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Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies

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Abstract

Human studies are reviewed concerning whether “aging”-related mechanisms contribute to Alzheimer’s disease (AD) pathogenesis. AD is defined by specific neuropathology: neuritic amyloid plaques and neocortical neurofibrillary tangles. AD pathology is driven by genetic factors related not to aging per se, but instead to the amyloid precursor protein (APP). In contrast to genes involved in APP-related mechanisms, there is no firm connection between genes implicated in human “accelerated aging” diseases (progerias) and AD. The epidemiology of AD in advanced age is highly relevant but deceptively challenging to address given the low autopsy rates in most countries. In extreme old age, brain diseases other than AD approximate AD prevalence while the impact of AD pathology appears to peak by age 95 and decline thereafter. Many distinct brain diseases other than AD afflict older human brains and contribute to cognitive impairment. Additional prevalent pathologies include cerebrovascular disease and hippocampal sclerosis, both high-morbidity brain diseases that appear to peak in incidence later than AD chronologically. Because of these common brain diseases of extreme old age, the epidemiology differs between clinical “dementia” and the subset of dementia cases with AD pathology. Additional aging-associated mechanisms for cognitive decline such as diabetes and synapse loss have been linked to AD and these hypotheses are discussed. Criteria are proposed to define an “aging-linked” disease, and AD fails all of these criteria. In conclusion, it may be most fruitful to focus attention on specific pathways involved in AD rather than attributing it to an inevitable consequence of aging.

Introduction and definition of terms

This review examines the relationship between Alzheimer’s disease (AD) biology and human brain aging. AD mostly affects older individuals. There has been debate about whether AD is linked mechanistically to “brain aging” and to cellular senescence mechanisms [44, 90, 142, 183, 192, 232]. This is an important issue, especially since the number of very old individuals is predicted to increase dramatically in coming decades ([116, 174], Fig. 1). Although animal models provide a valuable context for experimental work, their direct correlation with human neurodegenerative diseases is still being characterized. The human aging trajectory and other aspects of *Homo sapiens* brain biology are also unique to our species. Hence, in the present literature review, we focus on data derived from human studies.

Recent scholarship has called into question the idea that “age is the greatest risk factor for AD”. The current review focuses on the changes that occur in humans past 90 years of age since the central question we wish to address is whether AD is linked to aging. Both of these concepts—AD and aging—are incompletely understood, so our discussion begins with a definition of terms.

AD is defined by the presence of three different elements, each necessary (and together entirely sufficient) for definitive diagnosis [1]:

1. Clinical dementia (cognitive impairment with a memory component that impacts daily living skills);

2. Substantial numbers of neocortical neurofibrillary tangles (NFTs) at autopsy as quantified using Braak staging [37]; and
3. Substantial numbers of neuritic amyloid plaques as quantified using CERAD scores [139] at autopsy.

The neuropathology-based definition of AD is a key assumption of the present review. Despite controversy in this area [46], no rival method discriminates AD from other causes of cognitive decline in aging as accurately as does postmortem evaluation. AD neuropathology correlates well with cognitive impairment although the relationship is complex [151]. Like all diseases, there is an expected prodromal phase and imperfect clinical–pathological correlation [120, 189, 206]. As in other diseases such as cancer, increased patient age correlates with greater dissociation between clinical expectations and autopsy-proven pathology [36, 212].

A modicum of AD pathology may be present in “nondemented” aged brains [146, 147, 149, 175, 198]. NFTs are not disease-specific and may develop in hippocampi and elsewhere independently of the processes present in AD brains [38, 92, 137, 147, 149, 175, 222], which by definition contain numerous Aβ plaques surrounded by abnormal tau-containing neurites [1]. There are also many individuals whose brains harbor substantial diffuse amyloid plaques yet they do not meet criteria for MCI or AD clinically [77, 129, 148, 175]. It is important to acknowledge our incomplete understanding about how these cases relate to full-blown AD. However, given ADs well-documented multiyear prodromal period [45, 48, 51, 141, 182, 194, 197, 208], the observed AD-specific pathology (neuritic Aβ plaques combined with neocortical NFTs) closely matches expectations when one compares autopsy data and AD epidemiology [5, 149].

Alternative definitions of AD, emphasizing clinical and biomarker data, have been proposed recently that remove the need for postmortem (definitive) diagnosis in a practical attempt to support clinical trials and patient management [67]. Biomarkers assessed during life are only surrogates for pathology, not for cognitive symptoms, nor even for the prediction of future cognitive impairment (which often are due to factors other than AD). AD bio-markers are valid for the detection of preclinical AD inasmuch as they predict eventual cognitive impairment accompanied by plaques and tangles in the brain.

Whereas clinical–pathological correlation in AD defies simplistic interpretations, the concept of “aging” is even less completely understood. Multiple mechanisms have been described for decreased “molecular fidelity” in the mature epoch of a cell, organ, and organism [88, 93]. Senescence near the end of life has been attributed to mitochondrial dysfunction, telomerase activity, free radicals, oxidative stress, and other factors [47, 66, 71, 85, 88, 113, 114]. In addition, genes have been described that either augment natural aging processes deleteriously (see below) or that delay normal aging effects in some organisms (e.g., sirtuins).

One thing that is clear is that advanced human age is accompanied by characteristic medical conditions [221]. Diseases that affect 95-year olds are not identical to those that affect most 75-year olds [154]. In extreme old age, there is a lamentable combination of vascular pathologies accompanied by weaker regenerative capacity. The background of generalized infirmity, specific high-morbidity diseases, polypharmacy, mood and sleep disorders represent formidable challenges to determining if a specific process exacerbates AD per se, or contributes to impaired cognitive functioning through other mechanisms [13, 110, 136, 154, 190, 220, 227]. These are some of the complexities that may have led to conflation between cognitive impairment in advanced age (“dementia”), and AD. A key feature of

aging is that it is universally linked to the physical time dimension. The question then is the universality of the AD-aging linkage: is AD a manifestation of aging or is it not?

We propose five testable criteria which, if supported by experimental data, would indicate that AD pathogenesis is linked specifically to aging-associated mechanisms (Table 1):

- Criteria #1: No specific mechanism outside of aging causes most known AD cases;
- Criteria #2: Human genetic aberrations that hasten the aging process also increase incidence of AD and vice versa;
- Criteria #3: Everyone will develop AD if they live long enough;
- Criteria #4: An aged individual should have a higher likelihood of AD with each additional year of life; and
- Criteria #5: Other aging-linked mechanisms (diabetes and synapse loss) contribute specifically to AD.

The present review is organized to address critically the experimental data related to these testable hypotheses. Criteria #1 and #2 are discussed in the context of clinical trial data, AD genetics, and cancer biology. Criteria #3 and #4 can be assessed by focusing on the nexus of neurodegenerative disease epidemiology and neuropathology. Criterion #5 is discussed in connection with diabetes and synapse loss. The above criteria for “aging-linked” mechanisms are admittedly debatable. Whether or not one accepts these tenets, there are additional interesting observations relevant to the question of whether AD pathogenesis is linked specifically to “aging” mechanisms.

AD pathology: insights from clinical trials, genetics, and cancer

Significance of extant clinical trial data

No therapeutic strategy for AD has demonstrated long-term efficacy to date. However, the existing data on clinical trials need to be interpreted with caution. We briefly discuss clinical trials related to “anti-aging” or “anti-amyloid” mechanisms.

Extensive links have been made between reactive oxygen species (ROS), aging mechanisms, and AD pathologic changes [64, 127, 128, 157, 167, 216]. However, molecular interactions between aging-linked ROS mechanisms, amyloid protein processing (plaques, oligomers, etc.), and tau modification have not yet been clearly drawn [131, 215]. Beta-amyloid itself may promote excess oxidation species reactions, further complicating the relationships between aging, ROS and AD pathology [43]. Therapies oriented toward anti-oxidant or anti-aging strategies have not been clearly successful although future studies may prove otherwise [6, 32, 163, 164].

There have been a handful of reported cases where individuals with mid-to-late stage AD were administered anti-Aβ immunotherapy that apparently cleared a large proportion of brain amyloid plaques, but this clearance did not seem to alter the presence of NFTs or the inexorable course of the disease [94, 155]. These data have been interpreted to constitute a repudiation of the amyloid cascade hypothesis [214], and to indicate that it is “aging”, rather than Aβ-related mechanisms, that underlies AD progression [90]. However, the limitations of the conclusions that can be drawn from the few autopsied anti-Aβ immunotherapy cases have been acknowledged [34] and in fact some beneficial effects of the human immunotherapy studies have been seen in clinical trials [31, 35, 191, 202]. By far, the best clinical–pathological correlation in AD is between neocortical NFTs and cognitive impairment [14, 149] and no therapies that target cortical NFTs have been successfully tested in humans. The current clinical trial literature does not contradict the idea that there is

a pathogenetic synergy in which amyloid plaques kindle an auto-propagating process related to cortical NFTs, as has been hypothesized [49, 58, 72, 82]. Future drug trials oriented toward earlier stages of disease progression may help explain and reconcile these phenomena. For now, clinical trials have not provided definitive answers either way.

Progerias and AD

A subset of human genetic aberrations cause well-characterized phenotypes with specific features of advanced human aging in individuals of younger ages. These diseases are called “progerias” [40, 117, 178]. It has been suggested that progerias provide insights about the aging process and the pathways that are involved in human aging [42, 177]. Clinical signs and symptoms that may exist even in pre-teens, include cognitive impairment, wrinkled skin, atherosclerosis, brittle bones, cataracts, and many other changes, although there is not a single disease that can be said to definitely cause “accelerated aging”.

Characteristic features of human progerias are listed in Table 2. There is no firm indication that individuals with progeria have any increase in dementia with AD pathology. One nondemented individual with Werner syndrome and apolipoprotein E (APOE)-ε4 genotype was reported to have early AD-type pathology upon death at age 55 [126]. Otherwise, the link between Werner syndrome (or any other progeria) and AD pathology has been queried and not found to exist [132, 133, 160] although some of the progerias do in fact involve cognitive impairment (Table 2). Mutations of the lamin gene (LMNA) cause a severe autosomal dominant progeria syndrome, muscular dystrophy, and Charcot–Marie–Tooth disease, but not AD [42]. In contrast, gene defects in presenilin-1 (PSEN1) produce early onset autosomal dominant AD and a wide range of associated neurologic deficits, but not a progeria syndrome (see below). Nor is there any firm association between AD and other known aging genes including the sirtuins (for example SIRT1 or SIRT3) although these have been exhaustively analyzed for AD-linked polymorphisms [11].

In summary, genetic diseases provide important insights into human aging and senescence. The dissociation between premature aging-linked genetic aberrations and AD cannot by itself negate the hypothesis that AD is caused by aging mechanisms, but it is a pertinent clue. The lack of linkage between progerias and AD is all the more significant because there are indeed other genetic loci that strongly impact AD pathogenetically.

AD genetic risk factors

Human alleles that alter AD risk are critically relevant to any discussion of AD biology. Approximately 70% of a given individual’s risk for developing AD is conferred through her genetic repertoire [28, 75]. AD is thus like many predominantly genetic diseases, which are not linked to aging mechanisms, but which can manifest late in life with neurodegeneration —trinucleotide repeat diseases, familial prion diseases, familial motoneuron diseases, FTLDs, and dozens of other genetic diseases (see for example [7, 69, 84, 201, 230]).

The high-penetrant human gene loci that alter risk for developing AD are APP, PSEN1, PSEN2, and APOE. None of these genes are known to be directly related to the aging process, nor with aging-related processes such as combating oxidative stress. These AD-affecting genes all influence processing of the amyloid precursor protein (APP). The triplication of APP in the context of Down’s syndrome can induce AD-like pathology in the human brain as young as 8 years of age [124] with precursor lesions present even during infancy (Fig. 2). Even outside of Down’s syndrome, the focal duplication of the APP gene, and mutations in APP promoter regions that increase APP production, can cause AD [138, 207, 218]. AD-relevant mutations in the APP gene affect its proteolysis as do mutations in PSEN1 and PSEN2 [28].

By far, the strongest risk factor for late-onset AD is the ε4 allele of the APOE gene [52, 213]. The impact of APOE-ε4 allele in terms of boosting brain Aβ deposition is well established [29, 41, 111, 122]. APOE alleles alter Aβ plaque burden and cerebral amyloid angiopathy in dramatic fashion [26, 27, 180]. The strong genetic risk for AD in persons aged 50–80 leads to a survival bias in terms of individuals beyond that age range. Relatively few individuals with APOE-ε4 allele (much less with APP or PSEN mutations) survive AD-free past age 90 [78, 119, 144, 169, 187]. This survival bias has been discussed previously [107].

The fact that individuals without genetic risk tend to survive AD-free beyond the chronological peak for disease incidence (see below) indicates that aging and AD invoke discrete mechanisms of cerebral degeneration. High penetrance AD genetic loci all connect directly to APP mechanisms, but not aging; aging genes do not link to AD risk. Thus, criteria #1 and #2 (Table 1) are not met for AD pathogenesis being an aging-linked mechanism.

There are relatively recently discovered single nucleotide polymorphisms (SNPs) that alter AD risk and these include alleles in CLU, PICALM, SORL1, and BIN1 [25, 30, 109, 204]. The penetrance of these genes is far weaker (i.e. effect of the mutation on risk for the disease phenotype is less predictable) in comparison to mutations in APP, PSEN1, PSEN2, or APOE. SNP/GWAS data remain to be fully understood both in normal brain and in relation to AD manifestations. Aside from genetic polymorphism linked to this disease, some additional clues about what to expect with regard to AD expression in human aging may be gleaned by study of another aging-linked disease category, namely cancer.

Human aging and cancer

Other human diseases can provide valuable insights about AD and illustrate the need for pathology-based epidemiology. Cancer is one of the major aging-associated diseases [17, 20, 178, 192] that can be compared and contrasted with AD. We describe some features of cancer research with the caveat that human malignancies differ from each other in mechanisms and manifestations. Cancer biology diverges meaningfully from AD, but both AD and cancer mechanisms have been linked with cell maintenance pathways, oxidative stress, aberrant phosphorylation, immunity, and apoptosis [168].

As with neurodegenerative diseases, particular cancer subtypes tend to affect humans of distinct age ranges. Pathology-based epidemiology can provide clues about which subtypes of cancer are more strongly associated with advanced aging. Figure 3, derived from the publicly accessible SEER database [87], demonstrates the difference in death rates from two types of human genitourinary carcinoma—kidney and prostate—in American males. Both cancers are “age-associated”; mortality of both is increased in old age. However, the natural histories of the two cancers differ. Kidney carcinoma incidence increases in age 50–80s unlike prostate cancer that surges later in the aging scale; these differences may be relevant to clinical diagnostics and drug trials. Affecting an older population, prostate cancer is more strongly linked to senescence pathways [205]. Although seemingly remote from AD pathobiology, these data provide insights into the stochastic tendencies of human disease to manifest in distinct ways, for reasons that are currently not well understood, and help establish the need for sophisticated pathology-based epidemiology.

AD and dementia epidemiology

Dementia versus AD epidemiology: recent progress

The epidemiology of AD in advanced age is deceptively challenging to address [100, 123, 136, 229, 233]. Autopsy series are critical for understanding AD epidemiology for the simple reason that definitive AD diagnosis requires autopsy confirmation. This fact is

important to acknowledge because there is no truly epidemiological study cohort with a 100% autopsy rate. With that caveat in mind, recent scientific progress has been achieved through analyses of large high-quality autopsy series. Excellent studies, which have included community-based cohorts, have provided important new insights [8, 70, 91, 97, 156, 171, 198, 233]. European datasets have provided notably rich contributions [10, 38, 104]. In the US, some of these data derive from NIH-sponsored Alzheimer's Disease Centers (ADCs), which comprise many thousands of autopsies of clinically well-characterized patients, consolidated under the National Alzheimer's Coordinating Center (NACC) [22].

Recent autopsy series have established the central importance of previously ignored non-AD pathologies. The classic clinical–pathological studies of Tomlinson, Blessed, and Roth had substantial impact on researchers' views of AD clinical–pathological correlation, despite being necessarily unacquainted with prevalent brain diseases, such as dementia with Lewy bodies (which often coexists with AD pathology), hippocampal sclerosis, frontotemporal lobar dementia (FTLD) subtypes, and other diseases. The mean age at death for demented subjects and control subjects in the seminal Tomlinson, Blessed, and Roth papers [188, 219] were 76.4 and 75.4 years, respectively. This is 2–5 years below the *average* life expectancies for Western countries [16], and a critically distinct cohort from the many individuals that live beyond their 90th year. The large majority of cognitively impaired subjects in their mid-70s is affected by advanced AD pathology, but this is less true in extreme old age (see below). In summary, early clinical–pathological studies were scientifically important, but also misleading if read without recourse to subsequent scholarship.

AD pathology in persons past 90 years of age

Epidemiologic data initially appeared to support the concept that aging is a major risk factor for dementia, and therefore AD. According to many different studies, dementia prevalence in Western populations is approximately 2% at age 65 and then doubles every 5 years thereafter [73, 112, 118]. Dementia epidemiology is less thoroughly studied in extreme old age. Dementia incidence appears to level off after age 90 [83, 118, 123, 185, 186] although clinical dementia prevalence probably does keep increasing [54, 203]. Whereas dementia prevalence keeps increasing, this does not necessarily mean that AD has increased prevalence in the same cohorts. For example, ear infections can lead to hearing loss in children; elderly individuals often have hearing loss, but this does not necessarily indicate increased ear infections in elderly individuals.

Clinical data without rigorous pathological correlation can be misleading. In contrast to the increased prevalence of dementia with advanced age (a clinical observation), the appearance of neuritic amyloid plaques and NFTs by pathology seems to level off in older cognitively impaired individuals according to multiple autopsy series [2, 56, 86, 193, 222], with the caveat that not all studies agree (discussed in [96, 106]). Even in extreme old age, the presence of many neocortical NFTs correlates with antemortem cognitive decline [65, 148, 150, 228], the enigma relates to cognitively impaired individuals whose brains lack AD pathology at autopsy. Recall that AD is defined by the presence of neocortical neuritic amyloid plaques and neocortical NFTs [1]. If the prevalence of AD pathological hallmarks is leveling off, or even decreasing, after the ninth decade of life while the prevalence of dementia is still increasing, then there must be a scientific explanation. Three unproven—and not necessarily reconcilable—hypotheses could help explain the apparent paradox:

> Hypothesis #1: All demented subjects have AD unless proven otherwise. Because extremely old individuals often suffer from dementia without excessive burden of plaques and tangles, then plaques and tangles are mere epiphenomena that are not biologically important;

Hypothesis #2: There is a survival bias, whereby individuals genetically predisposed to AD are less represented in cohorts of extreme old age; or

Hypothesis #3: AD is indeed a distinct disease but like many other diseases (e.g., kidney carcinoma) levels off in prevalence prior to extreme old age, and the increased prevalence of dementia past age 90 is due to specific diseases other than AD, in combination with the frequent, but not increasing, AD in that cohort.

We consider that the existing published data best support Hypotheses #2 and #3, but not Hypothesis #1. The survival bias in AD has been described above, related to genetic disease risk. However, why are so many individuals in extreme old age cognitively impaired and lacking AD pathology? There are prevalent brain diseases, besides AD, that contribute to dementia in the elderly. Some of these brain diseases are particularly germane to populations beyond 90 years of age.

Consider the following two statements:

1. Mechanism “X” contributes to AD.
2. Mechanism “X”: contributes to dementia.

These two statements are critically different, but seem to be frequently confused because, for a given patient, mechanism “X” could worsen cognitive symptoms in either case. Yet if AD is a discrete disease then merging it with other dementias (as an abstract idea or clinically for particular patients) can be seriously misleading both for researchers and clinicians. Ideally, each disease should be expected to be studied using different experimental designs, diagnosed using specific tests, and each disease would probably require separate treatments.

Many diseases other than AD affect the aged brain (Table 3). Prevalent brain diseases in advanced age, include cerebrovascular disease (CVD), hippocampal sclerosis (HS-Aging), synucleinopathies, FTLD, hematomas, normal pressure hydrocephalus, and numerous other neurological conditions. These are all directly relevant to a discussion of “dementia versus AD” because they may worsen cognition irrespective of AD status. We focus here on four different non-AD mechanisms: CVD, HS-Aging, diabetes, and synapse loss. While each can contribute to dementia, none of them has been proven to relate specifically to AD pathogenesis.

Hippocampal sclerosis and cerebrovascular disease

With advanced age, it is normal for individuals’ cognitive abilities to decline from previous levels although the brains of many aged individuals lack abundant AD pathology [56, 154]. As possible explanations for this phenomenon, we describe two brain diseases that, unlike AD, preferentially affect people in extreme old age: CVD and HS-Aging. Study of both diseases is still evolving, and rubrics are still being developed for optimal clinical–pathological correlation.

CVD, unlike AD, occurs through many distinct mechanisms, progresses in an unpredictable fashion, and currently lacks a universally applied nosology for pathological characterization. There are large vessel pathologies, small vessel pathologies, diseases related to the heart or kidney, and CVD related to other diseases and their therapies (including chemotherapies for cancer) that may manifest as CVD. Embolism, hemorrhage, neuroinflammation, impaired perfusion, hypertension, hypoxia, vascular malformations, glycemic fluxes, and other disease-inducing vascular mechanisms are all relatively common conditions that can induce adverse changes throughout the CNS [4].

Whereas overt clinical strokes affect ~750,000 in America each year, over 11 million discrete, but clinically silent cerebrovascular events are thought to occur over the same interval [3, 12, 68]. Radiographically, discrete infarcts may be seen in only ~25% of octogenarians [60], yet MRI white matter hyperintensities are noted in over 80% of octagenarians [74, 226] and literally 100% of persons in extreme old age [172]. This is indicative of CVD pathology [39, 153] in advanced aging and a higher risk for clinical stroke [59]. On microscopic examination, at least subtle CVD pathology is detectable in 75–90% of persons over the age of 90 years [150, 224, 225]. The increased prevalence of CVD pathology with age is clearly seen in the NACC neuropathological dataset (Fig. 4a).

Why is the high prevalence of CVD directly and critically relevant to a discussion of AD? The frequency of cerebrovascular pathologies in advanced old age means that both cognition and other pathology need to be assessed entirely differently. An analogy can be made to a given patient's lung function and pathological outcomes if he had both asthma and pneumonia; this would magnify the impact of each separate disease. Accordingly, CVD (not limited to cases of "vascular dementia") often coexists, and synergizes, with AD along a broad spectrum of disease severity [103].

CVD causes more rapid cognitive deterioration in patients with coexisting AD pathology relative to patients without AD pathology [143, 181]. Subcortical and/or lacunar infarcts alter the detection threshold for dementia [81, 170, 171, 199, 200, 209]. The clinical impact of CVD—although difficult to predict confidently for any individual patient—is correlated with systematic changes in pathological outcomes related to AD. Persons with CVD pathology tend to have lower AD-related pathology with a given degree of cognitive impairment [150, 170, 234]. Correspondingly, as people become older (with more CVD), a larger percentage of AD cases die with more moderate AD pathology—i.e., Braak stage V rather than Braak stage VI (Fig. 4b).

The frequent presence of concomitant CVD dampens the association for other pathologies, such as neurofibrillary pathology, to the severity of antemortem cognitive decline. In summary, CVD alters autopsy results related to AD pathology without necessarily interacting with the disease-specific mechanisms. Some researchers have argued for a more direct link in pathogenetic mechanisms than can be supported by existing autopsy data, and this consideration warrants further investigation.

As with CVD *but unlike AD*, HS-Aging pathology appears to increase dramatically in extreme old age [53, 63, 101]. The presence of HS-Aging pathology is strongly correlated with antemortem cognitive impairment [148], which can be seen both with mental status assessment and, more specifically, with certain testing methods [152]. Pathogenetically, HS-Aging is probably not attributable to CVD, but is instead linked to aberrant TDP-43 pathology [108]. HS-Aging is a distinct brain disease in comparison to FTLD-TDP cases (which also have aberrant TDP-43 by definition) because of the far older age group affected in HS-Aging and the lack of frontotemporal dementia, progressive aphasia, or semantic dementia clinically [152]. Although by definition HS-Aging affects the hippocampal formation, evidence does not indicate any direct causative association with AD. The strongest genetic risk factor for AD (the APOE-ε4 allele) does not increase risk of HS-Aging [125, 165].

Based on the data from the largest series of HS-Aging cases to date (N = 106 pathologically confirmed HS-Aging cases compared with N = 1,004 controls), we consider it possible that prior low estimates of HS-Aging prevalence [9, 99] were partially biased by inclusion of younger patients. The average age at death for HS-Aging in this large cohort was 93.4 years at death [152] and in this age range HS-Aging pathology is seen in over one-fourth of cases.

These results are concordant with a recent autopsy study, showing that 43% of aged individuals' hippocampi harbored TDP-43 pathology [179]. In our large autopsy series, each year of life after age 95 brought higher risk for HS-Aging pathology, but lower risk for AD pathology (Fig. 5). HS-Aging shares a key biomarker with AD (shrunken hippocampi on MRI), so there is a high chance for confusion clinically [165].

Figure 5 provides empirical data to demonstrate that not all aged individuals have AD by pathology. Nor does each added year of life lead to increased prevalence of AD pathology (unlike HS-Aging and CVD). Thus, criteria #3 and #4 (Table 1) are not met. The high prevalence of non-AD pathologies in the "oldest old" helps account for increased dementia in this cohort. The "classic" epidemiology of AD and dementia, and a newer representation that reconciles these data, are presented in Fig. 6. This begins to explain some of the complex underpinnings of pathology-based epidemiology. However, we are also challenged to consider additional aging-associated mechanisms that also have been linked with AD pathogenesis.

Diabetes and synapse loss

Type 2 diabetes (T2DM) [57] and synapse loss [95] have been connected with both advanced age and with AD. If there were strong etiological connections between these aging-associated (but poorly understood) mechanisms, it would bolster the idea that aging and AD are linked with each other. However, how persuasive is the evidence that T2DM and synapse loss are specific, early contributors to AD, rather than parameters that correlate with dementia risk instead of AD risk?

T2DM is an aging-associated disease that has been linked to AD. A current Pubmed search of "Alzheimer's and diabetes" retrieves 1,906 published papers, of which 789 (41.4%) are review papers. Many of these papers hypothesize that AD is mechanistically linked with T2DM [153]. Yet of the research papers related to AD and diabetes, only a relative handful involve human patients with assessment of antemortem glycemic status correlated with postmortem autopsy results, i.e. AD pathology [8, 15, 24, 89, 98, 135, 153, 166, 210]. These studies, comprising 1,843 autopsies from nine different research centers, are summarized briefly in Table 4. Note that most of the published work demonstrates that there is no positive correlation between diabetes and AD pathology. To the contrary, studies that have evaluated the question of whether antemortem diabetes correlates with AD pathology have shown that persons dying with a history of diabetes have *less* AD pathology (but *more* cerebrovascular disease pathology) than individuals without T2DM. These data highlight a key study design feature—namely, incorporating autopsy studies for a disease that requires neuropathologic evaluation for diagnosis—which has been regrettably ignored in meta-analyses discussing the correlation between T2DM and AD risk.

Although autopsy studies argue against the link between T2DM with AD pathology, published data have established that T2DM is a strong risk factor for impaired cognition [50, 159]. Diabetes leads to small vessel ischemic disease including CVD, not to mention glycemic fluxes and neuroinflammation that can be neurotoxic [153]. There are still many unknowns and potential confounders. T2DM associated clinical–biological mechanisms, including metabolic syndrome, adiposity, hormone changes including leptin and insulin, lifestyle (diet and exercise), and inflammation-related factors that may be eventually linked specifically to AD [18, 55, 130, 223, 235]. At this time, the best-supported hypothesis, based on the human studies that include autopsy confirmation, indicates that T2DM induces CVD pathology (and thus is likely to worsen brain function), but T2DM itself does not lead to increased AD pathology.

Another process at the ill-defined interface between human brain aging and cognitive impairment is “synapse elimination”. In a recent review article, the elimination of synapses was considered a likely connection-point between aging mechanisms and AD pathogenesis [90]. There are at least two key pertinent questions, only one of which has been adequately answered:

1. How specific is synapse elimination to AD?
2. Are synapses eliminated upstream, downstream, or in parallel with plaques and tangles?

In AD, there is a wide distribution of synapse loss in both hippocampus and neocortex relative to non-demented controls [134, 195]. It has been stated that decreased synapses is the pathological feature that best correlates with cognitive decline in AD. Even if this were to be taken at face value (see below), this does not imply that synapse loss is a specific pathological occurrence, much less a diagnostic feature, of AD.

Synapse loss occurs during the course of a broad variety of brain diseases: stroke, FTLD, synucleinopathy, traumatic brain injury and many other conditions. In fact, we know of no human condition with progressive neurodegeneration lacking synapse loss. In this sense, synapse loss is utterly nonspecific.

Nor is the relationship between synapse loss and “normal aging” well understood. There have been surprisingly few human studies that have adequately addressed the question about whether there is a “normal” age-related loss of synapses independent of brain disease (see [196] for review). Most of the well-controlled studies report no significant loss of synapses in non-pathological aged brains. Interestingly, there is also not a substantial loss of neocortical neurons in the absence of brain diseases of aging [161, 162]. Age-related changes in synapse numbers may be either region specific or not a common feature of brain aging.

There are published reports in which synaptic markers do not closely correlate with the numbers of amyloid plaques or NFTs on the same cases ([33, 121] although see [62]), which have indicated synapse loss may be a superior metric of AD severity. However, in these and related studies, there is the potential for spurious results since there is a tendency to correlate synapse loss in a particular brain region with AD pathology using either ordinal variables (e.g., Braak/CERAD stages) or else pathological metrics that are not relevant for clinical–pathological correlations (e.g., hippocampal NFTs, “amyloid plaques”, or “amyloid load”). Further, these reports may be confounded by mixed pathologies so frequently seen in aged individuals’ brains.

Unfortunately, whereas synapse changes clearly occur in a variety of conditions, we still do not know whether there are specific synaptic changes upstream of AD-type pathology (plaques and tangles). It is thus unknown where the synaptic changes belong in the AD pathogenetic schema. As with diabetes, the links to AD are as yet too weak to satisfy our criteria #5 (Table 1). The biology of synapse changes in AD is an active and fascinating area of AD research, yet it needs to be kept in mind that synapse elimination is not specific for AD or for “brain aging” and much remains to be learned in this area.

Summary and conclusions

A summary of reviewed topics is presented in Table 5. Data from genetics indicate that APP pathway genes and not aging-related genes are associated with AD risk. AD pathology is not inevitable in all humans, even in advanced age. In contrast, there are diseases that increase in prevalence in extreme old age (especially HS-Aging and CVD pathology). Neither

diabetes, synapse loss, nor any other aging mechanism have been proven to be involved directly in AD pathogenesis although they may worsen cognitive symptoms independently of AD. Thus, none of the criteria for AD being linked specifically to aging mechanisms have been met (Table 1), so the null hypothesis is sustained, at least for now. The preponderance of data indicates that research aiming at diagnostic or therapeutic relevance will most productively be oriented toward those specific pathways known to be activated in AD, rather than focusing on aging-related mechanisms as a sole target for intervention in this devastating disease.

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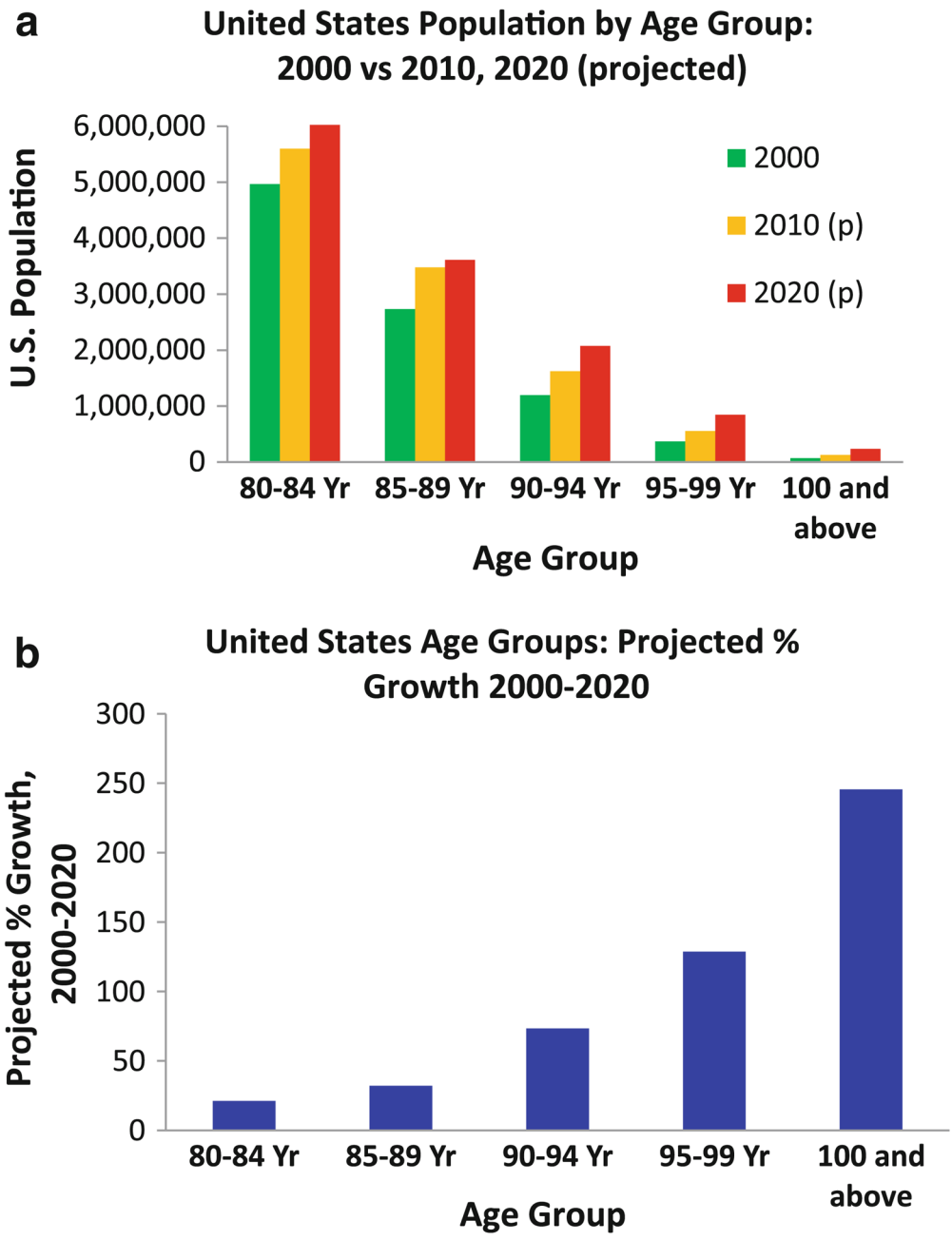

Fig. 1.

United States Census Bureau data and projections illustrate the practical need to understand the correlation between aging and Alzheimer's disease (AD). Raw numbers for the United States population (2000) rand projected (2010 and 2020) are shown (**a**). Note that the demographic changes between 2000 and 2020 in the US are not projected to affect all age groups the same. Projected increases over time (2000–2020) are shown in **b.** The number of persons between ages 85 and 89 years of age will increase by approximately 30% in that time period, whereas the number of people between ages 95–99 years of age will increase by over 100%. If aging itself is linked mechanistically to AD, then Western cultures are at gravely increased AD risk. However, it may be a mistake to conflate AD with other causes of cognitive impairment. Source: US Census Bureau

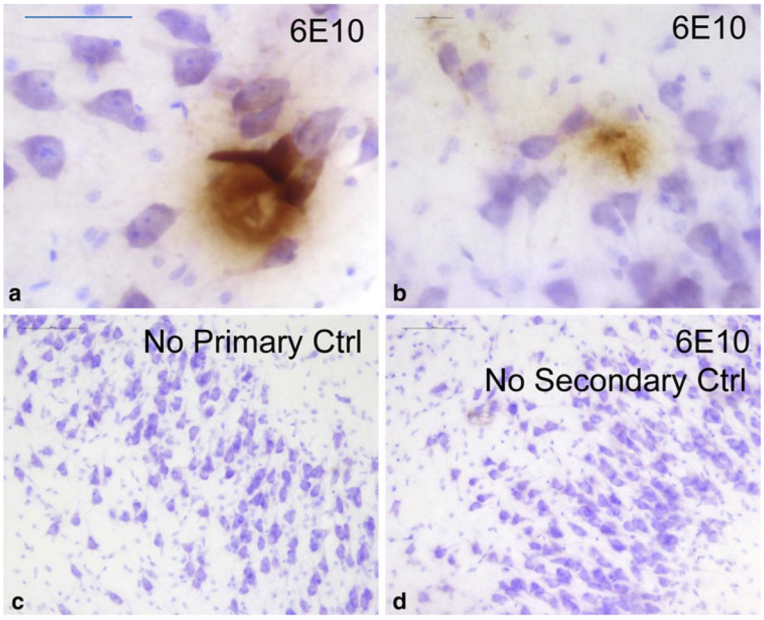

Fig. 2.

Aβ deposition in the hippocampus of a 5-month-old infant with Down syndrome (DS). DS is caused by triplication of chromosome 21 genes including the amyloid precursor protein (APP) locus. This Caucasian female died after 148 days due to complications of congenital heart disease. At autopsy, brain weight was 550 g with foreshortening of the anterior–posterior dimension as is characteristic of DS. Photomicrographs show hippocampus counterstained with Nissl stain (*blue*) and immunostained (*brown*) using anti-Aβ (6E10). Sections showed diffuse plaque-like structures (**a**) and smaller, more filamentous-looking Aβ deposits (**b**). Separate controls run in parallel without primary or secondary antibodies were completely negative (**c, d**). All persons with DS eventually develop Alzheimer's disease (AD). This drives home the point that although much is still unknown about AD pathobiology, genetic risk factors related to APP are of paramount relevance. *Scale bars* 50 μM (**a**), 20 μM (**b**), and 100 μM (**c, d**)

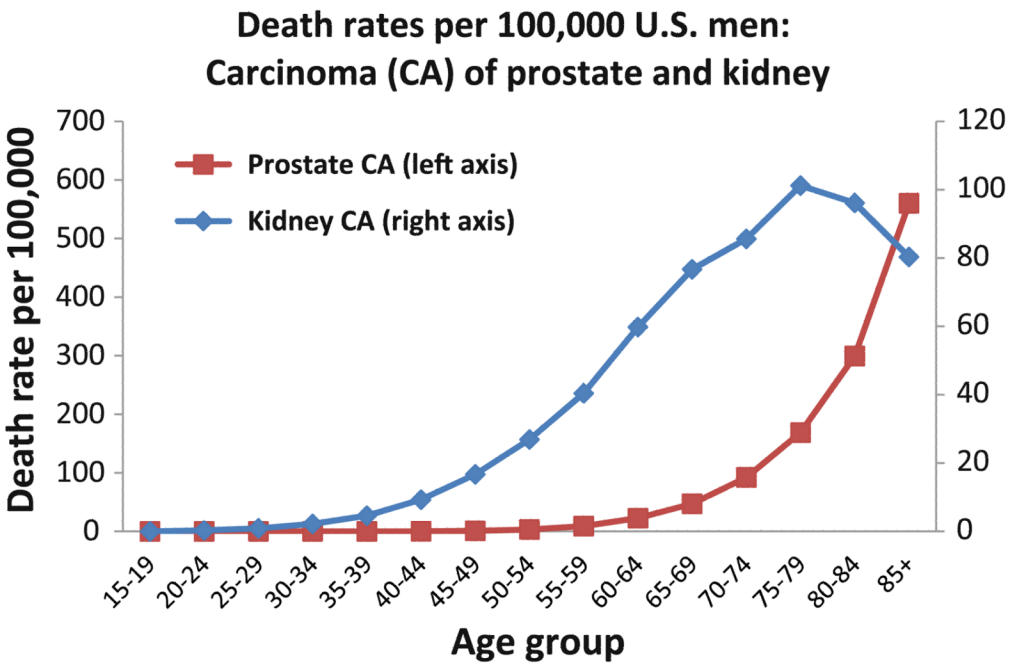

Fig. 3.

Death rates for prostate and kidney carcinoma (CA) in American males according to the SEER database [87]. These data are presented to show the different epidemiology of two different urothelial-derived cancers in men. This is a case where the epidemiology can help guide important research questions related to the biology of the cancers and the impact of aging and senescence. Although cancer is considered an aging-associated disease, the particular subtypes of cancer tend to inhabit particular ranges of the human age spectrum. This paradigm also applies to human neurodegenerative diseases which (like kidney cancer) may peak prior to extreme old age

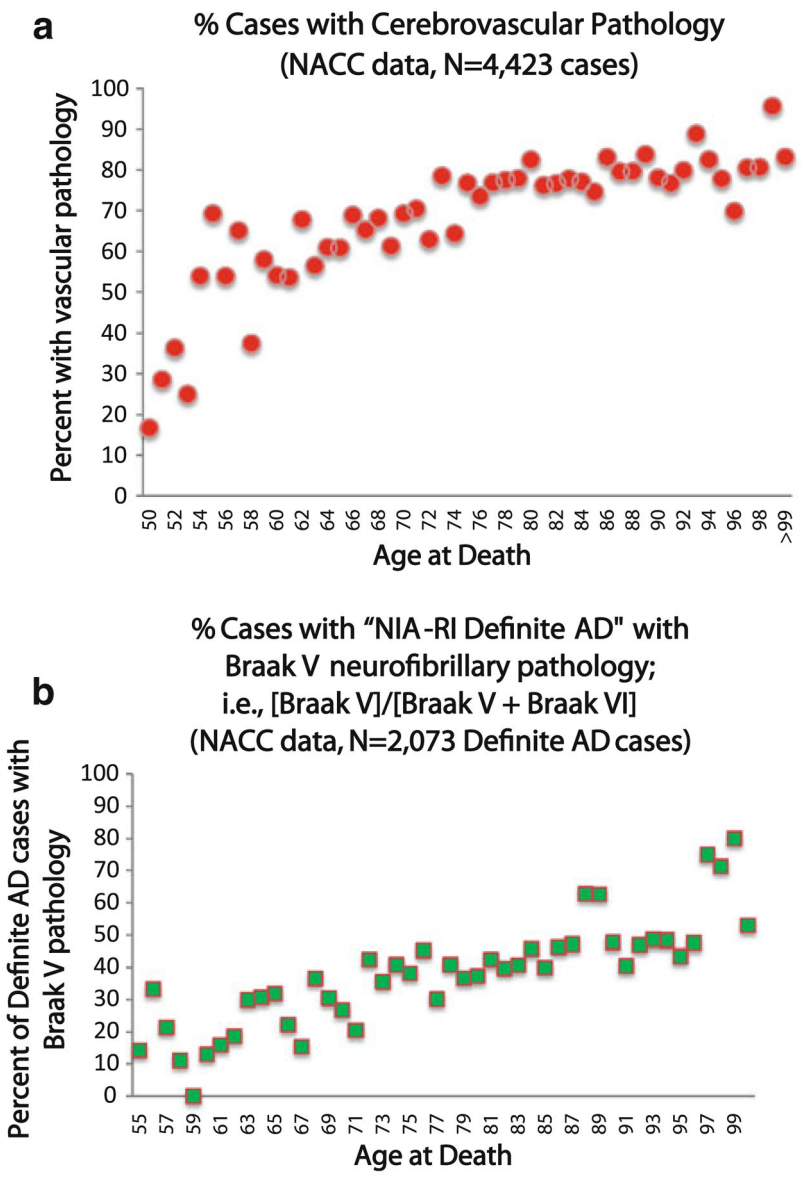

Fig. 4.

National Alzheimer's Coordinating Center (NACC) Registry data provide important clues about the correlations between aging, Alzheimer's disease (AD), and cerebrovascular disease (CVD). Data were obtained from 25 different Alzheimer's Disease research centers as described previously [23]. For the assessment of CVD pathology (**a**), all cases in the relevant age range (*N* = 4,423) were included. These show that CVD is strongly increased in advanced age with ~90% of centenarians showing at least subtle CVD pathology. In assessing AD (**b**), we only evaluated individuals with Braak stages V or VI neurofibrillary pathology (*N* = 2,073). Note that among brains with "definite" AD pathology, there is an increasing tendency for Braak V (instead of VI) in older individuals

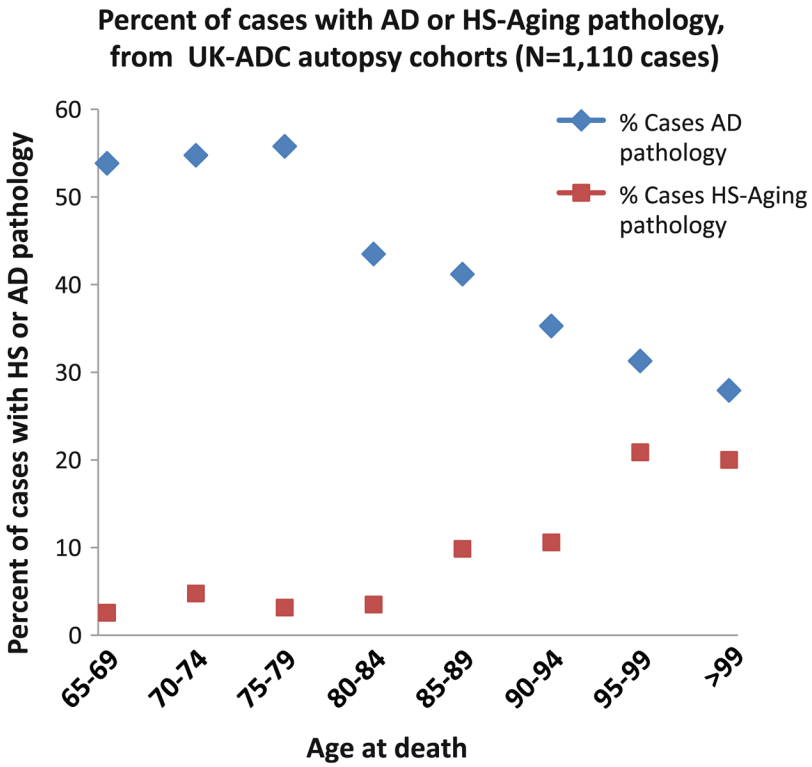

Fig. 5.

In a large clinical–pathological study that incorporated the UK-ADC autopsy cohort, The Nun Study [209], and The Georgia Centenarian Study [173], we evaluated 106 cases with hippocampal sclerosis (HS-Aging) and 1,004 controls [152], including many with AD. Collectively, these cohorts may be enriched for individuals with cognitive impairment at death because of recruitment bias; however, *N* = 625/1,110 or 57% had neither HS-Aging nor AD. Beyond 95 years of age at death, the prevalence of AD pathology (defined by numerous neuritic amyloid plaques and Braak stages V or VI on autopsy) appeared to decline, whereas the prevalence of HS-Aging pathology became almost as high as AD pathology

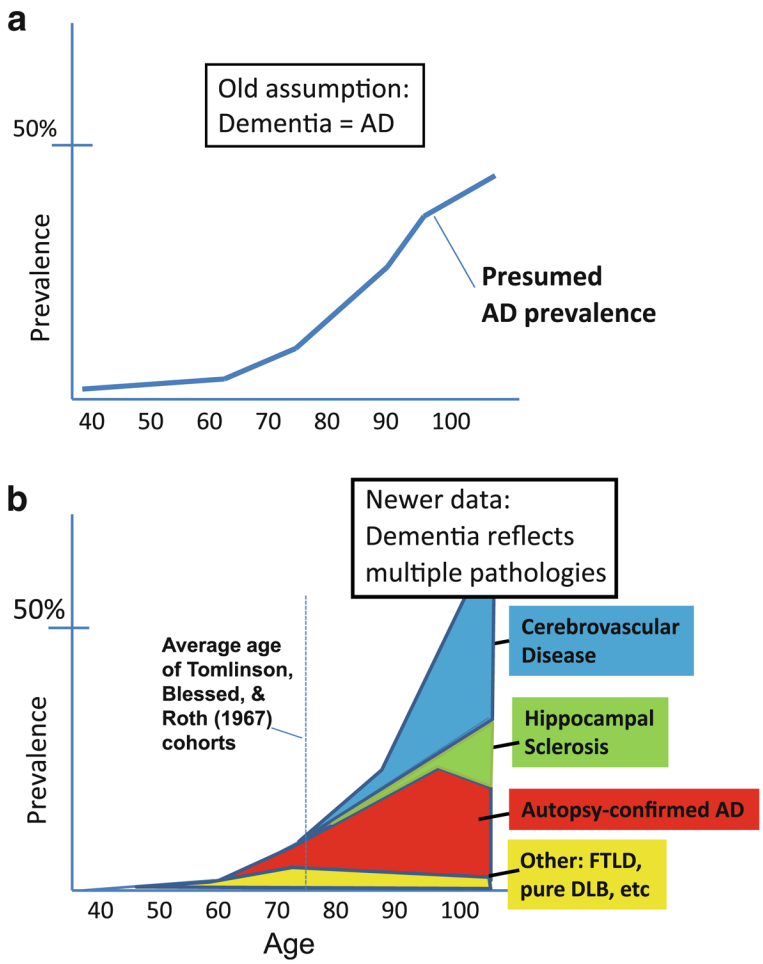

Fig. 6.

Epidemiology of clinical dementia and specific pathologies that contribute to dementia. The epidemiology of dementia (**a**) is based on well-characterized clinical cohorts (for review see [112]). The epidemiology of the different brain diseases—with autopsy confirmation—is far harder to know for sure because the data are critically dependent on autopsy-derived information including the neuropathological practices used at autopsy. Most autopsy series lack large numbers of individuals of extreme advanced age, and each study has distinct biases in terms of recruitment, inclusion, and neuropathological assessments. The chart (**b**) is a subjective amalgamation of multiple published studies pertinent to this important topic [19, 21, 61, 76, 79, 80, 96, 102, 105, 106, 115, 140, 145, 150, 156, 158, 171, 176, 184, 193, 198, 211, 217, 228, 231]

Table 1

Criteria for whether "aging mechanisms" specifically are linked with Alzheimer's disease (AD)

Criteria for whether or not the mechanism of AD pathogenesis is specifically linked to aging	Criterion satisfied?	Directly relevant research
1. There is not some other mechanism outside of aging that seems likely to cause AD	NO	Clinical trials, genetics, and cancer biology
2. Human genetic aberrations that appear to hasten the aging process also increase incidence or prevalence of AD, and vice versa	NO	
3. An elderly person should have a higher likelihood of dying with AD with every added year of life	NO	AD and dementia epidemiology
4. As with wrinkled skin and subtle cognitive impairment relative to baseline, everyone will experience AD if they live long enough (and cognitive loss in aging relates specifically to AD)	NO	
5. Other aging-linked mechanisms (diabetes and synapse loss) contribute specifically to AD	NO	Diabetes and synapse loss

Table 2

Progerias, human genetic diseases with “accelerated aging”: features and relationship to AD pathology

Accelerated aging syndrome	Clinical features	Mutated gene(s)	Life expectancy	Definitive increase of AD pathology?
Werner syndrome	Short stature, gray hair, hoarse voice, cataracts, wrinkled skin, diabetes, osteoporosis, cancers	WRN	40–50s	No but see [126]
Hutchinson–Gilford syndrome	Hair loss, thickened/wrinkled skin, atherosclerosis, premature frailty, usually die in teens	LMNA	Teens	No
Cockayne syndrome	Small stature, photophobia, small head, mental retardation, neurological symptoms (e.g. ataxia)	CSA/ERCC8, CSB/ERCC6	Childhood-30s	No
Trichothio-dystrophy	Short stature, brittle/sparse hair and nails, intellectual impairment, photosensitivity, infections	XPB, XPD, TTDA/GTF2H5	Childhood-40s	No

Table 3

Sample of relatively prevalent conditions in advanced age that can adversely affect cognition or performance on cognitive tests independent of AD status

Brain diseases in advanced age	Systemic illness that can affect cognition
Occlusive or embolic infarct(s), hemorrhagic infarct(s), frontotemporal lobar dementias, α-synucleinopathies, including Parkinson disease dementia and dementia with Lewy bodies, HS-Aging and other TDP-43 pathologies, tangle-predominant dementia, subdural or epidural hematomas, chronic traumatic encephalopathy, depression, anxiety, normal pressure hydrocephalus, and many others	Side effect of chemotherapy or other medication, side effect of other disease including cancers, heart failure and other causes of vascular insufficiency, hyperglycemia, hypoglycemia, renal dysfunction, liver dysfunction, pulmonary disease including emphysema and other causes of chronic hypoxia, metabolic fluxes (e.g. electrolyte imbalances), infection (CNS or outside CNS), vasculitis or other autoimmune/rheumatic disease, substance abuse, and many others
Number of the above that have been proven to specifically induce Alzheimer's disease, as opposed to co-morbidly altering the cognitive symptoms?	
None	

Table 4

Clinical–pathological studies that correlate the presence of antemortem diabetes with autopsy-confirmed Alzheimer's disease (AD) and cerebrovascular disease (CVD) pathology

Study	Diabetics	Non-diabetics	In diabetics, versus nondiabetics	
	N	*N*	Risk of AD pathology	Risk of CVD pathology
Heitner and Dickson [89]	49	52	Not increased	Not evaluated
Peila et al. [166]	216 total autopsies		Not increased[a]	Increased
Janson et al. [98]	28	19	Not increased[b]	Not evaluated
Beeri et al. [24]	61	324	Decreased	Increased
Arvanitakis et al. [15]	36	197	Not increased	Increased
Nelson et al. [149]	50	189	Decreased	Increased
Sonnen et al. [210]	59	137	Decreased[c]	Increased
Ahtiluoto et al. [8]	70	221	Decreased	Increased
Matsuzaki et al. [135]	135 total autopsies		Not clear[d]	Not clear[d]

[a] No effect of "diabetes only" on AD pathology overall, but a synergy was seen between APOE4 allele and diabetes that correlated with increased AD pathology for APOE4 + diabetics in this study

[b] No effect of type 2 diabetes in terms of amyloid plaques (diffuse or neuritic) or neurofibrillary tangles. Duration of diabetes appeared linked to AD pathology (although the significance of this is not clear) and clinical AD diagnosis was linked to diabetes although this impression was not confirmed with pathology

[c] Among individuals with dementia only; non-demented persons showed no difference

[d] Authors focused on amyloid plaque and sub-threshold pathology and not diagnostic pathology or neurofibrillary pathology (Braak stages). Data were interpreted to suggest insulin resistance correlates with increased amyloid plaques with synergy between glycemic factors, APOE, and AD pathology. However, presented data could be interpreted differently

Table 5

Summary

Summary points
Persons with many NFTs in neocortex always have cognitive impairment; in the presence of neuritic plaques this is the definition of AD
Genetic diseases that lead to premature aging (“progeria”) do not induce AD phenotype
Highly penetrant genetic diseases that lead to AD phenotype have no known link to aging but instead to APP processing
Persons with cognitive impairment may lack neocortical NFTs, especially in extreme advanced old age; this is probably due to the brain diseases other than AD that affect aged persons’ brains including HS-Aging, CVD, and diabetes
HS-Aging and CVD, unlike AD, increase in aged persons’ brains every year after age 95
Other human diseases including specific cancer subtypes have increased prevalence in seventh and eighth decade of life but lower prevalence thereafter
Aging-linked mechanisms, including HS-Aging, CVD, diabetes and synapse loss, have not been proven to induce AD pathology
There is no particular senescence-related biochemical mechanism that has been definitively linked to AD