prevalence of biologically defined AD is three times higher than that of clinically defined AD. The biological definition based on biomarkers of Aβ and tau has been suggested for research and may enter the clinic in due course. The earliest, cellular, phase of AD includes alterations in neurons, microglia and astroglia. Neuro-inflammation\</span\>\<span lang="EN-US" style="color: black;"\>,\</span\>\<span lang="EN-US" style="color: black;"\>\<sup\>1\</sup\> alterations in the vessels, aging, dysfunction of the glymphatic system act upstream or in parallel to accumulating Aβ in this cellular disease landscape. Aβ induces the spreading of tau pathology, which is associated with the appearance of necroptosis markers in neurons displaying granulo-vacuolar degeneration. Risk of AD depends for 60-80% on heritable factors. Causative genes include PSEN 1, PSEN2, APP and Sorl1. Risk genes include one or two alleles of APOE4. GWAS studies have identified another 40 risk genes. Protective genes include APOE2, and mutations in the PLCG2 , KLOTHO and the Icelandic \<i\>APP\</i\> A673T genes.\<o:p\>\</o:p\>\</span\>\</h6\> \<h6 style="margin: 2pt 0cm 0.0001pt; break-after: avoid; font-size: 12pt; font-family: Cambria, serif; color: rgb(36, 63, 96);"\>\<span lang="EN-US" style="color: black;"\>Next to the established CSF markers, novel biomarkers include plasma assays for Aβ and p-tau which show great promise for clinical use. Amyloid PET is now making its way into the clinical arena, while tau-PET is established in research. Multidomain lifestyle-based prevention trials suggest cognitive benefits in subpopulations of participants with increased risk of dementia. Lifestyle factors do not directly impact AD pathology, but can still contribute to a positive outcome in individuals with AD. Promising pharmacological treatments are poised at advanced stages of testing in clinical trials and include anti-abeta, anti tau, anti-inflammatory strategies.\<o:p\>\</o:p\>\</span\>\</h6\>

Seminar: Alzheimer's Disease 2020

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Brief summary

In this seminar the main developments in the field of Alzheimer's Disease (AD) are highlighted. Most recent data estimate a doubling of dementia prevalence in Europe by 2050. When prevalence estimates of AD are made on a biological, rather than a clinical definition of AD, the prevalence of biologically defined AD is three times higher than that of clinically defined AD. The biological definition based on biomarkers of Aβ and tau has been suggested for research and may enter the clinic in due course. The earliest, cellular, phase of AD includes alterations in neurons, microglia and astroglia. Neuro-inflammation,[1] alterations in the vessels, aging, dysfunction of the glymphatic system act upstream or in parallel to accumulating Aβ in this cellular disease landscape. Aβ induces the spreading of tau pathology, which is associated with the appearance of necroptosis markers in neurons displaying granulo-vacuolar degeneration. Risk of AD depends for 60-80% on heritable factors. Causative genes include PSEN 1, PSEN2, APP and Sorl1. Risk genes include one or two alleles of APOE4. GWAS studies have identified another 40 risk genes. Protective genes include APOE2, and mutations in the PLCG2 , KLOTHO and the Icelandic *APP* A673T genes.

Next to the established CSF markers, novel biomarkers include plasma assays for Aβ and p-tau which show great promise for clinical use. Amyloid PET is now making its way into the clinical arena, while tau-PET is established in research. Multidomain lifestyle-based prevention trials suggest cognitive benefits in subpopulations of participants with increased risk of dementia. Lifestyle factors do not directly impact AD pathology, but can still contribute to a positive outcome in individuals with AD. Promising pharmacological treatments are poised at advanced stages of testing in clinical trials and include anti-abeta, anti tau, anti-inflammatory strategies.

Fast Facts (see separate doc)

Search strategy

Between December 1 2019 and February 1, 2020, we searched the Cochrane Library (2010-2015), PUBMED (2016-2020), and EMBASE (2016-2020). We used the search terms "Alzheimer's Disease" in combination with the terms "pathology, imaging, diagnosis, therapy, trials, epidemiology, CSF, genetics, biomarkers". We largely selected publications in the past 5 years, and especially focused on changes that occurred after the publication of our previous Seminar in 2016.[2] We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for.

Disclosures

Author contributions

PhS set up the design of the paper and invited the other authors to provide parts of the text according to their expertise. PhS and WF combined, mixed and edited the texts and performed additional searches for references.

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none

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INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and quickly becoming one of the most expensive, lethal and burdening diseases of this century. Despite increased research efforts a causative treatment has yet to be registered. After the Seminar in 2016,[2] important developments have taken place in the understanding of the underlying pathology, the recognition of multiple causative and protective genes, the appearance of new blood-based biomarkers and new imaging biomarkers, as well as the first cautious signals of positive effects of both disease modifying treatments and life style interventions. The aim of this Seminar is to provide the reader with up to date insight in where we stand in the field of AD now, as compared to 2016. What has been achieved? What are the advances in the research of the past few years? And what are the open questions, challenges and the next steps to take? We start by describing the clinical context, emphasizing the well-known and also the less well-known clinical manifestations of AD. Next, we describe novel developments in the field of epidemiology, molecular pathophysiology, genetics, body fluid and imaging biomarkers and treatment.

Clinical signs and symptoms

In the panel, three cases illustrate the spectrum of AD in terms of clinical presentation. The impact of the diagnosis at different ages becomes evident, as well as the sheer lack of proper (causative) treatment. The first case (A) highlights a genetically determined AD case because of the ongoing global initiatives of the Dominantly Inherited Alzheimer Network (DIAN) and Alzheimer Prevention Initiative (API) and their clinical trial parts. The second case (B) represents a language variant of AD, usually occurring at younger ages and illustrates the difficulty of recognizing AD in those for whom memory problems are *not* the first and most prominent feature. The third case (C) is a typical amnestic variant, more commonly seen in older patients and clearly illustrates the growing problem of AD-dementia: elderly individuals, often living alone, yet increasingly dependent on care by others.

Insert Panel and figure 1 here

Diagnostic criteria: from clinical, clinical-biological to biological

The diagnosis of AD has gone from a purely pathological one in the days of Alois Alzheimer, to a clinical, exclusionary, approach in 1984 by the NINCDS-ADRDA criteria[3] via clinical-biological approach thanks to the initiative of the International Working Group[4,5] and subsequent efforts by the NIA-AA working groups,[6] incorporating biomarkers in the workup to increase or decrease the likelihood of AD, to a purely biological one (for a review see[7]). Given the developments in the biomarker field and the desire to operationalize their use in a diagnostic framework, a group led by Jack[8] grouped the biomarkers into A (amyloid), T (p-tau) and N (neurodegeneration) (see table 1). In this research framework, the diagnosis of AD is defined by A+ and T+. The observation of A+ (regardless of T and N) is coined Alzheimer's pathologic change.[8] Hence, the (research) diagnosis of AD is based on biomarker evidence only and clinical stages may range from cognitively normal to

MCI and dementia, stressing the continuum of AD, spanning a period of many years. The framework underpins the importance of β-amyloid (Aβ) and tau as the defining characteristics of AD, consequently proposes that AD can be diagnosed by biomarkers only, and has thereby disentangled the concept of AD from the concept of dementia (**see figure 2**).

Insert figure 2 here

Although critique was raised that other key etiologies of *dementia*, in particular vascular disease were omitted,[9] the authors of the framework argued that *dementia* has multiple underlying pathologies, of which AD is one, and AD is defined by Aβ and tau (acknowledging that many other pathologies may also be present).[10] The large number of categories, combined with the fact that other pathologies are not evaluated in the scheme, makes the ATN approach not yet suited for clinical practice.[11] The AT(N) based approach is however already the cornerstone of current trials with disease-modifying interventions in AD.[12]

The ATN framework clearly paves the way for a diagnosis before the stage of dementia. In clinical practice, a diagnosis in predementia stages in fact entails a prognosis, as patients want to know what they can expect. Using ATN biomarkers, individualized risk profiling for MCI patients becomes feasible.[13] A clinical encounter study evaluating doctor-patient communication in memory clinics revealed however that clinicians are quite reluctant to share specific prognostic information with MCI patients.[14] In the context of predementia diagnosis, SCD is even more challenging. A recent point of view paper provides a clinical characterization of SCD, and attempts to provide directions for clinicians.[15] Although on a group level, ATN biomarkers clearly predict incident dementia in SCD, individualized risk modeling remains challenging, as current models have suboptimal generalizability, due to the lack of truly longitudinal data.[16] Yet, the number of people wanting to know the status of their brain health with the ambition to maintain or improve their own brain health rapidly increases. In a Delphi study to identify topics most relevant to discuss in the diagnostic process, patients and caregivers indicated they value precise and specific information, even when that does not provide complete certainty.[17] Tools to support both clinicians and patients/families in decision making and communicating about AD diagnosis are therefore urgently needed. ADappt (www.adappt.health) is a first attempt at providing such a tool.[18]

INSERT Table 1 here

EPIDEMIOLOGY

Incidence and prevalence

In 2015, Alzheimer Disease International estimated a worldwide prevalence of 50 million and almost 10 million incident cases of dementia, mostly due to AD.[19] Most recent data estimate a doubling of dementia prevalence in Europe by 2050.[20] There is accumulating evidence that incidence of dementia may be declining in Western countries.[21] Evidence for a decline in prevalence is less convincing.[22]

Mortality

The relatively stable prevalence despite decreasing incidence could be explained by a longer disease duration. Studies on mortality do not support this notion. A US-based study evaluating survival after dementia diagnosis in almost 60 thousand individuals

reported survival times between three and four years.[23] In a European, memory clinic based cohort, median survival time was six years after a dementia diagnosis (AD dementia: 6.2 (6.0–6.5)).[24] This estimate coincides with a multicenter study that provided estimates of not only the dementia stage, but also the prodromal (MCI) and preclinical disease stages of AD.[25] For an individual aged 70 years, the duration of the dementia stage of AD was estimated to be six years, the prodromal (MCI) stage four years, and the preclinical stage 10 years, totaling 20 years.

Dementia vs AD

Epidemiological studies almost invariably focus on the dementia stage, and use clinical criteria or algorithms to define type of dementia, causing two problems. First, we know that clinical diagnosis of dementia subtypes is often incorrect. Prevalence and incidence of dementia therefore do not equal those of AD. In addition, the largest part of AD takes place before the onset of dementia **(see figure 2)**. A first attempt to estimate prevalence of AD based on biological, rather than clinical definition of AD, showed that at age 85, the prevalence of biologically defined AD is three times higher than that of clinically defined AD.[26]

Risk factors for dementia and AD

The main risk factors for AD are high age and APOE e4 genotype. In addition, women are more likely to develop AD, especially above the age of 80 years. Given a clinical diagnosis of AD, women are more likely to have a higher tau load, despite a rather similar amyloid burden compared to men.[27] In addition, cardiovascular risk factors and a suboptimal lifestyle have been associated with an increased risk of dementia. Taken together, the modifiable risk factors account for roughly one third of the lifetime risk of (any type of) dementia.[28] These estimates illustrate that prevention by intervening on modifiable risk factors is of great relevance, even if the majority of dementia burden cannot be prevented via a lifestyle intervention approach. A growing body of evidence suggests that vascular risk factors do not increase the risk of AD pathology as measured by amyloid in CSF or using PET.[29-31] This implies that although lifestyle and vascular risk factors contribute to cognitive decline and dementia, this may not be via the AD pathway.

GENETICS

Causative and risk genes

The genome represents a powerful tool for AD-risk prediction and provides valuable insights in the molecular mechanisms underlying AD. Twin studies revealed that risk of sporadic late onset AD (LOAD) depends for 60-80% on heritable factors.[32] However, apart from the impact of the common *APOE-ε4* risk-allele, the fraction of the total heritability explained is still limited across the AD spectrum,[33,34,35] suggesting that numerous genetic factors remain to be identified. To identifies these, large genome-wide-association studies (GWAS) have been set up. The latest AD-GWAS studies investigated a total of ~150,000 clinically diagnosed AD cases and age-matched cognitively healthy controls and >300,000 by-proxy AD-cases and controls (a parent did or did not have AD), which increased the number of AD-associated risk alleles to >40.[36] AD-risk alleles identified with GWAS are associated with much smaller contributions to the total AD risk (effect sizes range between 1.05-1.2) (**Figure 3B**). Based on the presence or absence of these risk-alleles in the genome of a single individual, a polygenic risk score (PRS) can be calculated, which is currently

able to classify AD patients from controls with 75-85% accuracy.[37,38] While the majority of this accuracy can be ascribed to the strong effects of the two alleles in the *APOE* gene, the ~40 other variants collectively contribute significantly to AD risk.[39] Functional annotation of these risk-loci indicate that next to β-amyloid metabolism, also the modulation of the immune response, cholesterol, lipid dysfunction, endocytosis and vascular factors play a role.[40-45] With the development of next generation sequencing techniques, rare protein-damaging variants in the *SORL1*[46], *ABCA7*[47] and *TREM2* genes[48,49] were observed to occur more often in AD cases than in controls. This suggests that the intact protein products of these genes are essential in maintaining brain health (**Figure 3A**).

Protective genes

Next to the identification of risk-increasing genetic variants, the interest in the identification of *protective* genetic variants has been fueled (**Figure 3C**). Carriers of the protective allele of *APOE, the ε2* allele, have a ~two-fold *decreased* lifetime risk of AD,[50] which translates to an exceptionally low likelihood of AD for homozygous AP*OE-ε2* allele carriers.[51] The discovery of the rare Icelandic *APP* A673T protective mutation[52] was associated with prolonged cognitive health. Similarly, compared to middle aged population subjects, a rare *Pro522Arg* amino acid change in the phospholipase Cγ2 (PLCG2) gene was recently associated with a near two-fold *reduced* risk of AD[53] and additionally with a two-fold reduced risk of Lewy-body Dementia and Frontotemporal Dementia and with a 2.3-fold *increased* chance of reaching 100 years in cognitive health.[54] Illustrative is the case of a centenarian homozygous for the *APOE-ε4* risk allele, who is currently alive at 104 and cognitively healthy. She carries the *PLCG2* variant, which may (in part) explain her resilience against *APOE-ε4* homozygosity.[55] Genetic resilience was also evidenced in a *PSEN1* case who lived beyond the age of onset of symptoms common in her family, potentially due to an homozygous rare protective variant in the *APOE-ε3* allele (Christchurch mutation).[35] Variants in the *KLOTHO* longevity gene were associated with a similar effect.[56] Such protective genetic variants hold great promise in AD research, as they may pinpoint mechanistic processes associated with endogenous prolonged cognitive health.

INSERT Figure 3 here

PATHOPHYSIOLOGY

Basic scientists coin the preclinical phase of AD the "cellular phase of AD". Alterations in neurons, microglia and astroglia drive the insidious progression of the disease before cognitive impairment is observed.[57] Neuro-inflammation,[1] alterations in the vessels,[58,59] ageing,[60] dysfunction of the glymphatic system[61] act upstream or in parallel to accumulating Aβ in this cellular disease landscape. Aβ induces, in an unknown way, the spreading of tau pathology.[62] Tau-pathology is associated with the appearance of necroptosis markers in neurons displaying granulo-vacuolar degeneration.[63]

Single cell transcriptome analysis has elucidated the microglia response.[64] ApoE and Trem2, two major AD risk genes, are important parts of this response.[64-66] ApoE binds to amyloid plaques and Trem2 interacts with apoE.[67] AD associated genetic variants TREM2 R47H, R62H and D87N decrease this binding (see figure 3).[68] Several other

proteins linked to genetic risk of AD such as SHIP1, CD2AP, RIN3, BIN1, PLCG2, CASS4, PTKB2 act presumably downstream of the APOE/TREM2 signal modulating endocytosis, motility, and phagocytosis in microglia **(see figure 4)**. CD33 acts opposite to Trem2,[69] and MS4A4A modulates sTrem2 secretion.[70] The fact that so many AD risk genes converge on microglial response pathways indicate their central role in AD pathogenesis. More work is however needed to elucidate whether this response is to amyloid plaques only[71] or that it also mediates toxicity induced by Tau pathology[72] or acts protectively against Tau.[73]

These contradictory results reflect partially the limitations of overexpressing mice models for the study of AD. It is possible that strong transgenic Tau overexpression[72] induces an artificially strong neuroinflammatory response which is not seen in milder Tau models.[71,73] Use of non-overexpression mice models[74] or mouse-human chimaeric mice[75,76] or new in vitro models derived from human iPSC cells[77] might help to solve this question. Of note, all preclinical models are reductionistic in nature, implying that any conclusions towards therapeutic developments need to be made with caution.

While cellular pathology has become central in the study of AD, stunning progress has also been made in the understanding of the preceding biochemical phase of the disease (in ATN terms: before A+). Thanks to cryo-electron microscopy we have now fine details of the amyloid[78] and Tau-fibrils.[79] Cryo-electron microscopy has also resulted in full insight in how presenilin, the catalytic subunit of γ-secretase, interacts with APP[80] and Notch substrates.[81] Complemented by functional studies on purified γ-secretase complexes,[82] we understand now that clinical mutations in Presenilin destabilize the γ-secretase-APP interactions, leading to premature release of longer, aggregation prone Aβ peptides. These insights pave the way towards new therapeutic approaches to tackle Aβ in AD.

The role of Aβ in the disease cascade needs to be re-integrated with concepts of resilience and vulnerability. In this view, the cellular responses of neurons, astroglia, microglia, pericytes, endothelial cells, which are largely defined by the genetic make-up of a patient, will determine whether and how long a brain affected by amyloid pathology will continue to function normally.[57,71] Once homeostasis collapses, AD manifests itself clinically. Where and when Tau influences this cellular phase is one of the most interesting questions for the field.

INSERT Figure 4 here

BIOMARKERS

As can be seen in table 1, the biological definition of AD is operationalized by the use of biomarkers of A, T and N. In the following paragraphs we highlight the current and future imaging and body fluid biomarkers

Imaging biomarkers
Established markers: MRI, FDG-PET and amyloid-PET
The three most validated neuroimaging biomarkers for AD are medial temporal lobe atrophy on MRI, posterior cingulate and temporo-parietal hypometabolism on FDG PET – as measures of N, and cortical amyloid deposition with amyloid PET imaging for A. These biomarkers are already widely used in research and in academic memory clinics for AD diagnosis. A 5-phase strategic roadmap showed that the three

biomarkers have almost achieved analytical and clinical validity (phases 1 to 3) while evidence for their clinical utility (phases 4 and 5) is considered insufficient.[83] Large prospective studies are ongoing that should provide answers regarding the clinical impact and utility of amyloid imaging. The ABIDE study showed that amyloid imaging improved diagnostic accuracy and confidence in a memory clinic setting with relatively young patients.[84] The IDEAS study, carried out in a population aged 65 years and above, showed that amyloid-PET imaging impacted clinical diagnosis and diagnostic confidence in about 60% of patients with MCI or dementia[85].

Hindering the widespread implementation of these imaging biomarkers is uncertainty regarding the order of tests. An interdisciplinary group of experts recently concluded that, while MRI is always recommended as the necessary first step after clinical evaluation, the decision on necessity and choice of the next biomarker depends on the specific clinical profile and the individual diagnostic question. Amyloid-PET is most useful to rule out AD, while FDG-PET has great value for the differential diagnosis of neurodegenerative diseases (including non-AD), prediction of short-term clinical outcome, and staging of extent and localization of neurodegenerative processes. Such algorithms can also be used to support clinicians in the choice of whether or not to perform an additional diagnostic test.[86]

Finally, considering regional instead of global cortical amyloid deposition could allow detecting the earliest amyloid stages (corresponding to temporobasal and frontomedial areas) with much higher sensitivity.[87]

Tau-PET

Tau-PET ligands allow the in-vivo characterization of tau tracer retention across the clinical spectrum of AD, consistent with Braak stages.[88] In contrast to amyloid deposition, tau-PET binding topography correlates with cognitive deficits,[89] is specific to the different AD clinical phenotypes,[90] and is predictive of subsequent rates of cognitive decline[91] and atrophy.[92] Tau-PET is a powerful biomarker for differential diagnosis between AD-tauopathy and other neurodegenerative tauopathies.[93] Finally, longitudinal tau-PET studies are emerging and they highlight the sensitivity of this technique to track the progression of the disease,[94] and the spread of tau along brain networks consistent with neuron-to-neuron propagation.[95] Tau-PET is also a powerful tool to grasp the pathological mechanisms of the disease in particular to better understand the role of tau and its interaction with Aβ. First data suggests that Aβ accelerates tau accumulation[96] and/or allows tau spreading outside the MTL.[97]

For Tau-PET to enter clinical practice, methodological refinement is needed. Off-target binding, non-specific binding, the optimal analysis procedure (e.g. which regions to include for early detection of tau deposition, which reference region to select, which threshold to use[98,99]), are still open questions. Second generation tracers have been developed that seem to have better signal-to-noise ratio, less off-target binding and lower non-specific binding.[98,99]

Other imaging modalities

Recent developments of PET ligands targeting synaptic vesicle glycoprotein 2A (SV2A) imaging has opened new avenues to explore brain synaptic density.[100] This is of particular interest in AD, with preliminary reports of decreased SV2A binding in the hippocampus in MCI/AD patients.[101] Further development of PET markers for neuroinflammation, α-synuclein, TDP-43, and neurotransmitter systems are also eagerly awaited. Better use of multimodal neuroimaging is needed and this includes development of dual-phase amyloid/tau PET imaging (allowing access to joint

information – N and A or T - from a single PET-tracer injection), hybrid PET/MR imaging and artificial intelligence.

Fluid biomarkers

As seen in table 1, A, T and N can also be ascertained via body fluid markers, greatly facilitated by the development of automated platforms for analysis of (A) Amyloid beta [1-42], (T) pTau-181 and (N) total Tau.[102-104] Through extensive global collaboration **(box 1)** reference methods and materials have been developed[105] and assay outcomes between providers of CSF AD biomarker assays have been aligned.[106] Standardized operating procedures for CSF collection and analysis[107,108] have been developed and a quality control program for monitoring consistency in analysis results has been firmly established.[108,109] All these endeavors are directed to generate global uniform cut-offs to define if someone's profile is AD-like.

Insert BOX 1 here

CSF markers
Aside from the established CSF abeta 1-42, 1-40 for A, p-tau 181 for T and total tau for N biomarkers, some new developments can be reported for CSF biomarkers. Especially markers reflecting axonal damage and synaptic dysfunction are interesting in view of synaptic pathology being present early in the disease course and its relation with functional outcomes and cognitive decline. Several of these biomarkers are emerging (e.g. Neurogranin, SNAP-25, synaptotagmin, the neuronal calcium sensing protein VILIP-1).[110-114] Of these, neurogranin seems the most promising, given its specificity for AD compared to other dementias and its increase in early stages over the AD spectrum. YKL-40, a microglia/astrocyte biomarker, is a promising marker to monitor treatment effect, is especially increased in FTD, and (less) in AD.[112,115] sTREM2 is interesting because of its link to genetics (*vide supra*). Increases in serum levels are observed on a group level independent of the presence of the mutation and levels appear to have a bimodal course along the AD spectrum.[116]
Some non-protein biomarkers are worth mentioning. Initial exciting results on a plasma metabolomics profile[117] were replicated,[118-120] although with different profiles. An important issue for the metabolome is the lack of specificity to a disease process and the subtlety of changes.

Serum and plasma biomarkers
Ultrasensitive technologies enable the accurate measurement of CNS proteins in blood. A poignant example is neurofilament light (Nfl), a major axonal cytoskeleton protein that is a cross-disease biomarker of neurodegeneration (N).[121] The levels in blood are increased similarly as in CSF, making clinical implementation of this marker feasible. In the dementias, NfL has particular potential in the diagnostic discrimination of FTD vs psychiatric patients.[122] A potentially very useful application is in monitoring of treatment response, similar as seen for other diseases where effective treatments are in place, such as in Multiple Sclerosis and Spinal Muscular Atrophy.[123-125]

Very exciting are the consistent and converging reports showing reductions in plasma amyloid levels in AD, by applying immunoprecipitation combined with mass spectrometry, or microfluidics and other advanced technologies, such as Simoa, Immunoreduction and Protein Amide Bond analysis.[126-132] Results of current

collaborative investigations will show which of the technologies provide the best specificity for different purposes (screening, stratification, effect monitoring) and hold the strongest promise for implementation for high-throughput analysis, needed when drugs become available and prescreening and monitoring of amyloid changes becomes relevant. As for T, two recent papers show strong evidence of plasma pTau-181 as a diagnostic biomarker for AD vs other dementias and for identification of both amyloid and Tau PET pathology.[133,134]

The exciting and rapid developments in plasma-based assays for A, T and N, hold promise for prescreening in research, reducing number of LP's and PET scans, as well as for diagnostic purposes, once decently validated, in clinical practice.

TREATMENT OPTIONS

Non-pharmacological
In 2019 the WHO released the first guidelines for risk reduction of cognitive decline and dementia.[135] The guidelines acknowledge that for some factors – e.g., physical activity, diet, overweight/obesity, tobacco and alcohol use, hypertension, diabetes – recommendation can be provided, although with different degrees of certainty. Some limitations in the current evidence include lack of harmonization (e.g. exposure definition), lack of long-term randomized controlled trials (RCT), and limited evidence from low-and middle-income countries where dementia numbers are increasing rapidly.

New trial results are emerging. The Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition IN Decreased Hypertension (MIND) trial reported that intensive blood pressure control (goal <120 mmHg) is more effective in reducing the risk of cognitive impairment than standard blood pressure control (goal <140 mmHg). These results further highlight the concept 'what is good for the heart is good for the brain', although the question of the optimal therapeutic target especially among oldest old individuals (85+ years) remains.[136]

Multi-domain interventions to prevent cognitive decline and dementia
The multifactorial nature of late-life cognitive impairment, AD and dementia, suggests that multidomain interventions targeting several risk factors and disease mechanisms simultaneously are needed for optimum preventive effects. Previous single-intervention failures further stress the critical need for a new multimodal preventive approach that has been successful in cardiovascular and diabetes prevention field.[137]

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first large-scale, long-term RCT showing that a multidomain lifestyle-based intervention can reduce the risk of cognitive impairment among at-risk persons from the general population. FINGER combined healthy balanced nutrition, physical exercise, cognitive training and social activities, and vascular/metabolic risk management. The trial showed benefits on cognition, even in people with genetic susceptibility for AD.[138,139]

Two other large multidomain lifestyle-based prevention trials have also been recently completed: the French Multidomain Alzheimer Preventive Trial (MAPT), which tested the association of a lifestyle intervention with omega-3 fatty acids supplements, and the Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA), mainly focused on the pharmacological management of vascular/metabolic risk factors.[140,141] Both trials reported no benefits of the intervention on the primary outcome, but subgroup analyses suggested cognitive benefits in subpopulations of participants with increased risk of dementia. In a later study using amyloid PET to select participants in the MAPT study, life style intervention alone or in combination with omega-3 fatty acids, was associated with improved primary cognitive outcome in subjects with positive amyloid status.[142] The latter study stresses that even when lifestyle factors do not directly impact AD pathology, they can still contribute to a positive outcome in individuals with AD pathophysiology. Details are given in table 2.

INSERT TABLE 2 here

Future directions: from complexity to precision prevention
In 2020, over 25 countries have joined WW-FINGERS (www.alz.org/wwfingers), which aims to adapt, test and optimize the FINGER model in different geographical, cultural and economic settings. Prospective data harmonization will enable joint-analysis and ultimately lead to the definition of effective and scalable preventive strategies in different settings and populations.

One of the WW-FINGERS studies, the Multimodal Prevention Trial for Alzheimer´s Disease (MIND-AD), evaluates the feasibility of the FINGER multidomain lifestyle intervention in subjects with prodromal AD. MIND-AD is an example of future trials where pharmacological and non-pharmacological preventive strategies can be tested in combination. The study is testing the feasibility of a multidomain intervention combined with a medical food product, which showed promising results after 2 years of treatment in a large RCT in subjects with prodromal AD[143] and sustained positive effects on CDR and hippocampal volume after 3 years.[144].

Overall, the co-occurrence of risk factors, as well as the time- and age-dependent effect imply that tailored, life-course approaches targeting multiple risk factors to specific risk profiles need to be developed. This means that middle-aged and older adults, as well as individuals with heterogeneous risk profiles, may benefit from different multidomain preventive strategies. Additionally, narrowing the gap between non-pharmacological and pharmacological trials, it is expected that multimodal interventions can be based on lifestyle + drugs combinations for the best preventive effect on an individual basis.

Pharmacological
Cognitive Enhancing Treatments for Alzheimer's Disease
Currently approved treatments that comprise the standard-of-care for many patients with AD include cholinesterase inhibitors and an N-methyl-D-aspartate (NMDA) receptor antagonist, memantine. Current pharmacotherapy for cognition is often accompanied by recommendations for a brain-healthy lifestyle as detailed above.[137] There has been no new symptomatic cognitive enhancing agent approved globally since our seminar in 2016.[2] Three programs assessing the utility of 5-HT$_6$ antagonists

for cognitive improvement have recently failed and demonstrate that this pathway is not a viable therapeutic approach for cognition.[145]

Drugs to Treat Neuropsychiatric Symptoms of Alzheimer's Disease
Progress is being made in developing AD- or dementia-specific psychotropic interventions. Pimavanserin is a 5-HT$_{2A}$ inverse agonist that was assessed in a basket trial for dementia-related psychosis (DRP) including patients with psychosis in the setting of AD, Parkinson's disease with dementia, dementia with Lewy bodies, frontotemporal degeneration spectrum disorders, and vascular dementia.[146] The trial was stopped early for success, and pimavanserin will be submitted to the US Food and Drug Administration (FDA) as a therapy for DRP.
Agitation is a common problem in dementia, occurring in up to 70% of patients with AD in the course of their illness. There have been recent trials supportive of treatment with brexpiprazole (an atypical antipsychotic), citalopram (a selective serotonin reuptake inhibitor), and nabilone (a cannabinoid).[147] These studies suggest that designing and conducting trials that show a reduction in agitation with appropriate interventions is plausible. Ongoing trials are assessing the efficacy of brexpiprazole, escitalopram, prazosin, dextromethorphan plus quinidine, and dextromethorphan plus bupropion for AD-related agitation.
Sleep and night-time behavioral disturbances disrupt the lives of patients and caregivers. A recent trial of suvorexant showed significant increases in total sleep and decreased awakening after falling asleep. Suvorexant is a dual orexin antagonist approved for insomnia, and the authorized prescribing information now includes clinical trial and adverse event information regarding the use of the agent to treat insomnia in AD.[148] Lemborexant, another dual orexin antagonist, is in a trial for irregular sleep-wake rhythm disorder in AD.

INSERT TABLE 3 HERE

Disease-Modifying Therapies for Alzheimer's Disease
Most of the AD drug development pipeline is devoted to disease-modifying therapies (DMTs; Table 3).[62,149] These agents are in secondary prevention trials of individuals with preclinical, prodromal or mild, or moderate to severe AD.
Amyloid has been the most common target of current drug development programs in Phase II and Phase III. Growing evidence suggests that by removing amyloid oligomers (soluble aggregates of Aß) and plaques (insoluble extracellular aggregates of fibrillar Aß) with monoclonal antibodies, disease progression can be slowed. Aducanumab, BAN2401 and gantenerumab all reduce plaque amyloid.[150] These agents also reduce p-tau, neurogranin, and neurofilament light (NfL) in the CSF; observations that suggest that removal of Aß is associated with "downstream" effects on tau pathology and neurodegeneration. In each case, ambiguities in the clinical trials remain to be resolved. None have been approved by regulatory authorities and Phase III clinical trials are on-going. Amyloid vaccines are being tested in active immunotherapy trials and comprise a promising area for AD therapeutics.
Beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors were a promising class of AD DMTs that markedly reduce levels of CSF Aß by inhibiting the generation of monomers from the amyloid precursor protein (APP). Several of these agents were in the AD drug development pipeline and all have been stopped when trials showed an acceleration of deterioration in cognition, elevated liver enzymes, or futility.[151] It should be noted that many trials were stopped early on, based on futility

analyses with less than half of the patients finished the trials and that it remains unclear whether longer treatments would have exerted beneficial effects. Since for some of the BACE1 drugs safety profiles appeared better than for others, a major point of discussion remains whether the benefits on the long-term cognition could outweigh the relative mild side effects on the short term. In addition, very high doses of the drugs were used which maximized the chance on side effects. Unfortunately, further development of this class of agents is unlikely unless major new insights into their safety and efficacy are forthcoming.

Tau biology is providing another repertoire of potentially important targets for DMTs.[152] Several monoclonal antibodies targeting different epitopes are in trials. The monoclonal antibodies are intended to engage extracellular tau as it spreads from cell-to-cell. Small molecules targeting tau aggregation and neurofibrillary tangle formation are being assessed. All these approaches come with potential side effects and the field should seriously think about risk-benefit and more complex trials with better dose finding and measurements of therapeutic target engagement. Otherwise it is not unlikely that tau-targeted trials will end in premature futility analyses with little additional learning from why trials fail and what can be improved.

Neuroinflammation is recognized as a major component of the pathology of AD contributing to disease progression and neurodegeneration. GV-971 (oligomannate) was approved in China in 2019 after a Phase III trial conducted in China demonstrated cognitive improvement.[153] This agent is hypothesized on the basis of nonclinical observations to reduce brain inflammation in AD through its effect on the gut microbiome, reducing dysbiosis, restoring normal gut bacterial composition, and decreasing peripheral inflammatory cell populations that may contribute to central inflammation. A global trial is planned to determine the extent to which these effects can be reproduced in other populations.
A variety of other mechanisms are being targeted in current AD drug development programs (Table 3). Infections are hypothesized to contribute to AD onset or progression and agents that target bacterial products or viruses are in clinical trials of AD patients. Neuroprotection is critical to successful disease modification, and some agents target neuroprotection directly through growth factors, mitochondrial function, or other mechanisms in an effort to slow disease progression.
The DIAN – Treatment Unit (DIAN-TU) is an adaptive prevention trial platform assessing multiple agents simultaneously in individuals with Autosomal Dominant AD (ADAD).[154] A recent readout showed that in a small sample of mutation carriers, neither solanezumab nor gantenerumab affected clinical outcomes compared to placebo. Gantenerumab, but not solanezumab positively affected biomarker outcomes.

An overview of the AD DMT pipeline shows that several agents demonstrate clinical or biomarker benefit and confirmatory trials are being pursued. Some agents have been submitted to the FDA/EMA for regulatory review. The development of improved trial designs, a larger repertoire of biomarkers reporting on a wider variety of cell processes, improved outcome measures, and better analytic approaches along with improving insight into the biology of AD support the optimism in the field that emergence of important new therapies for AD may be immanent.

CONCLUSIONS

Looking back to 2016, enormous progress has been made in the understanding of the pathophysiology and the genetic basis of AD. The amyloid cascade has been modified by a more thorough understanding of the cellular, preclinical, phase of AD. Genetics has moved from identifying three causal and one risk gene to a plethora of genes that can be put into a polygenic risk score, which may be used to predict AD. The developments in biomarker diagnosis have been astonishing and have led to a complete rethinking of how to label AD outside and before clinical symptomatology, enabling enrollment of patients in research in a much earlier phase of the disease. Further refinement of the diagnostic classification and pathological underpinnings will be made by molecular imaging, allowing visualization of co-pathology and regional protein aggregation. Promising treatments are poised at advanced stages of testing in clinical trials.

Following these developments, at some distance, are insights in risk reduction, primary and secondary prevention, using non-pharmacological and pharmacological approaches, ultimately given in parallel and at a much earlier timepoint than has been trialed before. If the field keeps up this pace, very early identification and multimodal treatment of patients will become a reality.

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Panel: Case vignettes

Mrs. A is a 42-year-old successful manager of an IT company, who presents at the Alzheimer Center because of self-perceived memory loss and hints of less oversight and loss of multitasking abilities. She recognizes these complaints all too well because of her mother who suffered from AD for 5 years and died at the age of 47. Two of her 4 brothers also suffered from AD and both of them had been tested and found to be carriers of a PSEN1 mutation. Although she has not been tested herself, she has always felt she would be a carrier and subsequently had chosen not to have children. She asked for a full evaluation because she wanted to have the option of participating in a clinical trial program. Her MMSE score was 27/30, the MOCA score was 24/30, indicating mild memory and executive disturbances, which were confirmed by neuropsychological testing. A brain MRI showed no abnormalities. CSF values were 750pg/ml for abeta 42, 335pg/ml for tau and 35 pg/ml for p-tau-181, all in the abnormal range. Serum neurofilament light chain value was 25 pg/ml, which is abnormal for her age, according the in-house defined reference curves. APOE status was E3/E4. All these biomarker values indicate presence of AD pathology and onset in a clinically mildly affected patient. Genetic testing confirmed the presence of the same PSEN1 mutation as her brothers. She was informed about the diagnosis and followed at 6 months intervals at the center and put on the list for a clinical trial within the DIAN-TU program. She informed her colleagues at work and agreed to have regular meetings with the company-physician.

Mr. B is a 62-year-old, high-school teacher, who presented to the neurologist with gradually progressive difficulty finding words and understanding sentences and slight memory loss. He had visited another neurologist because of suspicion of a vascular event but a brain MRI had revealed no abnormalities. On examination, the MMSE was 25/30 and the MOCA was 24/30, both within normal range, with normal findings at routine neurological and laboratory investigations. Neuropsychological and detailed language assessment revealed decrease in fluency, naming and repetition of long sentences. Review of the MRI showed slight asymmetry of the temporal lobes with grade 2 hippocampal atrophy on the left side and grade 1 on the right side, without any other abnormalities (figure 2b). Because of his young age and the desire of the patient and his family to obtain a firm diagnosis in order to plan ahead and make proper adjustments in his working life, an amyloid PET scan was performed showing diffuse cortical uptake of the ligand (figure 2a). As part of a research project, a TAU-PET scan was performed, showing left-temporal abnormal tau deposition (figure 2c). A diagnosis of logopenic variant of AD was made. Lifestyle advice was

given and regular visits to a speech therapist were offered.[3] Given the diagnosis and the perceived grim future as well as the high demands of his job on his language skills he decided to go on sick leave from his job.

Mrs C. is a 78-year old lady, living independently on her own after being widowed 6 years ago. She was known to her GP with controlled hypertension and moderate heart failure, for which she uses medication. Her oldest son lives in the US and her daughter lives 100 km away. Both have demanding jobs and young children. During telephone and Skype calls her children had noticed increasing forgetfulness and one of the neighbors had alarmed the daughter recently that her mother mixed up the days and forgot to eat and did not take care of herself that well anymore. Her daughter accompanied her mother to the Alzheimer Center upon referral of the GP, who had initially dismissed the worries of the daughter. Upon examination of the geriatrician, she appeared malnourished and underweight. The MMSE score was 17/30 and a brief neuropsychological test battery showed scores below the norm for memory and executive function. Her score on the Amsterdam IADL test[4] was 58 indicating severe impairment in instrumental ADL. MRI showed medial temporal atrophy score of 2 bilaterally and moderate to severe white matter changes (Fazekas score 2). A diagnosis of mild-to moderate dementia due to AD with some vascular contribution was made, a case manager was assigned to organize and supervise care in order to have her stay at home as long as possible. Vascular risk factors were checked and cholinesterase inhibitor therapy was started.

Table 1. The ATN framework

A: B-amyloid plaques or assoc. pathophysiology

- CSF Ab 42 (low), or low 42/40 ratio
- Amyloid PET

T: Aggregated tau or assoc. pathophysiology

- CSF phosphorylated tau (high)
- Tau PET

N: Neuronal injury and neurodegeneration

- Structural MRI
- FDG- PET
- CSF total tau (high)
- NfL

Table 2. Completed large, long-term multidomain intervention RCT

Study, country	Intervention	Duration	N	Recruitment strategy	Inclusion criteria	Primary Outcome	Primary outcome results	Secondary cognitive outcome results	Other results on cognitive outcomes
FINGER (ref) Finland	Multidomain intervention including dietary counselling, exercise and cognitive training, and vascular risk factor monitoring vs. regular health advice (control)	2-year intervention; 7-year follow-up	1260	Participants from previous population-based national surveys; individual randomization	Age: 60-77; Elevated risk for dementia based on CAIDE score >=6 points; and cognitive function at or slightly below average level	Cognition measured with NTB (a composite measure of 14 standard cognitive tasks)	Intervention had beneficial effect on NTB: between-group (intervention vs. control) difference for NTB change was 0.022 (p=0.030) per year	Beneficial effect of intervention on executive functioning (p=0.039), and processing speed (p=0.029), but not on memory (p=0.36)	Beneficial effect of intervention on memory, when including more complex memory tasks (p=0.036). Higher risk of decline in cognition in control group compared to the intervention group
PreDIVA (ref) The Netherlands	Multidomain cardiovascular intervention (advice) vs.	6-year intervention	3526	General practices; cluster-randomization of 116 general practices	Age: 70-78 years	Incidence of dementia	No effect of intervention on dementia: HR 0.92 (p=0.54)	No effect of intervention on MMSE and VAT.	Lower risk of dementia in participants with untreated hypertension at baseline who were adherent to the intervention (p=0.02).

Study	Intervention	Duration	N	Recruitment	Inclusion	Outcome	Results		
	usual care (control)							No effect of intervention on AD. Lower risk of non-AD dementia in the intervention group (p=0.007)	
MAPT France	Multidomain intervention including integrated cognitive training, physical activity and dietary advice, and preventive consultations plus omega 3 PUFAs vs. multidomain vs. omega 3 PUFAs vs. placebo capsule	3-year intervention	1680	Diverse strategies including patient databases and advertisements; individual randomization	Age: 70+ Presence of memory complaint or IADL limitation or slow gait speed	Cognition measured with a composite z score combining 4 cognitive tests	No significant difference between any of the 3 intervention groups compared to placebo: between group difference was 0.093 (p=0.142) for multidomain + PUFA; 0.079 (p=0.179) for multidomain; and 0.011 (p=0.812) for PUFA compared to placebo.	Multidomain plus PUFA (p=0.036) had less decline in 10 MMSE orientation items compared to placebo group. Other group comparisons and other cognitive outcomes (FCSRT, DSST, Category naming test, COWAT, MMSE, TMT A, TMT B, CDR-	Less cognitive decline in those that received multidomain intervention (2 groups pooled) compared to those that did not (other 2 groups pooled) (p=0.015). Beneficial effect of multidomain plus PUFA vs. placebo among those with CAIDE score >=6. Beneficial effect of multidomain plus PUFA (p<0.001) and multidomain (p=0.003) groups vs. placebo among those with amyloid positivity.

							SB) showed no effect.	

Table 3. Principal disease-modifying therapies in the AD drug development pipeline (adapted from Cummings et al, 2020[8]; arranged by Common Alzheimer Disease Research Ontology (CADRO) categories (Rofelo et al, 2012[9]and 2013 NIA update)).

Target Class	Drug	Type of Agent	Phase	Population	Diagnostic Biomarker
Amyloid	ABvac40	Active vaccine	II	Prodromal/mild dementia	None
	Aducanumab	Monoclonal antibody	III	Prodromal/mild dementia	Amyloid PET
	APH-1105	Alpha-secretase modulator	II	Mild-moderate dementia	None
	Azeliragon	RAGE inhibitor; anti-inflammatory; glucose modulation	II/III	Mild dementia	None
	BAN-2401	Monoclonal antibody	III	Prodromal/mild dementia	CSF or PET amyloid markers
	Gantenerumab	Monoclonal antibody	III	Prodromal/mild dementia and preclinical ADAD	CSF or PET amyloid markers
	CAD106	Active vaccine	III	Preclinical ADAD	ApoE-4 homozygotes
	Crenezumab	Monoclonal antibody	II	ADAD	PS1 mutation carriers
	Grapeseed extract	Reduces Aß oligomerization	II	Mild-moderate dementia	None
	LY3002813 (donanemab)	Monoclonal antibody	II	Prodromal/mild dementia	Amyloid PET
	PQ912	Glutaminyl cyclase inhibitor to reduce pyroglutamate Aß	II	Mild cognitive impairment/ mild dementia	CSF amyloid markers
	Solanezumab	Monoclonal antibody	III	Preclinical AD	Amyloid PET
	Thiethylperazine (TEP)	Activates ABCC1 transporter to remove Aß from the brain	II	Mild cognitive impairment/ mild dementia	None

Tau	ABBV-8E12	Monoclonal antibody	II	Prodromal/mild dementia	Amyloid PET
	BIIB080 (IONIS MAPTRx)	Antisense RNA	II	Prodromal/mild dementia	CSF amyloid markers
	BIIB092	Monoclonal antibody	II	Prodromal/mild dementia	CSF or PET amyloid markers
	LY3303560 (zagotenemab)	Monoclonal antibody	II	Prodromal/mild dementia	None
	RO7105705 (semorinemab)	Monoclonal antibody	II	Prodromal/mild dementia and mild-moderate dementia	CSF or PET amyloid markers
	TRx0237	Tau aggregation inhibitor	III	Mild-moderate dementia	Amyloid PET
Proteostasis/ protein opathies	Nilotinib	Tyrosine kinase inhibitor	II	Mild-moderate dementia	CSF amyloid markers
	Posiphen	APP production inhibitor; reduces Aß, tau, alpha-synuclein	II	Prodromal/mild dementia	CSF amyloid markers
Epigenetic regulators	GV1001	Mimics extratelomeric function of hTERT	II	Mild to moderate dementia	None
	Nicotinamide	Histone deacetylase inhibitor	II	Prodromal/mild dementia	CSF amyloid markers
	ORY-2001	Regulates HDAC demethylase and MAOB	II	Mild-moderate dementia	CSF amyloid markers
Synaptic plasticity and neuropro tection	ANAVEX-2-73	Sigma-1 receptor agonist; M2 autoreceptor antagonist; ameliorates oxidative stress and protein misfolding	III	Mild cognitive impairment/mild dementia	CSF or PET amyloid markers
	AGB101	SVA2 modulator	III	Prodromal/mild dementia	Amyloid PET
	AMX0035	Mitochondrial and ER stress modulator	II	Prodromal/mild dementia	Amyloid PET, CSF, FDG PET, or vMRI

	AR1001	PDE5 inhibitor	II	Mild-moderate dementia	None
	BPN14770	PDE4 inhibitor	II	Mild cognitive impairment/mild AD dementia	None
	Cilostazol	PDE3 inhibitor	II	Prodromal/mild dementia	None
	CT1812	Sigma-2 receptor antagonist	II	Mild-moderate dementia	CSF or PET amyloid markers
	Deferiprone	Iron chelating agent	II	Prodromal/mild dementia	Amyloid PET
	GV1001	Telomerase reverse transcriptase vaccine reduces Aß related neurotoxicity	II	Moderate-severe dementia	None
	GRF6019	Human plasma protein fractions	II	Moderate-severe dementia	None
	Icosapent ethyl (IPE)	Improves synaptic function; neuroprotective; reduces inflammation	III	Cognitively normal	None
	Levetiracetam	SV2A modulator	II	Mild-moderate dementia	None
	LM11A-31-BHS	P75 neurotrophin receptor ligand	II	Mild-moderate dementia	CSF amyloid markers
	Neflamapimod (VX-745)	Enhances endolysosomal function to reduce synaptic dysfunction	II	Prodromal AD	CSF or PET amyloid markers
	PTI-125	FLNA inhibitor	II	Mild-moderate dementia	None
	NA-831 (traneurocin)	Endogenous small molecule that exhibits neuroprotection, neurogenesis, and	II	Mild cognitive impairment	None

		cognitive protective properties			
	Riluzole	Glutamate receptor antagonist	II	Prodromal/mild dementia	None
	RPh201	Neuroprotective	II	Mild-moderate dementia	None
	Troriluzole (BHV4157)	Reduces synaptic levels of glutamate; improves synaptic functioning	III	Probable AD dementia	None
Inflammation and infection	ALZT-OP1 (cromolyn + ibuprophen)	Mast cell stabilizer (cromolyn), anti-inflammatory (ibuprofen)	III	Prodromal AD	CSF amyloid markers
	COR388	Bacterial protease inhibitor	III	Mild-moderate dementia	None
	Curcumin + aerobic yoga	Decrease inflammation and reduce oxidation-related neuronal injury	II	Mild cognitive impairment	None
	Daratumumab	Monoclonal antibody targeting CD38	II	Mild-moderate dementia	Amyloid PET
	Dasatinib + quercetin	Tyrosine kinase inhibitor + flavinoid	II	Mild-moderate dementia	None
	Elderberry juice	Antioxidant, anti-inflammatory, mitochondrial effects	II	Mild cognitive impairment	None
	GB301	Regulates T cells and reduced inflammation	II	Mild-moderate AD dementia	Amyloid PET
	Lenalidomide	Immunomodulator	II	Mild cognitive impairment	None
	L-serine	Amino acid	II	Prodromal/mild dementia	None
	Masitinib	Modulation of mast cell-related inflammatory processes	III	Mild-moderate dementia	None
	Montelukast	Leukotriene receptor antagonist	II	Mild cognitive impairment/ mild dementia	None

	Rifaximin	Anti-inflammatory; reduces cytokines derived from gut bacteria	II	Mild-moderate dementia	None
	Sargamostim	Immune system stimulation	II	Mild cognitive impairment/ mild dementia	Amyloid PET
	Valacyclovir	Antiviral agent to reduce impact of herpes viral influence in AD	II	Prodromal/mild dementia	None
Metabolism and bioenergetics	Banfotiamine	Improve glucose utilization and neuronal metabolism	II	Mild cognitive impairment/mild AD dementia	Amyloid PET
	Dapagliflozin	SGLT2 inhibitor	II	Mild-moderate dementia	None
	Elderberry juice	Antioxidant; anti-inflammatory	II	Mild cognitive impairment	None
	Ginkgo biloba	Mitochondrial modulator; cerebral blood flow enhancer	II/III	Dementia	None
	Insulin glulisine	Insulin sensitivity enhancer	II	Prodromal/mild dementia	None
	Liraglutide	Glucagon-like peptide I receptor agonist	II	Prodromal/mild dementia	None
	Metabolic cofactors	Enhances mitochondrial activity	II	Mild-moderate dementia	None
	Metformin	Insulin sensitizer to improve neuronal glucose utilization	III	Mild cognitive impairment + obesity	None
	S-equol (AUS-131)	Nonhormonal estrogen receptor B agonist; mitochondrial protectant	II	Mild-moderate dementia	None
	Tricaprillin	Induces ketosis as alternative neuronal energy source	III	Mild-moderate dementia	FDG PET
	T3D-959	PPAR agonist			

Vascular	Losartan + amlodipine + atorvastatin + exercise	Vascular risk reduction	III	Cognitively normal at elevated risk for AD	None
	Candesartan	Angiotensin receptor blocker	II	Prodromal/mild dementia	CSF or PET amyloid markers
	Omega-3 PUFA	Long chain fatty acid with anti-inflammatory properties	II	Cognitively normal or mild cognitive impairment with white matter hyperintensities	None
	Telmisartan plus perindopril	Angiotensin converting enzyme inhibitor	II	Mild-moderate dementia	None
Growth factors	Lupron	Growth factor; neuroprotection	II	Mild-moderate AD dementia	Amyloid PET

Aß - amyloid beta-protein; ADAD – autosomal dominant Alzheimer's disease; ApoE-4 – apolipoprotein E 4; APP – amyloid precursor protein; CSF – cerebrospinal fluid findings indicative of AD; ER – endoplasmic reticulum; FDG PET – fluorodeoxyglucose positron emission tomography; FLNA – filamin A; HDAC – histone deacetylase; hTERT – human telomerase reverse transcriptase; MAOB – monoamine oxidase B; MAPK – microtubule associate protein kinase; PET – positron emission tomography; PDE - phosphodiesterase; PPAR – peroxisome proliferator-activated receptor; PS1 – presenilin 1; RNA – ribonucleic acid; SGLT – sodium glucose transporter; SVA2 – synaptic vesicle glycoprotein 2A

BOX 1 Fluid Biomarker consortia relevant for the AD field

| Name	Aim	Website
Global Biomarkers standardization Consortium of the Alzheimer's Association.	Achieve consensus on the best ways to standardize and validate biomarker tests for use in global clinical practices.	https://www.alz.org/research/for_researchers/partnerships/gbsc
Society for CSF analysis and clinical Neurochemistry	Exchange high level international scientific experience, to facilitate the incorporation of CSF diagnostics into clinical practice and to give advice on inclusion of CSF analysis into clinical guidelines.	https://h001.ssl-redirect.de/www.neurochem.info/
fNIH Biomarkers Consortium	The Biomarkers Consortium brings together the expertise and resources of various partners to rapidly identify, develop and qualify potential high-impact biomarkers particularly to enable improvements in drug development, clinical care and regulatory decision-making..	https://fnih.org/what-we-do/biomarkers-consortium
IFCC Working Group 'CSF Proteins'	Development of certified reference material and reference methods for amyloid beta(42) or (40) and Tau in CSF.	https://www.ifcc.org/ifcc-scientific-division/sd-working-groups/csf-proteins-wg-csf/
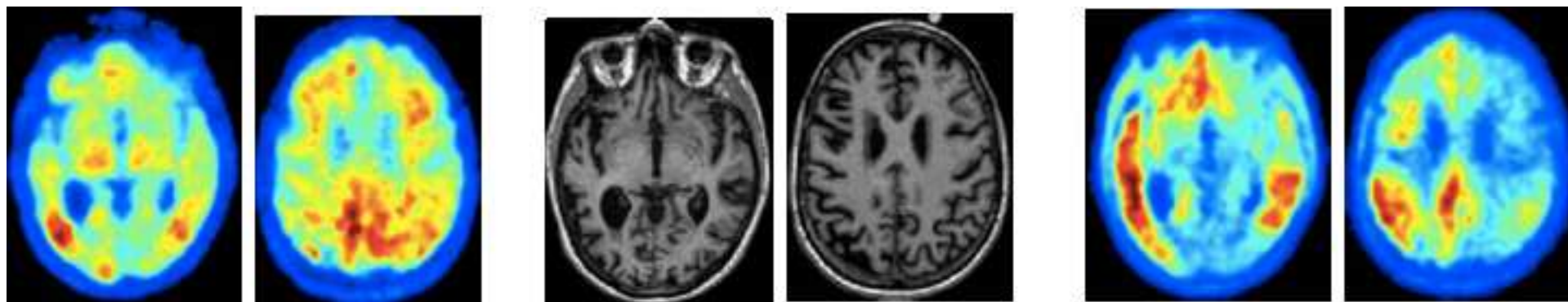
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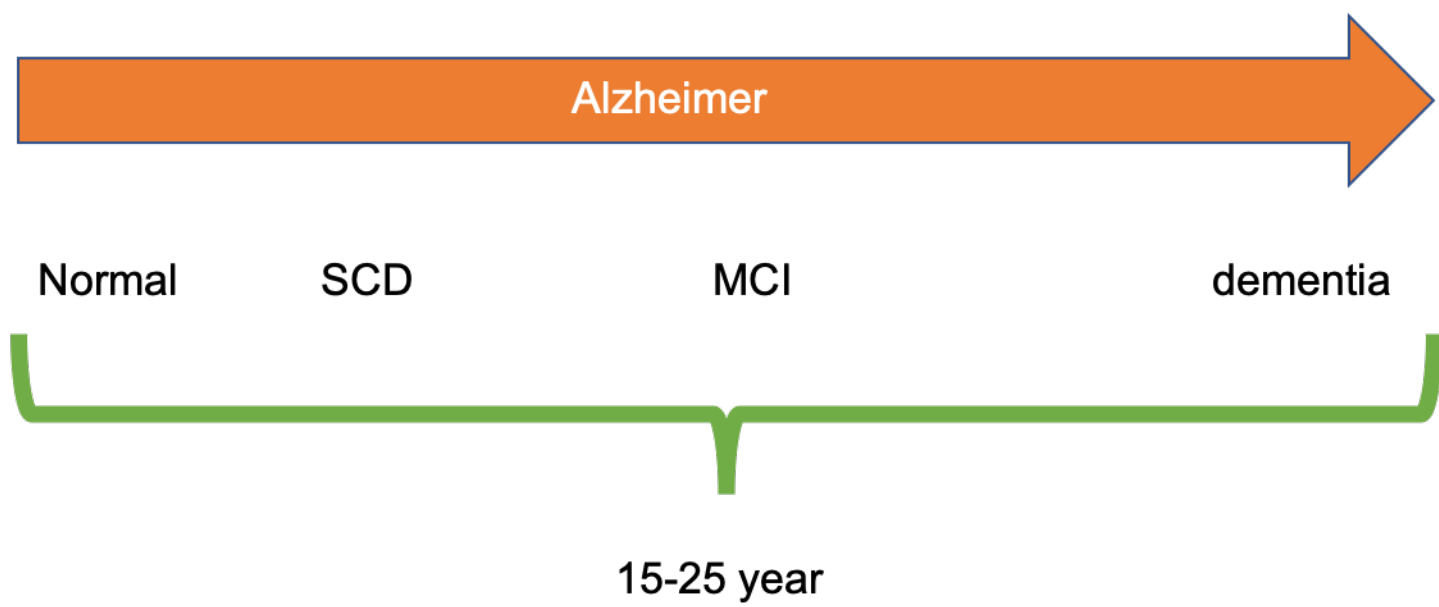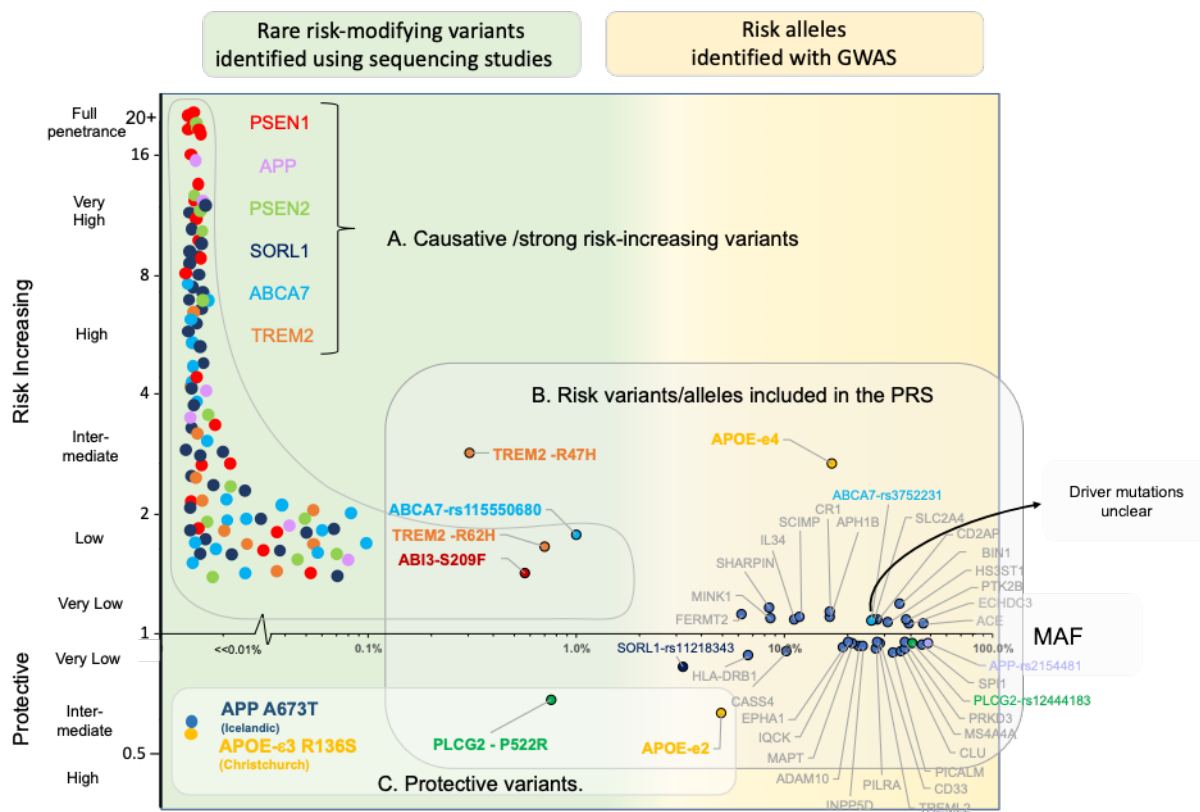
Figure 2

Figure 3

Figure 4
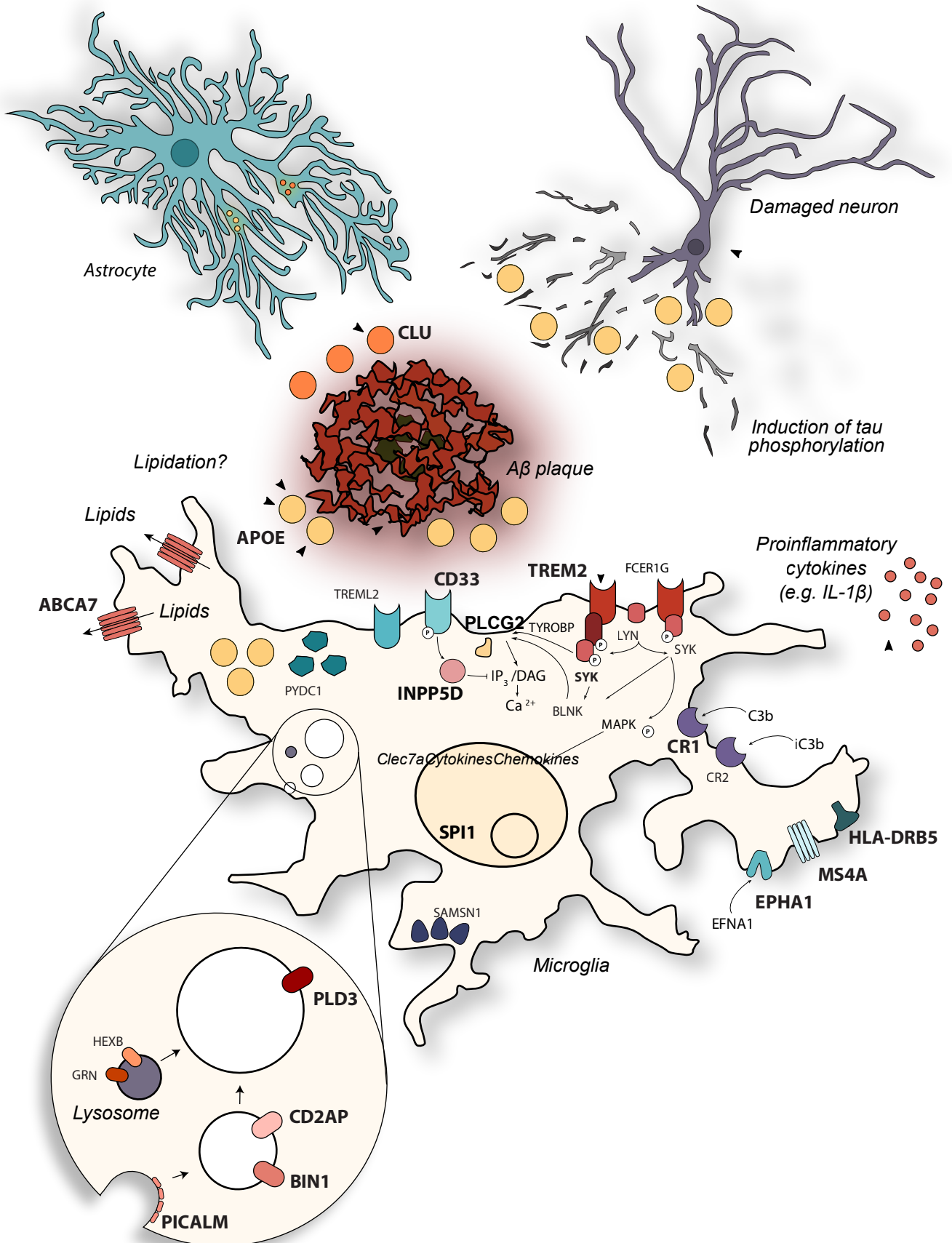
Figure captions

Figure 1: Imaging findings of a case similar to the one depicted in vignette 2.
The T1 weighted MRI images (b) show generalized cortical atrophy, left > right. An amyloid PET scan using PIB, shows amyloid deposition predominantly in the posterior cingulate region (a). The TAU-PET image using AV1451 tracer, shows left sided inferotemporal lobe, parietal and mild posterior cingulate deposition of tau (c). Image courtesy of Dr Rik Ossenkoppele and Prof Gil Rabinovici.

Figure 2: AD is a continuum
The arrow points to the continuum of AD stretching over a period of 15-25 years in which AD pathology may be present without any symptoms, into the phase of subjective cognitive decline, via a stage of MCI leading up to overt dementia, illustrating that dementia is only the end result of a long-time presence of AD pathology.

Figure 3: The genetic landscape of AD
X-axis: Minor allele frequency (MAF); the frequency at which, at a given genetic position, a non-reference allele occurs in the population (variant allele). Y-axis: Effect size, expressed odds ratio (OR), variant carriers and non-carriers have the same odds of developing AD when OR=1, variants with OR>1 are associated with an increased AD risk while variants with OR <1 are associated with protective effect.
A. Causative/strong risk increasing variants. A schematic representation of the distribution of individual rare variants for which odds ratios cannot be estimated due to extreme variant rareness. Specific rare variants (by convention MAF < 1%) in PSEN1, PSEN2 and APP cause autosomal dominant early onset AD: evidence from linkage studies in large informative families. Not all variants in these three genes give rise autosomal dominant AD, some may be risk modifiers or non-pathogenic. The AD-association in the SORL1 ABCA7, TREM2 genes were found in gene-based tests; carriers may come from small pedigrees with inheritance patterns of AD suggestive of autosomal dominant inheritance. B. GWAS hits are common variants (by convention MAF > 1%) that represent risk-alleles that occur with significantly different frequency in AD patients and controls. Each variant is represented by the gene in which it occurs, or when the variant is non-coding, by the gene that maps closest to the variant (depicted in grey). C. Protective variants are (very) rare variants suggested to confer resilience against age-associated or disease-associated risk factors of cognitive decline.

Figure 4: The cellular phase of Alzheimer's Disease.
While amyloid plaques (red, middle of the figure) and Tau phosphorylation and tangles (neurons, top right corner) are considered still the defining features of Alzheimer's disease, the focus of research has been widened from neurons to the response of other cell populations in the disease.[84] The microglia mediated inflammation, although known for decades to be present in AD,[116] has finally taken centre stage in functional research on the pathogenesis of the disease. Many of the risk genes (bold and capitals) identified in AD (see figure 3) are expressed and have functions in microglia. These genes become upregulated when microglia are exposed to amyloid plaques and many of the AD risk genes are enriched

in the disease associated microglia response that characterizes this cell state.[93,94,96] Other genes involved in this response and moderately positive in GWAS studies are indicated as well (figure kindly provided by Dr. Renzo Mancuso).[101]

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