Review

'Evolutionary medicine' perspectives on Alzheimer's Disease: Review and new directions

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ABSTRACT

Evolution by natural selection eliminates maladaptive traits from a species, and yet Alzheimer's Disease (AD) persists with rapidly increasing prevalence globally. This apparent paradox begs an explanation within the framework of evolutionary sciences. Here, I summarize and critique previously proposed theories to explain human susceptibility to AD, grouped into 8 distinct hypotheses based on the concepts of novel extension of the lifespan; lack of selective pressure during the post-reproductive phase; antagonistic pleiotropy; rapid brain evolution; delayed neuropathy by selection for grandmothering; novel alleles selected to delay neuropathy; by-product of selection against cardiovascular disease; and thrifty genotype. Subsequently, I describe a new hypothesis inspired by the concept of mismatched environments. Many of the factors that enhance AD risk today may have been absent or functioned differently before the modern era, potentially making AD a less common affliction for age-matched individuals before industrialization and for the majority of human history. Future research is needed to further explore whether changes in environments and lifestyles across human history moderate risk factors and susceptibility to AD.

1. Introduction

From the perspective of evolutionary sciences, Alzheimer's Disease (AD) represents an enigma. AD is highly prevalent (Wimo and Prince, 2010), highly deleterious with no offsetting benefit, and has some genetic basis (Licastro et al., 2007). On the surface, it would appear that natural selection (henceforth "selection") should eliminate AD from the human species, but instead incidence is rapidly increasing (Brookmeyer et al., 2007; Rocca et al., 2011). Thus the persistence and prevalence of AD requires evolutionary explanation. This two-part manuscript first summarizes and critiques evolutionary scientific theories for the persistence and prevalence of AD tendered by previous authors, and subsequently, suggests a new evolutionary hypothesis explained in greater detail than the others because no paper has yet been devoted to its complete description. The hypotheses are all presented with reference to AD, although many of the ideas could be similarly argued for other geriatric non-communicable chronic diseases. Previous theorists have proposed the following premises:

1) Novel extension of the lifespan, *i.e.*, that before the advent of Western medicine, individuals did not live beyond the fifth decade of life;

2) Age-related selection bias, *i.e.*, that traits affecting younger individuals are more sensitive to selective pressure because they are more likely to influence reproductive success;

3) Antagonistic pleiotropy (Williams, 1957), *i.e.*, that genes that are beneficial in one way or during certain phases of the life cycle may be detrimental in other ways or at other phases;

4) That AD is a by-product of rapid brain evolution;

5) That AD neuropathy is delayed in humans compared to ancestral species due to selection for grandmothering;

6) That novel alleles protective against AD were selected to delay disease onset;

7) That AD is a by-product of selection against cardiovascular disease;

8) That AD is caused by a thrifty genotype (Neel, 1962), *i.e.*, the idea that sacrificing energetically costly traits is adaptive in conditions of caloric stress.

The new hypothesis described here invokes the concept of environmental mismatch (Eaton et al., 1988), *i.e.*, that novel features of modern human environments may promote disease states that were absent or at lower frequency in the pre-modern world. The modern epidemiological era to which I refer is defined by the transition to industrialized human habitats beginning approximately 200 years ago

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(Stearns, 2012), with stark contrast to the hunting-gathering (foraging) lifestyles that characterized the vast majority (~93.4%) of human history (Bar-Yosef and Belfer-Cohen, 1989), acknowledging the intervening period of agricultural subsistence (12.5 thousand to 200 years ago) as a transitional phase for chronic degenerative disease propensity (Abbott and Peters, 1988; Ludwig, 2011). Some relevant information to which I refer comes from research among contemporary societies that practice hunting-gathering subsistence acquisition, as an imperfect proxy to help approximate disease risk factors in previous human environments, conceding the inherent limitations in this approach (Lee, 1992).

AD imposes extraordinary challenges to the research community as both an urgent threat, inflicting immeasurable suffering on its victims and their loved ones, as well as a scientific quandary, involving dysfunction across multiple physiological pathways, spanning central and peripheral systems, with limited treatment effectiveness (Casey et al., 2010). The ubiquity, complexity, and inefficacy of currently-available therapeutics for AD necessitate a broad range of perspectives to unravel the biomechanisms, evolutionary history, and suite of interacting risk factors that give rise to relevant phenotypes. Evolutionary medicine can offer unique insights that may contribute to public health and medical disease prevention, treatment, and eradication strategies (Nesse, 2001; Nesse and Williams, 1996).

2. Previous hypotheses

2.1. Alzheimer's was not subject to selection because human ancestors had shorter lifespans

A widely held idea is that longevity beyond life's fourth decade is a recent trend, making geriatric diseases modern phenomena (Davies, 1986; Garcia-Ruiz and Espay, 2017; Karasik, 2008; Stearns et al., 2010). This line of thought suggests that AD persists in our species because there has not been ample time for selection to influence the frequency of associated alleles. The logical extension would be that AD is the result of normal brain senescence during this new extension of the lifespan, and not a pathological condition.

A weakness of this hypothesis is that—despite dramatic increases in life expectancy *at birth*—the adult mortality curve has probably much retained a similar shape across human history (Marlowe, 2005). We can approximate pre-modern mortality hazards by observing contemporary hunter-gatherers because of their limited use of Western medicine, lifestyles, and environments that more closely resemble our pre-modern antecedents. Among a composite of contemporary hunter-gatherer groups, modal age of adult death was over 70 years, and two-thirds of those who survived to sexual maturity lived to age 70 (Gurven and Kaplan, 2007; Hawkes and Paine, 2006). Among the !Kung (Biesele and Howell, 1981) and Hadza (Hawkes, 2010) ~10% of the population was over 60 years. If our pre-modern predecessors exhibited similar lifespans, traits that emerge after age 60 years would have been prevalent and subject to selection.

As for the possibility that AD is normal senescence rather than pathology, some researchers suggest that if all people lived to age 130 years then essentially all people would have AD (Terry and Katzman, 2001). However, distinguishing aging and diseases of aging may be a theoretical exercise that does not have empirical relevance. Rather than conceiving of AD as a by-product of normal aging, it can be considered instead as a set of biochemical and neuropathological changes that can be activated by age-related mechanisms (Ashford et al., 2005).

2.2. Antagonistic pleiotropy

Genes that are beneficial in one way may be detrimental in another, and genes that are beneficial during certain phases of the life cycle may be detrimental later. This phenomenon of 'antagonistic pleiotropy' is hypothesized to account for senescence to the extent that age-related selection bias favors the beneficial characteristics of genes with age-dependent effects (Williams, 1957). AD may be conserved in the human population not because it is invisible to selection, as the above hypothesis would suggest, but rather because susceptibility genes may have pleiotropic effects, serving adaptive functions in other processes or at other times. Evidence for cancer-related genes promoting fecundity (Kang et al., 2009; Smith et al., 2011) and coronary artery disease-related genes positively associated with fertility (Byars et al., 2017) provides support for the possibility that antagonistic pleiotropy may be relevant for understanding the evolutionary context of other non-communicable chronic diseases (review (Corbett et al., 2018)).

It was postulated that AD may be the result of selection for genes related to cerebral cortex neuronal activity, especially neuroplasticity, which could make the brain better at learning but more vulnerable to AD-type dysfunction (Bufill and Blesa, 2006). However, no evidence has been presented to support this hypothesis to date. Further, the observation that during early and middle adulthood, individuals who will later develop AD perform more poorly on cognitive assessments (Twamley et al., 2006) opposes the hypothesis of AD as the result of pleiotropic cognitive benefits earlier in the lifespan.

It has also been suggested that the APOE-ε4 allele confers pleiotropic effects *via* protection against hepatitis-C associated liver damage (Wozniak et al., 2002), cardiovascular stress (Ravaja et al., 1997), miscarriage (Zetterberg et al., 2002), age-related macular degeneration (Klaver et al., 1998), better outcomes for children with diarrhea (Oria et al., 2005), and protection against malaria (Wozniak et al., 2004). The ε4 allele was also associated with greater completed fertility in a high (but not low) pathogen exposed population in rural Ghana (van Exel et al., 2017), and higher eosinophil (Trumble et al., 2017) and C-reactive protein concentrations (Vasunilashorn et al., 2011) among forager-horticulturalists in Bolivia, suggesting anti-parasitic effects. However, the disease-promoting effect of ε4 is evident not only in AD but also in cardiovascular disease (Martins et al., 2006), HIV and herpes simplex virus infections (Kuhlmann et al., 2010).

Amyloid-β (Aβ), the protein comprising senile plaques characteristic of AD, may itself have pleiotropic effects (Finch and Martin, 2016). Aβ exhibits antimicrobial properties (Soscia et al., 2010), such as *in vitro* protection of cultured cells against influenza A virus (White et al., 2014), herpes simplex virus (Bourgade et al., 2015; Eimer et al., 2018), and pathogenic yeast, and *in vivo* protection in murine models of AD against herpes simplex virus (Eimer et al., 2018), meningitis and in transgenic *C. elegans* against pathogenic yeast (Kumar et al., 2016). Interestingly, oligomerization of Aβ is necessary for enacting these antimicrobial properties (Kumar et al., 2016). On the other hand, evidence is converging to suggest that soluble oligomeric Aβ may be responsible for AD neuropathy, and Aβ plaque formation may be an adaptive, neuroprotective response that staunches damage (Finch and Martin, 2016; Glass and Arnold, 2016; Hefti et al., 2013; Lee et al., 2005). Additionally, fibrilization is necessary for Aβ to enact its anti-herpetic function (Eimer et al., 2018), suggesting that fibrilized Aβ may be both neuroprotective *via* viral entrapment and damaging *via* neuritic plaques.

Wick et al. refer to possible pleiotropic effects of the immune system in AD etiology. Activation of innate immune response initially protects neurons against Aβ toxicity, but, chronic activation has destructive effects (Wick et al., 2003). Not only are the relevant cytokines toxic when produced chronically and at high concentrations (Jeohn et al., 1998), but also they stimulate the production of amyloid precursor-protein (APP) (Goldgaber et al., 1989) and, in certain combinations, Aβ (Blasko et al., 1999). Similarly, activation of adaptive immune response initially targets and clears Aβ (Trieb et al., 1996) even in aggregated form (Schmitt et al., 1997), but chronic activation leads to neuroinflammatory damage (Grubeck-Loebenstein et al., 2000). Summarily, it is plausible that balancing selection (Kojima and Yarbrough, 1967) could lead to retention of alleles that confer both protection and risk, and further research is needed to discern their advantages and

disadvantages in different contexts.

2.3. Alzheimer's is a result of rapid brain evolution

Over the past approximately three million years, our ancestors' brains more-than-tripled in average volume from *afarensis'* 400 cm^3 to *sapiens'* 1450 cm^3 (Boyd and Silk, 2015). Some authors have suggested that AD neuropathy could be considered a phylogenetic feature, as the parts of the brain most damaged in the course of AD are those that were subject to the most extreme enlargement during our ancestral species' shift from chimpanzee-like brains to modern ones (Bruner and Jacobs, 2013; Powell, 2010; Rapoport, 1989) (*e.g.* frontal, parietal, temporal neocortices, hippocampus). This idea would require that at least some of the same (or linked) genetic variants that caused enhanced encephalization across hominin history are also, themselves, the causal agents of the features of those brain regions (*e.g.* frontal, parietal, temporal, neocortices, hippocampus) that make them more vulnerable to AD insult compared to other brain regions. I would posit a likely candidate feature would be structural location of these regions. The first step in testing this hypothesis may include consideration of genes that are strongly implicated in human-specific expansion, *e.g. NOTCH2NL* (Fiddes et al., 2018), *HARE5* and promotor *Fzd8* (Silver, 2016), to test whether they confer differential AD vulnerability.

Strong selection on encephalization-promoting genetic variants could, hypothetically, override deleterious effects of the same genetic variants if the selection pressure benefits outweigh costs. This hypothesis seeks evidence that the same (or functionally linked) alleles promoted encephalization across the hominin lineage and AD risk.

2.4. Alzheimer's is not subject to selection because it is typically restricted to post-reproductive individuals

A few publications have suggested that AD persists in the human population despite its obvious deleterious effects because it manifests after reproductive cessation, and therefore is not responsive to selective pressure because it wouldn't alter the number of offspring an individual produces (Bufill and Blesa, 2006; Nesse et al., 2017; Reser, 2009). Recently, Nesse et al. proposed the hypothesis that because AD does not manifest until the sixth decade of life, it is not subject to meaningful selective pressure, and may be the by-product of selection for shorter sleep duration compared to our species' ancestors, highlighting the ways in which sleep deprivation and disruption promote AD neuropathy (Nesse et al., 2017). The authors acknowledge an alternative or simultaneous pathway by which AD instigates sleep deprivation and disturbance.

Contrary to the supposition that AD evades selection because it manifests after reproductive cessation, propensity to later develop AD may impose disadvantage during the reproductive phase of the lifespan. Longitudinal studies evince that during early and middle adulthood, individuals who will later develop AD perform more poorly on assessments of attention, verbal learning and memory, executive functioning, processing speed, and language, compared to peers who will not develop AD (reviewed by Twamley et al. (2006)). For example, the well-known Nun Study demonstrated that low linguistic ability in early adult life was a strong predictor of AD in later life (Snowdon et al., 1996). A genetic risk for AD also promotes risk of cardiovascular disease during mid-life (Martins et al., 2006).

Furthermore, a long period of geriatric dependence would have deleterious impact upon the rest of the family, thus undermining inclusive fitness (Hamilton, 1964), *i.e.*, perpetuation of genes across generations *via* survival of kin. Individuals with AD gradually lose their autonomy as the disease progresses, and eventually are dependent on their families for support with every aspect of living. Importantly, anthropological theory argues that grandmothers are not essentially post-reproductive, as there are still many ways in which they can influence their inclusive fitness (Hawkes et al., 1997, 2000). Grandmothers who

are able to pass down valuable information, perform domestic duties that subsidize the energetic and time limitations of reproductive adult children, and care for grandchildren are able to enhance their number of descendants (Fox, 2012; Reiches et al., 2009). Unlike geriatric diseases that bring about sudden increases in mortality, upon AD diagnosis typical remaining lifespan is 7–10 years (Zanetti et al., 2009), implying a prolonged, costly burden on kin as well as loss of opportunity to benefit kin. Summarily, selective pressure may resist AD-promoting genes due to pre-reproductive disadvantages and post-reproductive burden on kin and inclusive fitness detriments.

2.5. Alzheimer's neuropathy is delayed in humans compared to other animals because of the adaptiveness of grandmothering

Sapolsky and Finch (Finch and Sapolsky, 1999; Sapolsky and Finch, 2000) suggest that as the primate lifespan extended, maternal care was needed at progressively later ages, creating a selective pressure to delay AD onset until after maternal care had concluded. They hypothesize that the estradiol associated with reproductive activity may be a contributing mechanism for the delay of AD neuropathy. Among primates, reproductive success requires not only giving birth, but also raising offspring to independence (Williams, 1957). Therefore, selection among primates may delay AD neuropathy until after females have raised their last offspring to independence (Finch and Sapolsky, 1999; Sapolsky and Finch, 2000). But human AD onset is typically decades after reproductive cessation. The authors (and others) account for this by arguing that grandmothering continues to increase an individual's inclusive fitness and thus human females must rear their youngest grandchild to independence before they can develop AD without experiencing fitness detriments (Glass and Arnold, 2016; Sapolsky and Finch, 2000). Their proposed mechanism for how our species manages to delay AD onset decades after estradiol diminishes follows below, along with a critique of both parts of their hypothesis.

Glass and Arnold further Sapolsky and Finch's argument by including not only late age at independence, but also increased altriciality of infants among hominins compared to chimpanzee-like ancestors (Glass and Arnold, 2012). The prolonged period of altriciality resulted in prolonged need for parental care. Post-menopausal women would have been competent allomothers only if they remained cognitively competent (Glass and Arnold, 2012). This hypothesis confounds altriciality with cooperative breeding, as duration of offspring dependence does not obligate grandmaternal (or any allomaternal) care.

2.6. APOE-ε2 and ε3 are new isoforms in humans that were selected for protection against AD

There is consensus in the medical research community that the ε4 allelic variant of APOE is the primary genetic risk factor for late-onset AD (Corder et al., 1993). APOE-ε4 is the ancestral allele, and all other primates have only one APOE allele that is nearly identical to ε4 with arginine codons at positions 112 and 158 (Ashford, 2002; Finch and Sapolsky, 1999; Hanlon and Rubinsztein, 1995). After the *Pan/Homo* split, APOE-ε3 emerged from a single base mutation (C→T) approximately 300 thousand years ago, and a second similar mutation occurred at amino acid position 158 creating APOE-ε2 approximately 200 thousand years ago (Ashford, 2002; Glass and Arnold, 2012; Singh et al., 2006).

Being that the ε3 and ε2 alleles emerged relatively recently, they are more common than would be expected for neutral substitutions, suggesting that they have been actively selected (Glass and Arnold, 2012). While 28% of people carry a copy of ε4, only 1–2% are homozygotes, and approximately 95% of all living people are estimated to carry at least one copy of ε3 (Gerdes, 2003). It appears unlikely that these allelic frequencies could be attributed to drift, as their gene product's involvement in disease-related processes argues against selective neutrality, and even if the allelic variance were neutral, over the many

generations and relatively small population sizes of ancestral hominins, neutral variation would likely be lost due to sampling error, resulting in either extinction or fixation of neutral alleles (Keller and Miller, 2006). And yet APOE-ε4 persists despite its role in increasing AD risk as well as cardiovascular disease risk.

Sapolsky and Finch's hypothesis implies that AD neuropathy should begin at roughly the same time in homozygous ε4 humans as it does in non-human primates who all carry ε4-like alleles, and progressively later in humans who have ε3 and/or ε2 alleles. While the second part of this prediction is supported by evidence – people with at least one ε3 or ε2 allele have later AD onset than ε4 homozygotes (Blacker et al., 1997) – the first part of the prediction does not entirely hold. Among female non-human primates, AD brain changes begin to occur shortly after their last pregnancy if not before it (reviewed in Finch and Sapolsky (1999)), while in ε4 homozygous humans, these changes are somehow kept at bay for two decades after the last pregnancy, with age 66.4 as the average onset in ε4 homozygotes (Blacker et al., 1997). Average age at last birth in natural fertility populations is 41 years (Beets et al., 2011; te Velde and Pearson, 2002) and ovarian hormones cease production on average at age 50.5 (McKinlay et al., 1992). Therefore, there are two asymptomatic decades that are unaccounted for in Sapolsky and Finch's model.

2.7. Delay of Alzheimer's is a by-product of selection for protections against cardiovascular disease

Finch and Stanford posit that selection against APOE-ε4 occurred in hominid history with the shift from herbivory to meat eating (Finch and Stanford, 2004). ApoE regulates cholesterol uptake, and individuals who have ε4 alleles have higher cholesterol, more oxidized blood lipids, and increased risk of coronary artery disease (Finch, 2010). While orangutans and gorillas are largely herbivorous, chimpanzee and human diets contain more meat. This theory posits that the trend of meat eating enhanced risk for atherosclerotic disease, and thus created a selective pressure on cholesterol regulators. The emergence and increasing prevalence of APOE-ε3 may have been in response to the selective pressures of cardiovascular disease caused by the high cholesterol content of meat (Finch and Stanford, 2004).

Support for this hypothesis comes from a consideration of the APOE allelic frequencies between world populations. APOE-ε3 has its highest frequencies among groups that have practiced agriculture for the longest time, such as Mediterraneans (Corbo and Scacchi, 1999), who, they argue, would have had a more consistent food supply and thus perhaps greater longevity and higher risk of cardiovascular disease. APOE-ε4, the ancestral allele, is found at its highest frequencies amongst contemporary hunter-gatherers and other populations with inconsistent food supply at least until recently (Corbo and Scacchi, 1999), for whom increased cholesterol absorption could provide a survival advantage.

However, the emergence of ε3 300 thousand years ago pre-dates the advent of agriculture by approximately 288 thousand years (Lev-Yadun et al., 2000; Shelach, 2000), making it difficult to justify that the shift to agriculture explains selection for this allele. Also, if atherosclerosis risk from meat eating explained positive selection on ε3, it would be surprising (although possible due to stochasticity of mutation) that the ε3 variant emerged not in chimpanzees, the first regularly meat consuming apes (Stanford, 1999), but in humans, who consumed progressively less meat (Cordain et al., 2002). Furthermore, the shift from hunting-gathering to agricultural food acquisition may at first glance support the hypothesis, but upon deeper reflection undermines it. The hypothesis suggests that meat eating plus agriculture-induced lifespan extension caused fitness costs for ε4 (compared to ε3) carriers due to greater atherosclerosis risk. However, hunter-gatherers rely more on meat than do agriculturalists and so they may have stronger selection than agriculturalists for adaptations avoiding atherosclerotic disease, depending on age at atherosclerosis onset. Exemplifying the likelihood

that hunter-gatherers were indeed at risk of atherosclerotic disease to any meaningful extent at pre-geriatric ages, CT scans of mummies from agricultural and hunter-gatherer populations in a geographically, culturally, and temporally diverse range of individuals show atherosclerosis in all groups (Thompson et al., 2013). Three Unangan hunter-gatherers from the Aleutian Islands mummies of individuals ages 25–51 exhibited definite atherosclerosis (while the two Unangan mummies of individuals ages 4–5 and 18–24 did not) which is preliminary pilot evidence of potentially higher disease prevalence among hunter-gatherers than among horticulturalist and agriculturalist populations estimated from ancient Egyptian (38% atherosclerosis rate), ancient Peruvian (25%), and Ancestral Puebloan (40%) mummies (Thompson et al., 2013), and also among forager-horticulturalists in Bolivia (16%) (Kaplan et al., 2017). If hunter-gatherers have stronger selection against cardiovascular disease than agriculturalists, the hypothesis would predict that ε4 alleles should be less frequent in hunter-gatherers compared to agriculturalists. But in fact the opposite is true, with ε4 more frequent among contemporary hunter-gatherers (Corbo and Scacchi, 1999). Further research is necessary to explore atherosclerosis risk, APOE genotypes, and age-specific rates among hunter-gatherer populations either using forensic remains (Thompson et al., 2013) or with contemporary populations who practice traditional subsistence strategies (Kaplan et al., 2017).

2.8. Pre-clinical Alzheimer's is an adaptive sacrifice during times of caloric stress

Reser proposes that pre-clinical AD is an adaptive way to limit metabolic expenditure on the brain, because in the simple lives of hunter-gatherers, activities become rote and repetitive by old age, and there is not the same need to maintain the ability to learn or improve skills (Reser, 2009). He suggests that in a person's fourth decade, they are no longer as skillful at obtaining food as they were previously, and thus become calorically restricted. The near-starvation advantages those who conserve energetic resources by sacrificing brain function (Reser, 2009). This idea describes a 'thrifty genotype' (Neel, 1962) approach to understanding AD.

The importance of higher cognitive function in our species, mortality scheduling in hunter-gatherers, intellectual challenges of foraging lifestyle, and physiological prioritization of brain function are in conflict with this hypothesis (Dunbar, 2003; Gurven and Kaplan, 2007).

3. Mismatch hypothesis for Alzheimer's

The theories described above assume that AD risk functions in much the same way as it would have in the past, and people are at the same age-specific risk of AD today as we might have been before the industrial revolution 200 years ago. These theories assume, for instance, that carrying an APOE-ε4 allele would confer similar AD risk then as it does today. However, there is reason to suspect that age-matched people in the pre-industrial world would have been less susceptible to AD than they are today. Here, I present a hypothesis based on the evolutionary medicine concept of mismatch, *i.e.*, the idea that novel features of modern life in the developed world may induce or enhance incidence of diseases that were absent or rare during previous phases of human history. I emphasize that in addition to inducing or enhancing disease incidence, modern factors may hasten onset of diseases that would have occurred significantly later in the lifespan (therefore with less influence on fitness) in pre-modern environments. With more immune stimulation, better insulin sensitivity, and different female reproductive life-histories, our pre-industrial counterparts may have been at lower age-matched AD risk (Fox, 2012). If AD is indeed a "disease of civilization" and today's risk factors did not confer risk in pre-industrial environments, this would relieve evolutionary scientists of the onus to account for the maintenance of the AD phenotype or of the ε4 allele, which has been the focus of several of the hypotheses chronicled above.

3.1. Insulin resistance

The role of insulin resistance is so central to AD risk that some researchers have referred to AD as "type-3 diabetes" or "diabetes of the brain" (Steen et al., 2005). The malfunction of glucose utilization and energy metabolism in the brain may be a proximate mechanistic explanation for much of AD neuropathology (Meneilly and Hill, 1993; Watson and Craft, 2004). Individuals with type-2 diabetes mellitus exhibit brain insulin resistance, cognitive impairment, and enhanced AD risk (de la Monte and Wands, 2008; Haan, 2006), demonstrating the connection between peripheral and central energy metabolism.

Like contemporary hunter-gatherers, pre-modern people would have been unlikely to frequently exhibit insulin resistance, and therefore may have been less susceptible to the glucose metabolism malfunctions characteristic of AD pathogenesis (Cordain et al., 2002; Pontzer et al., 2012). Based on patterns of contemporary hunter-gatherers, it has been estimated that our hunter-gatherer antecedents would have expended ∼3000 kcal per day and consumed ∼1.5% of the diet as simple sugars, compared to contemporary people in the developed world who expend only ∼2000 kcal per day and consume ∼20% of the diet as simple sugars (Cordain et al., 1998; Eaton, 1992; Eaton et al., 2002). Metabolic syndrome, obesity, and type-2 diabetes are at epidemic levels in the industrialized world today compared to probable low levels in the pre-industrialized world, and have overlapping risk factors and biological manifestation with AD (Glass and Arnold, 2016), suggesting the likelihood that these contributors to AD risk would have been lower in the past (Fox, 2012).

3.2. Estrogenic neuroprotection

Estrogens have myriad neuroprotective functions that defend against the AD pathological cascade. Estrogens have been shown to inhibit Aβ formation (Amtul et al., 2010; Manthey et al., 2001), promote Aβ clearance (Bruce-Keller et al., 2000; Rogers et al., 2002), inhibit neuronal apoptosis (Pike, 1999; Stoltzner et al., 2001), inhibit tau hyperphosphorylation (Goodenough et al., 2005), and reduce brain oxidative stress and inflammation (Garcia-Estrada et al., 1993; Nilsen et al., 2007; Rice-Evans et al., 1996; Subbiah et al., 1993), among other neuroprotective functions.

Pre-modern women likely exhibited divergent ovarian hormone profiles compared to women in the industrialized world. Pre-modern women were likely exposed to a shorter timespan of estrogen exposure due to later menarche (estimated by mean 17 years among contemporary hunter-gatherers (Goodman et al., 1985; Howell, 1979)) than industrialized populations (U.S. 1980s mean 12 years (Demerath et al., 2004)). Pre-modern women were also likely exposed to lower baseline levels of estrogen compared to industrialized populations (estimated by comparisons with contemporary hunter-gatherers (Eaton et al., 1994; van der Walt et al., 1978)). However, pre-modern women were also likely exposed to repeatedly higher doses of estrogen compared to women in industrialized environments, due to higher parity (reviewed in Eaton et al. (1994)). Estrogen levels during pregnancy are the highest experienced in the lifespan, during the third trimester averaging 14.5 ng/ml (Tulchinsky and Little, 1994) compared to 0.33 ng/ml during the peak of a typical ovulatory cycle (Hall, 1986). This increase of nearly 44-fold minimizes all other fluctuations in hormone levels including menarche and menopause. In a cohort of elderly British women, our lab found that women who spent more cumulative months pregnant across the lifespan were at lower risk of AD than those who spent fewer months pregnant (Fox et al., 2013a). Women in the pre-modern past would have experienced more time spent with pregnancy's high estrogen levels due to higher parity. While among the British cohort, median cumulative months pregnant, including incomplete pregnancies, was 21 months, the mean computed from a set of contemporary hunter-gatherer groups is 70.8 months pregnant in lifetime and this is only measuring full-term pregnancies

(range: !Kung 56.4 months – Aché 96 months) (Eaton et al., 1994). This is preliminary evidence that women in the past would have been at lower AD risk to the extent that pregnancy-associated estrogens are neuroprotective. However, the relative influence of timespan, baseline levels, and pregnancy levels of estrogen exposure on AD risk should be explored further in order to elucidate whether historical changes in women's estrogen profiles have increased or decreased AD risk across human history.

3.3. Inflammation

Inflammation is an important contributor to AD pathogenesis. Decades before symptom onset, there is upregulated type-1 inflammation (Schwarz et al., 2001), potentially due to insufficient repositories of immunosuppressive regulatory T-cells (T_{Regs}) (Pellicano et al., 2012). Such immune dysregulation is typical of autoimmunities that have previously been attributed to insufficient immunological challenge during early life (Kivity et al., 2009; Rook, 2010). As our hunter-gatherer ancestors likely experienced more, constant, low levels of immune activation due to more contact with animals, feces, and soil, it is likely they would have developed higher concentrations of T_{Regs} (Rook, 2007, 2009). In the developed world today, low stimulation from benign microorganisms may lead to low rates of lymphocyte turnover during the life course, which subsequently may cause insufficient development of T_{Regs} compared to pre-industrial populations. This 'old friends hypothesis' (Rook, 2010) could be extended to include AD at least to the extent that low pathogen exposure could increase risk of AD by virtue of an insufficient immunosuppressive lymphocyte repository.

Evidence for this hypothesis comes from our lab's previous observation that countries characterized by generally low pathogen exposure exhibit higher age-adjusted rates of AD (Fox et al., 2013b). Rates of infectious disease, urbanization, and percent population with access to decontaminated drinking water and toilet infrastructure may serve as proxies for exposure to diverse (including benign) microorganisms. Importantly, public health infrastructure and antibiotic therapies have been critical for protection against deadly infectious pathogens, but an unintended side effect may be diminished exposure to benign microorganisms that are essential for development of immunoregulatory capacity. The observed correlations between historical (corresponding to the years during which the contemporary geriatric population would have spent their childhoods) scores on these proxies indicating low immune stimulation and contemporary AD risk provides the first evidence suggestive of links between loss of diverse microorganism exposure, immunodysregulation, and AD risk (Fox et al., 2013b). Further research is needed to establish biomechanistic causality.

Early-life immune stimulation from benign microbes encountered during critical stages of development are beneficial for immune education, helping to avoid excessive inflammation later in the life course. The inflammation that results from either acute or chronic infections throughout the life course may induce brain insults that exacerbate AD risk or pathogenesis. For example, evidence has suggested that chronic infection with *Helicobacter pylori* (Kountouras et al., 2006; Roubaud-Baudron et al., 2012), *Chlamydia pneumoniae* (Balin et al., 1998), or *herpes simplex virus type 1* (Itzhaki et al., 1997; Readhead et al., 2018; Wozniak and Itzhaki, 2010) may enhance AD risk *via* neuroinflammation. The 'old friends hypothesis' would imply that infection-related inflammatory brain insult may be even worse if the immune system lacks the regulatory mechanisms that would otherwise limit inflammation-related damage to the host.

3.4. Environmental toxins

The Industrial Revolution brought about both novel and increased exposures to environmental toxins (Allan et al., 2015; Clapp, 2014). Pre-industrial human history would have been characterized by AD

rates lower by whatever degree industrialization-related environmental toxins enhance AD risk. A similar argument has been made for Parkinson's Disease: industrial toxicants have been argued as a major candidate accounting for higher rates of Parkinson's Disease in the industrialized era and industrialized world regions (Goldman, 2014).

Various industrial or occupational toxins that would have been absent from pre-modern environments have been implicated in AD risk. It is plausible that environmental agents could produce insults to the central nervous system in ways that exacerbate AD risk because endogenous neurotoxic agents play a crucial role in AD pathogenesis (Gao and Hong, 2008). Support is emerging that air pollution (Block and Calderón-Garcidueñas, 2009), and heavy metal exposure including lead, mercury (Monnet-Tschudi et al., 2006), and cadmium (Notarachille et al., 2014) may enhance AD risk, while others found no relation between exposure to toxic chemicals or heavy metals and AD risk (Heyman et al., 1984). Evidence remains ambiguous regarding aluminum exposure (Colomina and Peris-Sampedro, 2017; Gupta et al., 2005) and herbicide, insecticide, and pesticide exposures (Baldi et al., 2003; Gauthier et al., 2001).

3.5. ApoE

Environmental mismatch between the formative environment of human evolution and contemporary environments in which people experience inadequate early-life immunodevelopment may render pro-inflammatory alleles that were neutral or even adaptive in previous environments deleterious in certain contemporary environments.

APOE-ε4 is considered by the medical community to be the primary genetic risk factor for sporadic AD (Coon et al., 2007; Liu et al., 2015). The way in which the ApoE protein modifies AD risk is probably not through lipid metabolism, its first identified function—indeed, studies have found that even after statistically adjusting for cholesterol level and blood pressure, carrying an ε4 allele remained a risk factor for AD and the extent to which carrying an ε4 allele accounted for variance in AD risk was unaltered (Kivipelto et al., 2002; Minihane et al., 2007). More likely, APOE genotype modifies AD risk through its effect on inflammation. The ε4 allele has been associated with increased risk and poorer outcomes in other conditions characterized by neuroinflammation (Jofre-Monseny et al., 2008) including traumatic brain injury (Friedman et al., 1999), post-operative cognitive dysfunction (Lelis et al., 2006), multiple sclerosis (Pinholt et al., 2006), HIV-associated dementia (Corder et al., 1998), as well as psoriasis (Campalani et al., 2006).

However, the studies establishing APOE as an AD risk factor were all conducted in developed, relatively wealthy countries (Coon et al., 2007; Liu et al., 2015). These are the kinds of environments in which insufficient immune stimulation in early life leads to excessive inflammatory response in adulthood, as has been extensively discussed as a contributing factor in atopic and autoimmune conditions (Kivity et al., 2009; Rook, 2010, 2007, 2009). Consistent with a mismatch hypothesis, non-industrialized societies appear to exhibit little connection between the ε4 allele and AD risk while industrialized societies exhibit a strong connection, even given massive geographic and cultural diversity of each set of environments. The ε4 allele had no association with AD risk among geriatric Ibadan Yoruba Nigerians (Gureje et al., 2005), Nyeri Kenyans, Tanzanians (Sayi et al., 1997), Wadi Ara Arab Israelis (Farrer et al., 2003), Bantu and Nilotic African cohorts (Chen et al., 2010), or with mid-life AD risk factors among the Khoi San (Sandholzer et al., 1995). This was not the case for Americans with a wide range of ethnic ancestry, for whom ε4 conferred significantly increased AD risk (Farrer et al., 1997). It is conceivable that ApoE-ε4 does not cause inflammation in non-industrialized environments in which individuals' immunoregulatory capacity is stronger. In support of this possibility, a recent study in rural Ghana observed that ε4 status was not correlated with C-reactive protein or interleukin-6 levels (van Exel et al., 2017). We can speculate that carrying an ε4 allele may not have conferred AD risk in pre-modern peoples whose environments closer resembled those of non-industrialized societies today. Further research is needed to explore this intriguing possibility.

APOE alleles are present at different frequencies across global populations today, *e.g.* within Europe ε4 is most frequent at high-latitudes with decreasing frequency further south, ε3 is highest in low-latitude and ε2 is at highest frequencies in mid-latitude Europe (Siest et al., 2000). Because when ε3 and ε2 emerged during the Middle Paleolithic, Europe was populated by other species of hominins (*e.g.* Neanderthals), not Homo sapiens (Roebroeks, 2001), it is impossible to attribute initial emergence and distribution of alleles among Homo sapiens to local selection. However, it is conceivable that subsequent selection on APOE within Europe explains latitude-associated allelic gradients. Given the differential influence of APOE alleles on risks of not only AD but also infection (Kuhlmann et al., 2010), cardiovascular disease (Martins et al., 2006), and miscarriage (Zetterberg et al., 2002), it is difficult to attribute geographic allelic variation to some of these risks over others. In order to attribute these patterns to AD as a force of selection, the time-depth of latitude-associated APOE allelic gradients would have to be compared against the time-depth of AD incidence. Here it is argued that understanding the history of AD incidence requires information on demographic and life-history patterns as well as the population history of risk factors such as inflammatory and metabolic dysregulation.

4. Conclusion

Evolutionary perspectives have generated a series of hypotheses and predictions regarding AD. Assertions that AD is invisible to selection are undermined by evidence that human lifespans regularly extended into the geriatric phase throughout pre-modern history (with short life expectancy largely attributable to high early-life mortality risk) (Gurven and Kaplan, 2007; Hawkes and Paine, 2006) and geriatric individuals are not fundamentally post-reproductive because of inclusive fitness benefits they can bestow (Hamilton, 1964; Reiches et al., 2009) and detriments they can impose (Fox, 2012). Several possible pleiotropic features of AD deserve further research and have implications for understanding how selection has shaped the AD phenotype, particularly the balance of protective and pathological influences of Aβ, ApoE-ε4 (Finch and Martin, 2016; Glass and Arnold, 2016; Lee et al., 2005), and AD-associated neuroinflammation (Wick et al., 2003). Additionally, I propose the hypothesis that AD may be a mismatch disease and describe preliminary evidence supporting the possibility that AD risk factors, including insulin resistance, estrogenic neuroprotection, inflammation, and ApoE may have functioned differently in pre-modern human environments, such that age-matched AD risk may have been far lower for the vast majority of human history compared to today. If age-matched risk were lower in the past, disease onset would have been later in the lifespan closer to age at mortality, diminishing the fitness effect of disease. The possibility that AD is a "disease of civilization" would undermine the need for evolutionary explanations for persistence of the AD phenotype and the ε4 allele across human history.

Unravelling the evolutionary story behind AD could have implications for medical and public health research and practices, for instance, by helping distinguish between the body's functional, adaptive, protective responses to pathological insult *versus* dysfunctional disease processes in which intervention could benefit patients. By identifying features of our modern environments or lifestyles that enhance risk, we may be able to recognize new opportunities for public health intervention or explore new therapeutic targets.

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Conflicts of interest

None.

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