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## Alzheimer's disease and symbiotic microbiota: an evolutionary medicine perspective

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### Abstract

Microorganisms resident in our bodies participate in a variety of regulatory and pathogenic processes. Here, we describe how etiological pathways implicated in Alzheimer's disease (AD) may be regulated or disturbed by symbiotic microbial activity. Furthermore, the composition of symbiotic microbes has changed dramatically across human history alongside the rise of agriculturalism, industrialization, and globalization. We postulate that each of these lifestyle transitions engendered progressive depletion of microbial diversity and enhancement of virulence, thereby enhancing AD risk pathways. It is likely that the human life span extended into the eighth decade tens of thousands of years ago, yet little is known about premodern geriatric epidemiology. We propose that microbiota of the gut, oral cavity, nasal cavity, and brain may modulate AD pathogenesis, and that changes in the microbial composition of these body regions across history suggest escalation of AD risk. Dysbiosis may promote immunoregulatory dysfunction due to inadequate education of the immune system, chronic inflammation, and epithelial barrier permeability. Subsequently, proinflammatory agents—and occasionally microbes—may infiltrate the brain and promote AD pathogenic processes. *APOE* genotypes appear to moderate the effect of dysbiosis on AD risk. Elucidating the effect of symbiotic microbiota on AD pathogenesis could contribute to basic and translational research.

### Keywords

Alzheimer's disease; dementia; microbiome; evolutionary medicine; immunoregulation

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Competing interests

The authors declare no competing interests.

## Introduction

Chronic inflammatory diseases are increasingly recognized as attributable (at least partially) to immunodysregulation resulting from inadequate or adverse exposure to microorganisms.<sup>1</sup> In order to appreciate the complex etiology of these diseases, it is necessary to consider the critical role of symbiotic microorganisms in healthy development and function of the human immune system. In addition, understanding how microbiota affect risk and etiology of a specific disease can help us trace human vulnerability to that disease across the evolutionary history of our changing symbiotic microbiota.

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that involves both peripheral and central immunodysregulation.<sup>2</sup> Chronic inflammation and impairment of immunoregulatory function precedes cognitive decline by decades,<sup>3</sup> suggesting that immunodysregulation may be an early hallmark of AD progression.

Given the association of immunodysregulation and AD pathogenesis, evaluation of a possible relationship between AD and symbiotic microbiota should be investigated. We previously described global epidemiological patterns suggestive of a negative correlation between environmental microbial diversity and age-adjusted AD rates;<sup>4</sup> and another group conducted a pilot study suggesting that AD patients, compared with healthy controls, had lower intestinal microbial diversity.<sup>5</sup> The relationship between AD and symbiotic microbiota has, otherwise, not been explored, and the evolutionary origins of AD are essentially unknown.<sup>6</sup>

We focus on the sporadic form of AD, which afflicts individuals most often from age 65 onward. Anthropological evidence suggests that the human life span likely increased into the eighth decade tens of thousands of years ago.<sup>7</sup> Although life expectancy at birth is, today, markedly increased compared to earlier epochs of history, this metric is heavily influenced by early life mortality rates (e.g., during infancy and childhood). Evidence suggests that adult-specific life expectancy (i.e., expected years of life for those who already survived to adulthood) has exhibited only a small shift in the recent era,<sup>8</sup> although a more dramatic change occurred for a minority of the global population (~15% of nations).<sup>9</sup> Long life span is a hallmark feature of the human species, and natural selection may have favored this trait because of human reliance on intelligence and functional competence during later life phases (further discussion of this issue is beyond the scope of our review here).<sup>10</sup> Yet, almost nothing is known about when AD emerged alongside the history of humans living into old age.

We adopt an evolutionary medicine approach to advance an argument that recent changes in human microbiota have enhanced AD risk. Evolutionary medicine is a multidisciplinary academic area that applies the concepts of evolutionary biology to the study of human health and disease.<sup>11</sup> This approach highlights human coevolution with symbiotic microorganisms and how recent changes in human environment and lifestyle—such as agriculture or industrialization—have altered the composition of symbiotic microbiota.<sup>12</sup> These alterations—which include severe reduction or loss of certain microorganisms, adoption of new pathogenic microorganisms, alterations in relative abundances, and overall reduction of

microbial diversity—are implicated in chronic inflammatory disease etiology.<sup>13</sup> Human<sup>14</sup> and murine<sup>15</sup> studies have shown that low microbial diversity is associated with disease states. Indeed, the major changes in the human microbiome likely occurred alongside the major epidemiological transitions in human history.<sup>16</sup>

We briefly review how the microbiome changed across history of major lifestyle transitions, and then review how residential microorganisms of the human gut, oral cavity, nasal cavity, and brain may influence AD pathogenesis. Specifically, we review epidemiological evidence linking the composition of microbes in each body region to AD risk and etiology, the mechanisms by which this influence may occur, and how changes in the composition of microbes in each body region across human history may have enhanced AD risk. We use the term “microbiota” to describe symbiotic microorganisms, and “microbiome” to refer to their genetic composition. We focus on bacteria because they account for the majority of symbionts in the human body, though we acknowledge that other microbes—viruses, fungi, and archaea—may also play a role.<sup>17</sup> We limit our discussion to microbiota of the gut, oral, and nasal cavities, and pathogenic microbial infiltration of the brain, while acknowledging that other body regions host microbes that could potentially be involved in modulating AD risk.

## Microbial transitions in human history

The human species has experienced at least three major lifestyle shifts over the last 15 thousand (k) years consisting of changes in demography, environments, subsistence, and epidemiology—which, we surmise, coincidentally enhanced AD rates. The shifts were gradual, and different regions of the world experienced these shifts at different rates.<sup>18</sup> We highlight below how each transition involved exogenous (e.g., demographic, environmental, dietary, and sanitation) changes that led to endogenous alterations to the composition of microbial communities (Fig. 1). We then speculate that each of these changes in microbial composition likely led to increased risk of immune dysregulation and chronic inflammation (and in some cases, increased risk of microbial translocation to the brain), and thereby progressively to enhanced risk of AD immunopathology. We use the term “industrialized” to refer to any population that experienced an industrial transition, inclusive of what economists may refer to as “postindustrial.”

### Agricultural revolution

The advent of agriculture, initially in the Fertile Crescent ~12k years ago (ya) and subsequently spreading to most parts of the world by ~4k ya,<sup>19</sup> increased the geographic stability of human habitats, leading to increased population size and density. Pathogenic virulence likely increased due to the evolutionarily selective opportunity of larger numbers of potential human hosts living in closer proximity.<sup>20</sup> As for microbial diversity, theoretically, increase to host population density could impose any number of changes upon host microbiota.<sup>21</sup> However, experimental<sup>22</sup> and correlational<sup>23</sup> evidence suggests that increasing symbiont–host encounters when host microbial diversity is low results in greater pathogen transmission between hosts. And the reduced likelihood of dead-end hosts can lead to increased microbial uniformity across hosts.<sup>21</sup>

With the introduction of agriculture, dietary, social, and demographic changes altered the composition of the human microbiome.<sup>24</sup> People living in stable camps planted crops and raised animals, which increased human interaction with fecal mud (both humans and animals).<sup>18</sup> Diet diversity decreased and there was a marked increase in grain consumption.<sup>20</sup> There was likely an increase in Helminth colonization and orofecal transmission of bacteria, which would have brought novel pathogens into the symbiotic communities of the human body.<sup>18</sup>

### Industrial revolution

The advent of factories and industry further increased the geographic stability of human habitats, giving rise to large, concrete cities with higher population sizes and densities. Initially occurring in 1760s Great Britain and rapidly expanding thereafter, much of the world was industrialized by 1830.<sup>25</sup> By living in cities, people experienced less contact with animals and fecal-contaminated mud than before.<sup>26</sup> Pathogens likely benefitted from even more advantageous opportunity to infect human hosts due to shared indoor environments and higher population density, and were thereby likely selected to become even more virulent.<sup>20</sup> Air pollution became increasingly prevalent as industrial manufacturing and motorized transportation proliferated.<sup>27</sup> Given contemporary evidence that indoor, outdoor,<sup>28</sup> and dust storm air<sup>29</sup> can contain significant microbial load, it is plausible that industrial pollution altered the composition of airborne microbiota.

Additionally, technological advances in transportation led to greater volume and distance of population movement, and the resulting greater human mobility also transported microbes to new habitats. For example, *Vibrio cholerae* was confined to the Indian subcontinent until the 19th century, when intercontinental railroad systems and steamships transported humans harboring it, resulting in cholera pandemics in four continents.<sup>30</sup>

Agriculture became dominated by single-crop yields,<sup>31</sup> which may have further reduced intestinal biodiversity. Food started to be industrially washed and cooked in more sterile environments.<sup>26</sup> Eventually, the industrial era brought about indoor plumbing and sewage systems and, beginning in 1945, use of antibiotic medications for humans and livestock that would eventually become widespread.<sup>32</sup> Because of these changes in food processing, antibacterial products, and plumbing infrastructure, we speculate that the diversity of the human microbiota decreased.

### Globalization era

The past ~50 years have seen exponential acceleration of certain changes that began with industrialization, as well as other novel changes.<sup>33</sup> Population density and mobility that began in the era of industrialization dramatically increased. As of 2008 and for the first time in history, the majority of the human population resides in urban rather than rural habitats.<sup>34</sup>

The composition of air pollution changed, owing to a substantial reduction of coal smoke of the industrial era, for example, in London levels went from 400 mg/m<sup>3</sup> in 1922 to <10 µg/m<sup>3</sup> today.<sup>35</sup> Air pollution today is mostly derived from vehicle emission of airborne particulate matter from combustion of hydrocarbon fuel.<sup>36</sup> In addition, commercial passenger aviation

became globally available in the 1970s,<sup>37</sup> leading to a surge in global mobility that continues today, for example, between 2000 and 2017 saw a 49% increase in international migration.<sup>38</sup>

Sedentism due to ever-increasing reliance on machinery and technology,<sup>39</sup> and diets primarily composed of high-fat, high-sugar, processed foods<sup>40</sup> promote exponentially increasing rates of obesity and metabolic disease.

From the 1960s to the 1980s, there was a steady increase in the discovery and development of antibiotic classes,<sup>41</sup> with concomitant, prolific use of antibiotic therapies in humans and animals.<sup>32</sup> Overuse of antibiotics imposes evolutionary selection for antibiotic resistance<sup>42</sup> and pathogenic virulence.<sup>43</sup> An expanding catalogue of highly virulent, multidrug-resistant bacteria now causes diseases across the globe, for example, in Europe there are ~400,000 new multidrug-resistant bacterial infections annually.<sup>44</sup>

Major changes have occurred in perinatal practices, including increases in caesarean (C) section deliveries<sup>45</sup> and declines in rates of breastfeeding.<sup>46</sup> C-sections and formula feeding can contribute to dysbiosis during critical phases of development.<sup>47</sup>

Next, we describe how these changes may successively contribute to immunodysregulation and other features of AD pathogenesis, potentially enhancing AD risk across human history.

## Gut microbiota

Loss of biodiversity in the human gastrointestinal tract may contribute to AD incidence. The gut hosts the largest microbe reservoir in the body, providing the main source of immune education through sampling of antigens of anaerobic bacteria (99% of the gut microbiome), fungi, protozoa, and archaea.<sup>48</sup> Additionally, the gut participates in maintenance of brain homeostasis by producing neurotransmitters, metabolites, and nerve signals that are transmitted along the gut–brain axis.<sup>49</sup> Insufficient microbial diversity in the gut can lead to decreased immune efficacy, increased peripheral inflammation, and increased barrier permeability, all of which may perturb brain homeostasis and ultimately contribute to AD pathogenesis (Fig. 2). Lifestyle transitions across human history may be responsible for the depletion of gut microbial diversity that could have enhanced AD risk via this pathway.

### Epidemiological patterns linking gut microbiota to AD

Gut dysbiosis—a high number of pathogenic species or a pathological lack of species diversity in the gut—has been associated with aging, metabolic inflammatory diseases (MIDs), and disorders of the brain, including neurodegenerative disorders. These conditions have overlapping etiologies with AD, and the ways in which gut dysbiosis affects risk (via inflammation and gut epithelial permeability) may also apply to AD.

Aging is the primary AD risk factor. Changes in the gut microbiome across the major lifestyle transitions of human history parallel the age-related changes in the gut microbiome across an individual's adult life span, such as diminished microbial diversity.<sup>50</sup> Geriatric aging is often associated with lower microbial diversity, degradation of gut mucosal barriers,<sup>51</sup> and reduced repositories of naive T cells.<sup>52</sup> Gut microbial composition is relatively stable over time within an individual.<sup>53</sup> However, there is wider interindividual

variation among geriatric individuals' gut microbiomes than among those of younger individuals;<sup>14</sup> some geriatric individuals may therefore have more resilience than others to dysbiosis-related immunodysregulation. Additionally, geriatric individuals exhibit lower Bacteroidetes:Firmicutes (B:F) ratios compared with the guts of younger individuals,<sup>14</sup> suggesting age-related changes that mirror the difference between contemporary hunter-gatherer (high B:F ratio) and contemporary industrialized populations (low B:F ratio).

Evidence that the gut microbiome can affect MIDs and that MIDs can induce neuronal damage highlights a possible mechanistic pathway linking gut dysbiosis and AD. MIDs, such as obesity,<sup>54</sup> hypertension,<sup>55</sup> and type-2 diabetes mellitus (T2DM),<sup>56</sup> are each independent risk factors for AD. Distinct gut microbiome alterations are associated with MIDs, and the consequent high levels of circulating lipids, glucose imbalance, inflammation, and amplified oxidative stress can lead to neuronal damage.<sup>57</sup> AD pathogenesis may exhibit a similar pathological cascade to MIDs, with peripheral inflammation leading to blood-brain barrier (BBB) permeability, neuroinflammation, brain insulin resistance, activated microglia, and neuronal damage.

Obesity may be—at least sometimes or partially—promoted by a dysbiotic gut, which may in turn promote peripheral inflammation, neuroinflammation, and neuronal damage.<sup>58</sup> Obesity in human studies has been associated with gut dysbiosis.<sup>59</sup> In mice, an obesity phenotype can be transferred through transplant of gut microbiota,<sup>60</sup> suggesting gut dysbiosis as a causal factor. Additionally, in obese humans, adipose tissue releases proinflammatory cytokines, adipokines, and chemokines.<sup>61</sup> These can contribute to peripheral and central inflammation,<sup>62</sup> damage to the hypothalamus,<sup>63</sup> decline in white matter integrity,<sup>64</sup> and microglial activation.<sup>58</sup>

T2DM is also an established risk factor for AD,<sup>65</sup> a link that may be partially attributable to gut dysbiosis. Lower abundance of butyrate-producing bacteria has been associated with higher T2DM risk in murine and human studies.<sup>66</sup> Butyrate and other bacterially produced short-chain fatty acids (SCFAs) may affect host metabolism through modifying ATP<sup>67</sup> and glucose<sup>68</sup> production. SCFAs may also affect host inflammation by modifying intestinal epithelium integrity<sup>69</sup> and differentiation of regulatory T cells (T<sub>reg</sub> cells).<sup>70</sup> These alterations to peripheral metabolism and inflammation may not only affect T2DM risk, but also ultimately may affect central metabolism and inflammation, which are systems whose disturbance is associated with AD.

AD involves neurological dysfunction and can be compared to other psychiatric syndromes that also involve atypical brain circuitry.<sup>71</sup> Evidence that gut microbiota can affect the brain in other psychiatric disorders bolsters the theory that gut microbiota could potentially affect AD risk and etiology. Evidence indicates that there are distinct human microbiome profiles for major depressive disorder (MDD),<sup>72</sup> autism spectrum disorders (ASDs),<sup>73</sup> and schizophrenia.<sup>74</sup> Gastrointestinal symptoms are also more prevalent and severe in children with ASD, compared with control children.<sup>75</sup> Schizophrenic individuals, compared with controls, have more inflammation and gastrointestinal dysfunction, including bacterial translocation from gut to bloodstream;<sup>76</sup> Severance *et al.* posit that this may lead to



overactivated inflammatory responses along the gut–brain axis that lead to psychological changes.

Rodent studies suggest that manipulations of the gut microbiome, such as administering pathogenic bacteria, antibiotics, or germ-free (GF) rearing, can lead to alterations in anxiety-like behaviors.<sup>77</sup> Social avoidance behavior in adult mice, used as a model of human anxiety or autism, has been associated with a specific gut microbial profile<sup>78</sup> and can be induced by implanting those microbes in the gut.<sup>79</sup> Other studies induced depression-like behavior in rodents by fecal transplant from human MDD patients.<sup>72,80</sup> Another study observed schizophrenia-like behavior in mice after fecal transplantation from human schizophrenia patients.<sup>81</sup>

Evidence is emerging that individuals with neurodegenerative diseases have distinct gut microbial profiles. In one study, fecal samples of 25 AD patients contained less microbial richness and diversity compared with 25 control (non-AD) patients.<sup>5</sup> Others found the depletion of gut microbes in transgenic mice influenced cerebral  $\beta$ -amyloid deposition, a feature of AD.<sup>82,83</sup> Parkinson's disease (PD) patients have distinctive fecal microbial profiles compared with healthy peers.<sup>84</sup> Others have found that when  $\alpha$ -synuclein-enriched Lewy bodies (protein aggregates implicated in PD) were injected into the intestinal wall of adult wild-type rats, Lewy bodies were subsequently found in brain tissue.<sup>85</sup> These recent studies are among the first to establish patterns between gut dysbiosis and neurodegenerative diseases.

### Changes in gut microbiota across human evolutionary history

The major lifestyle transitions in human history were likely each associated with progressively less intestinal biodiversity, which, we argue, can exacerbate AD risk. These historical transitions likely altered gut microbiota through changes in human exposure to animals and soil, food production activities, and diet.

It has been suggested that before the Agricultural Revolution, human gut microbiota comprised a greater variety of species with different relative abundances compared to today. After the Agricultural Revolution, with diets composed of a smaller variety of domesticated species, human gut microbiomes likely exhibited lower diversity<sup>86</sup> and relative abundances that reflect grain-dominant diets.<sup>87</sup> The transition to agriculturalism also brought an increase in fermentation practices, for example, fermented milks beginning ~10k ya and alcoholic fermentation of barley and grapes beginning ~5k years ago.<sup>88</sup> Fermentation converts sugars in an anoxic environment to other products, removing toxic compounds and supplying probiotic bacteria.<sup>89</sup>

Dietary changes related to the Industrial Revolution likely had significant effects on taxonomic composition and metabolic features of human gut microbiota.<sup>90</sup> Postindustrial diets are associated with higher abundance of pathobionts in the gut, which tend to survive on sugar better than other symbiotic species, which survive best on high-fiber diets.<sup>91</sup> This transition also marks a distinct decrease in the consumption of fermented foods, likely due to the introduction of refrigeration and shelf-stable processed foods, likely associated with decrease in microbial diversity.



The decrease of dietary and agricultural diversity in the Globalization Era<sup>92</sup> likely correlates with lower-than-ever gut biodiversity. The United Nations' Food and Agricultural Organization described a 75% loss of agricultural biodiversity since the 1900s, with the majority of food today produced by only 12 plant and 5 animal species.<sup>93</sup> Gut biodiversity may also be diminished by extensive use of antibiotics in human medicine, antibiotics in domesticated animals, and pharmaceutical-grade pesticides on plants.

Evidence for these historical shifts comes from analyses comparing the gut microbial compositions of contemporary people who practice hunting–gathering subsistence strategies in nonindustrialized communities (Fig. 1). Studies found U.S. individuals' gut microbiomes have 15–30% fewer species than contemporary hunter–gatherer individuals' gut microbiomes.<sup>94–96</sup> Furthermore, while there is enormous overlap in composition of symbiotic microbes between different industrialized populations, contemporary hunter–gatherer gut microbial compositions were independent both of each other and of the microbiome compositions from industrialized populations.<sup>97</sup> The observation that human gut microbial composition is similar across industrialized populations is consistent with the possibility that symbiotic microbial uniformity could partially account for epidemiological similarity across otherwise disparate world regions. Additionally, the guts of dogs parallel human gut diversity because of domestication;<sup>98</sup> indeed, the guts of modern dogs of industrialized populations also show dysbiosis and higher incidence of inflammatory bowel disease.<sup>99</sup>

We contend that there exists a causal pathway from low gut microbial diversity to enhanced AD risk, and that this pathway contributes to the pattern of increasing AD prevalence in today's industrialized, globalized world.

### Biomechanisms potentially linking gut microbiota to AD

Gut microbiota can influence brain function and health in various ways that could be relevant for AD, including producing neuroactive metabolites and amyloids, and promoting systemic inflammation, barrier permeability, and microglial activation. The gut hosts critical immunodevelopmental process by mucosal dendritic cell exposure to microbes, which prompts T<sub>reg</sub> cell population expansion, thereby establishing tolerance to symbiotic microbiota.<sup>48</sup> T<sub>reg</sub> cell maturation may be specifically induced by particular bacterial products (e.g., SCFAs) as well as certain chloroform-resistant, spore-forming bacteria (e.g., *Bacilli*, *Clostridia*, and Firmicutes).<sup>100</sup>

**Neuroactive metabolites.**—Gut microbes produce neuroactive molecules and neurotransmitters whose dysfunctions have, elsewhere, been linked to AD.<sup>101</sup> For example, gut *Bifidobacterium* and *Lactobacillus* produce the neurotransmitter gamma-aminobutyric acid (GABA)<sup>102</sup> and may regulate brain GABA-receptor expression by communication along the vagus nerve.<sup>103</sup> GABA dysfunction is implicated in AD neuropathy.<sup>104</sup> Also, gut microbes may regulate the serotonergic system directly by producing serotonin (*in vitro* evidence, e.g., *Lactobacillus plantarum*, *Escherichia coli* K-12) or by producing (e.g., *E. coli*) or degrading (e.g., *Bacteroides fragilis*) serotonin's precursor molecule, tryptophan.<sup>105</sup> Gut-derived serotonin likely has only indirect effects on brain serotonergic

function. However, the gut is the only source of tryptophan, derived either from the diet or microbial production.<sup>105</sup> Tryptophan crosses the BBB to become available for serotonin synthesis in the brain.<sup>106</sup> Dysfunction of peripheral<sup>107</sup> and central<sup>108</sup> serotonergic systems has been implicated in AD pathophysiology. Additionally, an *N*-methyl-D-aspartate (NMDA)-targeting neurotoxin that was observed to be elevated in the brains of patients with AD<sup>109</sup> may be produced by gut cyanobacteria.<sup>110</sup>

**Amyloids.**—Amyloidosis, or the accumulation of amyloid proteins causing damage to the body, is implicated in AD by virtue of the hallmark feature of A $\beta$  accumulation. Amyloid formation is also a widespread, naturally occurring feature of many bacterial clades, including members of Proteobacteria, Bacteroidetes, Chloroflexi, Actinobacteria, and Firmicutes, which utilize amyloids in biofilm development and surface adhesion.<sup>111</sup> Further research is needed to clarify whether bacterial amyloids affect host amyloidosis pathogenesis.<sup>111</sup>

**Systemic inflammation.**—Gut dysbiosis may induce chronic, systemic inflammation, a condition implicated in AD immunopathogenesis. Typical development of the mammalian immune system requires education by colonizing microbiota in a mutualistic exchange that involves microbes residing within the rich environment of the host's body, particularly the gut, performing various functions necessary for host survivorship (e.g., nutrient extraction). This careful balance is mediated by the mucus membrane, which minimizes contact between host tissues and microbiota.<sup>48</sup> This balance allows the gut to respond appropriately when exposed to pathogenic or mutualistic microbiota.<sup>48</sup> When the intestinal ecosystem is out of balance, pathological problems may arise. A dysbiotic gut inadequately educates host T cells, causing exaggerated inflammatory responses and, potentially, chronic inflammation.<sup>112</sup> While short-term inflammatory response restores biological equilibrium (e.g., fighting acute infection), chronic inflammation can damage host cells and tissues, causing excessive epithelial permeability. Chronic inflammatory conditions hold open endothelial junctions, which would otherwise only briefly open during acute inflammatory response, to permit inflammatory mediators and immune cells to cross endothelial barriers freely.

**Barrier permeability.**—Gut dysbiosis may compromise barrier integrity, which may promote AD pathogenesis by allowing translocation of pathogenic agents out of the gut and into the brain. One study demonstrated that butyrate-producing bacteria enhance intestinal epithelial barrier integrity and their absence can contribute to barrier dysfunction.<sup>113</sup> Others found more *Helicobacter pylori* in the sera and gut mucosa of AD patients compared with controls.<sup>114</sup> The BBB has been shown to exhibit increased permeability in GF mice compared with pathogen-free conventionally colonized (CC) mice. Transferring microbiota of CC mice to GF mice led to decreased permeability and higher expression of tight junction proteins.<sup>115</sup> Pathogen-associated molecular patterns of some microbiota can promote BBB permeability by activating T helper cells to produce type-1 cytokines.<sup>116</sup> Barrier permeability can lead to tissue inflammation and bacterial translocation.<sup>117</sup>

**Microglial activation.**—Gut microbiota have also been shown to influence microglia. Altered microglial function is implicated in AD pathogenesis.<sup>118</sup> One study demonstrated that GF mice (compared with CC mice) expressed global defects of microglia (immature phenotype) causing impaired immune responses.<sup>119</sup> Mice with lower microbial diversity had dysfunctional microglia, and recolonization was restorative to microglia. Mice with sufficient SCFA-producing microbes had homeostatic microglia, while mice deficient in SCFA had defective microglia more similar to GF mice.<sup>119</sup>

## Oral cavity

We propose that composition of oral microbiota may be associated with AD via oral infection, leading to microbial translocation to the brain either through the bloodstream or by bypassing the bloodstream via breach of oral mucosal barriers (Fig. 2). Shifts in the composition of oral microbiota over human history may have enhanced AD risk via this pathway. Evidence for this link comes from associations between periodontal disease (PDD) and tooth loss with AD, as well as evidence that oral bacteria are disproportionately prevalent in the trigeminal nerves and brains of AD patients.

## Epidemiological patterns linking oral microbiota to AD

Epidemiological evidence suggests that tooth loss may be associated with AD incidence. In a Japanese study, individuals with fewer than half of their teeth by age 50–60 were 2.6 times more likely to later develop AD.<sup>120</sup> Similarly, in a Swedish study examining monozygotic twin-pairs discordant for AD, having lost half or more of their teeth by age 35 was strongly associated with AD (odds ratio (OR) = 5.5).<sup>121</sup> The authors of these studies speculated that poor oral hygiene and concomitant PDD were the causes of tooth loss, although this was not directly observed. In a longitudinal study of Wisconsin nuns without AD at initial recruitment (ages 75–98), those with fewer teeth (<10) went on to develop AD over the 12-year study period with 2.2 times the risk of peers with more teeth (10+) at the start of the study.<sup>122</sup> The temporal order of events in this longitudinal study is consistent with the possibility of causality. A recent study suggests causality in a rodent model: oral infections of *Porphyromonas gingivalis* in mice led to brain colonization and subsequent brain A $\beta$  production.<sup>123</sup> A small-molecule inhibitor targeting *P. gingivalis* toxic proteases (gingipains) blocked A $\beta$  production, reduced neuroinflammation, rescued neurons in the hippocampus, and reduced bacterial load.<sup>123</sup> Altogether, evidence is consistent with the hypothesis that PDD-associated tooth loss contributes to AD risk; further research is needed to establish causality in humans.

## Changes in oral microbiota across human evolutionary history

We posit that dietary changes across human history may have enhanced AD risk through changes in microbial composition of the oral cavity. Supportive evidence is beginning to emerge that major lifestyle transitions led to increases in PDD and PDD-associated oral microbiota, and that both have been correlated with AD risk. PDD is considered by archaeologists to be relatively new in human history, emerging around the time of the Agricultural Revolution and then escalating during the Industrial Revolution. Oral pathologies—including tooth decay and PDD—are rare in archaeological assemblages

from early hunter–gatherer populations.<sup>124</sup> Principal component analysis of microbial beta-diversity comparing the dental calculus of 6 hunter–gatherer European skeletons from the Mesolithic (7550–5450 ya, pre-Agricultural Revolution) and 22 agriculturalist European skeletons from the late Neolithic and Medieval periods (750–400 ya, post-Agricultural Revolution) shows a distinct shift in the composition of oral microbiota.<sup>124</sup> Skeletal evidence from other studies suggests a simultaneous increase in PDD incidence.<sup>125</sup> This could be due to the decrease in diet diversity during the Agricultural Revolution, relative to the subsistence strategy of hunting–gathering.<sup>20</sup> The aforementioned microbial DNA extracted from dental calculus in individuals from agricultural communities in the late Neolithic and Medieval periods shows the presence of PDD-associated microbes, including *P. gingivalis* and *Tannerella*, which are absent from the Mesolithic hunter–gatherers.<sup>124</sup> Additionally, the dental calculus of individuals from the Neolithic and Medieval farming communities, compared with the Mesolithic hunter–gatherers, had higher concentrations of *Treponema*,<sup>124</sup> which has also been associated with PDD and found at a greater frequency in postmortem brains from AD patients, compared with healthy controls.<sup>126</sup> Later, the Industrial Revolution brought an influx of processed and refined sugars to the human diet, which have been implicated in enamel demineralization, subsequent dental caries, and eventual tooth loss, which have been associated with AD risk.<sup>120,122</sup>

### Biomechanisms potentially linking oral microbiota to AD

Oral microbiota may influence AD pathogenesis either indirectly by promoting oral barrier permeability that permits oral microbes or inflammatory mediators to enter the bloodstream, or directly by microbial translocation from oral cavity to brain. Evidence that oral microbes are observed disproportionately in the brains of AD patients supports the plausibility of oral microbial translocation as a contributor to AD pathogenesis.

Oral microbes promote PDD, which can damage oral mucosal barriers allowing microbes to enter the bloodstream.<sup>127</sup> Observed associations between oral microbial composition and AD may be attributable to damage from trauma, microabrasion, or PDD-caused breaches in mucosal and vascular barriers.<sup>128</sup> In PDD, plaque in the area between the gums and tooth is filled with Gram-negative bacteria.<sup>129</sup> Damaged barriers in the oral cavity allow for bacteria to enter the bloodstream (transient bacteremia), thereby provoking a proinflammatory response, including cytokines, that may enter the central nervous system (CNS).<sup>130</sup> Both PDD<sup>127</sup> and AD<sup>131</sup> are characterized by type 1 inflammation; type 1-associated cytokines in circulation can traverse the BBB and cause microglial activation, which in AD patients promotes the production of A $\beta$ , tau, cerebrovascular pathology, and neuron death.<sup>132</sup>

The maxillary and mandibular branches of the trigeminal nerve connect the oral cavity directly to the brain. Studies suggest that microbes may translocate from the oral cavity to the brain directly via the trigeminal nerve, with evidence in AD patients of the PDD-associated bacteria *Treponema* in the saliva,<sup>126</sup> tooth pulp chambers,<sup>133</sup> trigeminal ganglia, pons, and, finally, brain structures afflicted in AD.<sup>134</sup> Specifically, in postmortem specimens from AD and control subjects, *Treponema* was detected in the trigeminal ganglia, with more *Treponema* species in AD compared with control specimens.<sup>126</sup> *Treponema* has been detected in the pons (site where trigeminal ganglia enter brain) as well as in the

hippocampus and the frontal lobe cortex at significantly greater concentration and higher number of *Treponema* species among AD than control brains.<sup>126</sup> Six PDD-associated *Treponema* species have been associated with increased prevalence in AD brains.<sup>135</sup>

## Nasal cavity and respiratory tract

We propose the possibility that air pollution (including microbial) may influence AD risk and shifts in air quality/composition over human history may have increased AD risk. Particulate matter (PM<sub>10</sub>) in urban environments—but not, for example, natural dust storms—contains high concentrations of Gram-negative bacterial lipopolysaccharides (LPSs),<sup>136</sup> suggestive of an industrialization-specific AD risk factor. The olfactory bulb is the part of the brain most exposed to the outside environment. Therefore, this area is particularly vulnerable as a route by which microbes from external environments may affect brain health.<sup>137</sup> Additionally, the olfactory bulb is one of the first and hardest hit areas in AD pathogenesis, and olfaction deficit has been implicated in early AD pathology.<sup>138</sup> It is plausible that the composition of microbiota in the nasal cavity and respiratory tract could be altered by air pollution in such a way that pathogenic microbes penetrate the olfactory bulb or take other routes to the brain, ultimately inducing AD pathogenic insult (Fig. 2).

## Epidemiological patterns linking nasal and respiratory tract microbiota to AD

**Air pollution.**—Epidemiological evidence links exposure to air pollution to AD incidence and brain insults. In a cross sectional, case-control study in Taiwan, exposure to high concentrations of PM<sub>10</sub> and ozone (O<sub>3</sub>) was positively associated with having AD.<sup>139</sup> Jung *et al.* corroborate these findings in another Taiwanese population in a 9-year longitudinal study by showing that for every 4.34 µg/m<sup>3</sup> increase in fine particulate matter (PM<sub>2.5</sub>) in the local environment, individuals aged 65+ exhibited a 138% increased risk of developing AD, and for every 10.91 parts per billion (ppb) increase in O<sub>3</sub>, a 211% increased risk.<sup>140</sup> A retrospective study among a Canadian cohort aged 55–85 showed higher risk of AD onset for those living <50 miles from a major road, compared with individuals living further away (hazard ratio (HR) = 1.07).<sup>141</sup> Longitudinal studies of traffic-related air pollution showed that more long-term exposure to nitrogen oxides was associated with greater risk of AD onset in a Swedish cohort (HR = 1.38),<sup>142</sup> and long-term exposure to black carbon was associated with greater risk of having a low mini mental state exam (MMSE) score in a U.S. cohort (OR = 1.30).<sup>143</sup>

Autopsy studies have demonstrated AD-associated features in the brains of children and young adults in industrial zones of Mexico City—where there are among the highest concentrations in North America of PM<sub>10</sub>, especially PM<sub>2.5</sub>, and O<sub>3</sub>—compared with matched samples from low-air-pollution Mexican cities.<sup>144</sup> Mexico City specimens exhibited more Aβ in olfactory ensheathing cells (OECs), more degradation and particulate contamination of nasal and olfactory bulb epithelia<sup>145</sup> and BBB,<sup>146</sup> as well as greater frontal lobe extracellular Aβ and hyperphosphorylated tau, as well as frontal lobe upregulated gene expression of pattern recognition receptors that respond to microbial contact and genes indicative of neuroinflammation and oxidative stress.<sup>144</sup>

**Olfactory impairment.**—We posit that microbial agents in the nasal cavity may contribute to AD neuropathy in the olfactory bulb, which in turn may explain olfactory impairment in AD. Impaired olfaction (and eventually total loss of the sense of smell, i.e., anosmia) is often an early clinical sign of AD.<sup>147,148</sup> AD patients, compared with age-matched controls, exhibit impairment in olfactory detection and identification.<sup>149,150</sup> Longitudinal studies of elderly adults without dementia found that olfactory impairment was associated with greater risk of developing mild cognitive impairment (MCI)<sup>151</sup> and AD<sup>152</sup> over the study periods. A longitudinal study of MCI individuals found that olfactory impairment was associated with greater risk of developing AD.<sup>153</sup> Another longitudinal study found that anosmic individuals had 1.9 times higher odds of developing AD compared with normosmic individuals.<sup>154</sup>

Degree of olfactory impairment among AD patients appears to be correlated with degree of AD neuropathy. Olfactory impairment among AD patients has been correlated with hippocampal volume reduction,<sup>155,156</sup> neurofibrillary tangle density in the central olfactory system (entorhinal cortex, CA1-subiculum;<sup>157</sup> also among MCI patients<sup>151</sup>), blood oxygenation level-dependent signal reduction in the primary olfactory cortex,<sup>158</sup> and interruptions in the olfactory processing network.<sup>159</sup> Another study found that A $\beta$  load was higher among MCI participants who performed poorly on olfactory identification tests compared with healthy controls, but no differences in olfaction between MCI subgroups by A $\beta$  load.<sup>160</sup>

Olfactory impairment is strongly associated with air pollution, and the relationship may be *APOE*-genotype conditional.<sup>145</sup> The observed correlations between air pollution, anosmia, damage to the olfactory system, AD neuropathy, and AD incidence justify further investigation of the role of nasal cavity microbes in enacting these relationships.

### **Changes in nasal and respiratory tract microbiota across human evolutionary history**

Several observations suggest a relationship between air pollution and changes in nasal and respiratory tract microbial composition. Bacterial or viral infection of the respiratory tract is inherently reflective of alteration to the microbial communities in the respiratory tract. By 1900, the leading cause of death in the United States was pneumonia.<sup>161</sup> Bacterial pneumonia has been linked to nitrogen dioxide and PM<sub>2.5</sub> exposure.<sup>162</sup> Air pollution is also strongly associated with viral infection of the respiratory tract. Longitudinal studies observed dose-dependent relationships between air pollution and croup (typically caused by viral infection) in Germany<sup>163</sup> and between air pollution and acute respiratory infection in Kenya<sup>164</sup> and Finland.<sup>165</sup> Today, microbial infection of the respiratory tract is the singular leading cause of global burden of disease,<sup>166</sup> underscoring that the industrialization-related increases in air pollution cause disease primarily through a microbial mechanism. Further research is needed to discern how microbial composition of air pollution affects nasal cavity microbial composition and subsequent health problems.

The Industrial Revolution saw the emergence of manufacturing and motorized transportation, and resultant increase in air pollution.<sup>167</sup> For example, sulfur dioxide emissions were negligible before the Industrial Revolution, rose globally across the 19th and 20th centuries,<sup>168</sup> and since 1980 have continued to rise in Asia and Africa but have



fallen in Europe, South America, and North America.<sup>167</sup> We propose that the degree to which air pollution enhances AD risk has mirrored these large-scale patterns, which are consistent with Globalization Era surges in AD rates in developing countries.<sup>169</sup>

### Biomechanisms potentially linking nasal and respiratory tract microbiota to AD

The observed associations between air pollution, nasal and respiratory infection, anosmia, and AD risk may be operating through two routes: first, nasal microbes transmitted along olfactory receptor neurons, and second, respiratory tract microbes transmitted to the brain via lung capillary blood infiltration.

Olfactory mucosa—containing axons directly exposed to the external environment—provides a direct route from the olfactory system to the CNS. Agents, such as bacteria, viruses, prions, nanoparticles, and heavy metals, can damage the olfactory endothelium,<sup>170</sup> thereby entering the brain via the olfactory mucosa.<sup>171</sup> Air pollution may promote microbial infiltration of the brain either indirectly by residential nasal microbes that take advantage of inorganic-pollution-associated damage to nasal epithelia,<sup>172</sup> or directly by airborne microbes that cross from nasal cavity to CNS with microbial barrier breach not relying on barrier damage by inorganic compounds.

Located on the bottom of the brain and separated from the oral cavity by the cribriform plate and olfactory epithelium, the olfactory bulb is particularly vulnerable to exogenous agents. The outer two layers of the olfactory bulb contain OECs. These specialized glial cells ensheath bundles of non-myelinated olfactory nerve axons.<sup>173</sup> OECs provide a channel for olfactory nerve axons to grow from the peripheral nervous system to the CNS by guiding axonal growth of olfactory receptor neurons in olfactory mucosa through the cribriform plate to the olfactory bulb.<sup>174</sup> Microbes that have penetrated the olfactory epithelium may be transported along the olfactory or trigeminal nerves to the brain.<sup>137</sup> Pathogenic microbes, particularly *Chlamydomphila pneumoniae*, from air pollution can infect the nasal cavity and thereby contribute to AD risk or pathogenesis. *C. pneumoniae* is one (but not the only) cause of pneumonia and up to 20% of all lower respiratory tract infections.<sup>175</sup> Pneumonia is the most common cause of death in patients with AD,<sup>176</sup> but evidence suggests that *C. pneumoniae* infection may participate in AD etiology long after pneumonia symptoms resolve.<sup>177</sup> Chronic *C. pneumoniae* infection may gain entry to the CNS by two routes, either of which may contribute to AD neuropathy. The bacteria may migrate directly from the nasal cavity to infiltrate the brain—indeed, an autopsy study of AD patients found *C. pneumoniae* in the olfactory bulb epithelium<sup>178</sup>—or *C. pneumoniae* may infiltrate lung capillary monocytes that then cross the BBB.<sup>179</sup>

*C. pneumoniae* has been observed in the CNS of AD patients more frequently than in non-AD individuals and at CNS locations specifically implicated in AD, suggestive of a role in AD neuropathogenesis. In one study, individuals with AD exhibited *C. pneumoniae* in their cerebrospinal fluid (CSF) more frequently (44% of AD group) than individuals with vascular dementia (10%) or nondementia controls (1%).<sup>180</sup> A postmortem study found *C. pneumoniae* in AD-affected brain regions among 89% of AD patients and 5% of nondementia controls, unrelated to whether the individuals had pneumonia at the time of death.<sup>181</sup> In the brains of AD patients, *C. pneumoniae* has been found in 20% of neurons,



as well as in astrocytes and microglia.<sup>182</sup> Astrocytes and microglia react to pathogenic bacteria by producing proinflammatory cytokines and reactive oxygen species (ROS), both associated with AD.<sup>182</sup>

Herpes simplex virus type 1 (HSV1) may gain access to the brain via the olfactory system, its presence in the brain has been associated with *APOE*-genotype conditional AD risk, and *in vitro* studies suggest that HSV1 can cause A $\beta$  deposition and tau phosphorylation.<sup>183</sup> HSV1 was shown to migrate from nasal mucosa to the CNS via the olfactory nerve in mice,<sup>184</sup> and postmortem study of humans who died of herpes simplex encephalitis detected HSV1 antigen in the olfactory tract, olfactory cortex, and olfactory-connected regions of the limbic system.<sup>185</sup> There is evidence supporting the possibility that other microbes may also migrate from the nasal mucosa directly to the CNS bypassing the bloodstream, but the relation of these microbes to AD remains understudied, including viruses such as influenza A, Nipah virus, Sendai virus, equine encephalitis virus, rabies virus, and vesicular stomatitis virus,<sup>137</sup> and bacteria such as *Neisseria meningitides* (which accomplishes this migration by damaging cellular junctions in the olfactory epithelium),<sup>186</sup> *Burkholderia pseudomallei*<sup>187</sup> (which can colonize the nasal cavity via inhalation of airborne bacteria),<sup>137</sup> and *Streptococcus pneumoniae*.<sup>188</sup> Given that *S. pneumoniae* is the most common cause of bacterial pneumonia—which is highly comorbid with AD—evidence that nasal *S. pneumoniae* could directly access the CNS should, in particular, be further investigated in the context of AD.

## Brain

The brain connects peripheral dysbiosis to the neurodegenerative processes that characterize AD. Unlike the symbiotic microbiota of other body regions, bacteria in the brain are almost always pathological. Therefore, in this section, we do not focus on epidemiological patterns and lifestyle transitions in human history, but rather directly on how microbial effects in the gut, oral, and nasal cavities coalesce to affect the brain in ways that could influence AD risk or pathogenesis (Fig. 2).

## Neuroinflammation

Neuroinflammation may be induced by either peripheral inflammation or microbial translocation in concert with BBB permeability. Systemic inflammation has been shown to increase BBB permeability.<sup>189</sup> BBB permeability can expose the brain to cytokines that can lead to neuroinflammation. Extensive exposure to proinflammatory cytokines can impair microglia, decreasing microglia's ability to clear toxic A $\beta$ , reducing the synaptic remodeling capacity of microglia, leading to irreversible neuronal damage.<sup>190</sup> Neuroinflammation is an early feature of AD pathogenesis, preceding A $\beta$  accumulation.<sup>191</sup>

## Reactive oxygen species

The cellular metabolism by-products ROS are involved in redox homeostasis, but excessively high levels of ROS cause oxidative stress, which is implicated in AD etiology. At moderate levels, ROS exhibits antimicrobial properties<sup>192</sup> and can be produced by host phagocytes in response to certain pathogenic microbes, such as *E. coli*.<sup>193</sup> In excess, ROS

can increase epithelial cell differentiation, proliferation, and apoptosis, which can lead to epithelial injury and inflammation.<sup>194</sup> Gut-mediated release of proinflammatory cytokines can also cause oxidative stress.<sup>195</sup> ROS may enter the brain via compromised BBB and thereby promote AD-associated processes through destruction of brain tissue,<sup>196</sup> increasing the accumulation of A $\beta$  and neurofibrillary tangles<sup>197</sup> and A $\beta$ -associated neuronal death.<sup>198</sup>

### Microbial translocation

AD patients exhibit greater abundances of pathogenic microbes, overall bacterial load, and LPS in their brains compared with control patients. In postmortem studies, AD patients had greater abundance of pathogenic microbes in their brains compared with non-AD controls, specifically *C. pneumoniae*,<sup>199</sup> HSV1,<sup>183</sup> and *Treponema*<sup>135</sup> (discussed above), as well as *Borrelia burgdorferi*, which a meta-analysis found was 13 times more frequent in the brains of AD patients than controls.<sup>135</sup>

AD brains exhibited relatively lower Proteobacteria levels and greater Actinobacteria levels compared with controls, mostly attributed to high levels of *Propionibacterium acnes*, a species of symbiotic bacteria on skin and in the oral cavity, which has elsewhere been associated with inflammatory disease.<sup>200</sup> Additionally, postmortem AD brains were shown to have 5- to 10-fold more bacterial reads than controls.<sup>200</sup>

Gram-negative bacterial LPS of the human gut are abundantly present in AD-implicated brain regions; specifically, neocortex (7-fold) and hippocampus (21-fold) compared with controls.<sup>201</sup> A growing body of evidence suggests that oral microbes can enter human brain tissue specifically in the context of AD. *P. gingivalis* DNA was observed in CSF and saliva of living people with probable AD.<sup>123</sup> Another study found LPS of *P. gingivalis* in the postmortem brain tissue of 40% of AD patients but absent among controls.<sup>202</sup>

When BBB permeability increases, more microbes can enter the brain. Microbes may cross the BBB transcellularly (*E. coli*, *S. pneumoniae*, *Mycobacterium tuberculosis*), paracellularly (protozoans, *Trypanosoma* sp.), or through infected phagocytes (*Listeria monocytogenes* and *M. tuberculosis*).<sup>203</sup>

### $\beta$ -Amyloid

A $\beta$  exhibits antimicrobial properties, and its production may be a feature of the innate immune response to microbes in the brain. We posit that microbial translocation from the periphery would increase A $\beta$  production in the brain.

While A $\beta$  may serve an adaptive, antimicrobial function, it may also exacerbate neuronal damage in the context of excessive barrier permeability and microbial translocation. It was first suggested by Soscia *et al.* that A $\beta$  may be an antimicrobial peptide; they demonstrated that A $\beta$  is active against at least 12 different microorganisms, including Gram-negative and Gram-positive bacteria and the yeast *Candida albicans*.<sup>204</sup> A $\beta$  production has also been shown in response to influenza A,<sup>205</sup> herpes simplex virus,<sup>206</sup> and pathogenic yeast.<sup>207</sup> Exposure of *B. burgdorferi* spirochetes to rat brain cell cultures induced A $\beta$  production.<sup>208</sup> Recent authors, expanding on this evidence (using transgenic *Caenorhabditis elegans* and

murine models), posited that A $\beta$  may be a host response to protect against microbial infections.<sup>204,207</sup>

## APOE

The APOE gene (*APOE*) and its encoded protein are well-known modifiers of AD risk. *APOE* allelic variation may play a moderating role in the relationship between dysbiosis and AD risk. APOE isoforms exhibit differential effects at several stages of this pathological cascade: A $\beta$ –microbe complex clearance from the brain, neuroinflammation, and oxidative damage. There are three alleles of *APOE* (*APOE4*,  $-3$ , and  $-2$ ), which each translates a unique protein isoform (APOE4, APOE3, and APOE2). *APOE4* is also associated with lower peripheral and central concentrations of the APOE protein<sup>209</sup> partially due to faster degradation.<sup>210</sup> *APOE4* is an established risk factor for sporadic AD.<sup>211</sup>

### Evolutionary history of APOE

Evidence suggests that the *APOE4* allelic variant associated with AD is the ancestral version of the gene. All other primates have only one allele nearly identical to *APOE4*.<sup>212–214</sup> *APOE3* was later formed from a single base mutation ~300 k ya, and another single base mutation formed *APOE2* ~200 k ya.<sup>212,215,216</sup> It seems unlikely that selection against AD was solely or primarily responsible for the emergence or spread of *APOE3* and *APOE2*. Not only is *APOE4* implicated in many different diseases (therefore hard to attribute selection to one over another), but also, nonindustrialized populations exhibit little connection between the *APOE4* allele and AD risk.<sup>217</sup> We argue that *APOE4* might exacerbate some of the deleterious effects of dysbiosis, but in the absence of widespread dysbiosis among premodern human populations, we might suppose that carrying an *APOE4* allele may not have independently conferred AD risk.<sup>217</sup>

### APOE and $\beta$ -amyloid–microbe complex clearance

Recalling the antimicrobial properties of A $\beta$ , it is reasonable to speculate that the ApoE4 isoform prevents A $\beta$  from clearing microbes from the brain more than other isoforms. This speculated higher microbial load in the brains of *APOE4* carriers could promote greater neuroinflammatory response. Low-density lipoprotein receptor (LDLR), the main lipoprotein receptor in the brain, mediates the cellular uptake of APOE and A $\beta$ <sup>218</sup> and therefore likely also A $\beta$ –microbe complexes. Studies have suggested that APOE and A $\beta$  are in competition for cellular uptake through LDLR.<sup>218</sup> Among APOE isoforms, LDLR possesses the highest affinity for the E4 allele (E4 > E3 >> E2).<sup>219</sup> The higher affinity between LDLR and APOE4 could, conceivably, clear APOE4 at the expense of greater A $\beta$ , and thereby A $\beta$ –microbe complex, retention.

This idea is consistent with observations that *APOE4* carriers exhibit reduced A $\beta$  clearance and greater microbial load in the brain. *APOE4*-expressing mice, compared with other genotypes, exhibited higher levels of A $\beta$  in interstitial fluid and slower rates of A $\beta$  clearance from interstitial fluid.<sup>211</sup> A study of postmortem brains of AD patients found those who carried *APOE4*, compared with noncarriers, were more likely to exhibit *C. pneumoniae* in AD-afflicted brain regions. The study also found *C. pneumoniae* in 90% of the brains of

*APOE4* carriers with AD, but only 5% of *APOE4* carriers without AD,<sup>181</sup> demonstrating an AD-specific effect. Another study by the same group found that among postmortem AD brains the number of *C. pneumoniae*-infected cells in AD-afflicted brain regions was higher for *APOE4* carriers than other genotypes.<sup>220</sup>

These studies together demonstrate that *APOE4* is associated with reduced A $\beta$  clearance and greater microbial load in the brain specifically in the context of AD, suggesting that AD etiology could, at least sometimes, involve microbial translocation to the brain. While A $\beta$  may typically facilitate microbial clearance from the brain, the *APOE4* isoform may be inefficient, compared with other isoforms, at clearing A $\beta$ -microbe complexes from the brain.

### APOE and neuroinflammation

APOE is generally an anti-inflammatory molecule. APOE inhibits proinflammatory cytokines, while proinflammatory cytokines downregulate and anti-inflammatory signals upregulate APOE production.<sup>221</sup> *APOE4* has the weakest anti-inflammatory properties. *APOE4* knock-in mice are more susceptible, compared to other genotypes, to LPS- or A $\beta$ -induced inflammation and inflammation-associated damage, such as in traumatic brain injury experiments.<sup>222</sup> *APOE4* is also more lipid depleted than other isoforms, which may result in less neuronal protection and repair.<sup>223</sup> *APOE4* is also associated with more AD-specific insult from viruses in the brain, potentially related to inferior capacity to regulate neuroinflammation and consequential neuronal damage. The presence of HSV1 in the brain was associated with AD risk only for *APOE4* carriers.<sup>183</sup>

*APOE4* may also exacerbate the effect of oronasal inflammation on AD neuropathy. *APOE4* carriers, compared with other genotypes, exhibited more AD-relevant brain pathology<sup>144</sup> and AD-associated olfactory dysfunction<sup>145</sup> in response to air pollution. Additionally, a longitudinal study found that *APOE4* carriers, compared with other genotypes, exhibited stronger relation between olfactory impairment and AD onset.<sup>154</sup>

### APOE and oxidative damage

APOE may also modulate AD risk through its antioxidant qualities,<sup>224</sup> with *APOE4* exhibiting the weakest protection. *APOE4* appears to be less effective against oxidative toxicity<sup>225</sup> and more associated with oxidative damage<sup>224</sup> than other isoforms. These effects could hold relevance for oxidative stress induced by microbial infection. For example, a study using murine cell culture found that *APOE4* cells, compared with *APOE3*, exhibited greater membrane oxidation and more nitric oxide production in response to *Salmonella enteritidis* LPS stimulation.<sup>226</sup> In a study using synaptosomes isolated from mouse brains, A $\beta$ -induced oxidation caused greater ROS formation among *APOE4* specimens compared to other genotypes.<sup>227</sup> Others found increased levels of F2-isoprostanes in brains of *APOE4* male mice but no genotype differences in female mice.<sup>228</sup> Greater ROS production may cause oxidative stress that can lead to a feedback loop of increased A $\beta$  accumulation, neurofibrillary tangles,<sup>197</sup> and neuronal damage.<sup>198</sup>

## Conclusion and future directions

Human experiences and exposures to disease risk factors have varied across the course of evolutionary history. As human lifestyles underwent major transitions including the Agricultural Revolution, Industrial Revolution, and globalization, it is likely that major alterations also occurred in the composition of our symbiotic microorganisms. While other diseases have received more attention for their relation to modernization like obesity,<sup>229</sup> T2DM,<sup>230</sup> and cardiovascular disease<sup>231</sup> because links to modernization may seem more obvious, AD should also be considered a disease enhanced by similar pathways during this era.<sup>6</sup>

Changes across human history to composition of microbial communities in the gut, oral cavity, nasal cavity, and brain may influence immune function and epithelial barrier permeability to modulate various aspects of the AD pathological cascade. The huge scale of changes in human habitats and experiences across history provides a natural experiment to elucidate whether certain disease risk factors or pathogenic processes that appear unavoidable in the globalized world today could be modifiable. As human environments continue to change, this information will aid in forecasting and preparing for disease burden in diverse future habitats.

Improvement in our understanding of the relationship between symbiotic microbes and AD has not only clinical relevance, but also may help us discern what the experiences of aging and the roles of elderly individuals may have been in premodern human society—an issue of interest and debate among anthropologists.<sup>6</sup>

The interdisciplinary perspective offered by the burgeoning field of evolutionary medicine encourages inquiry into the ultimate origins of diseases,<sup>11,20</sup> with potential to contribute to basic and translational research and public health.

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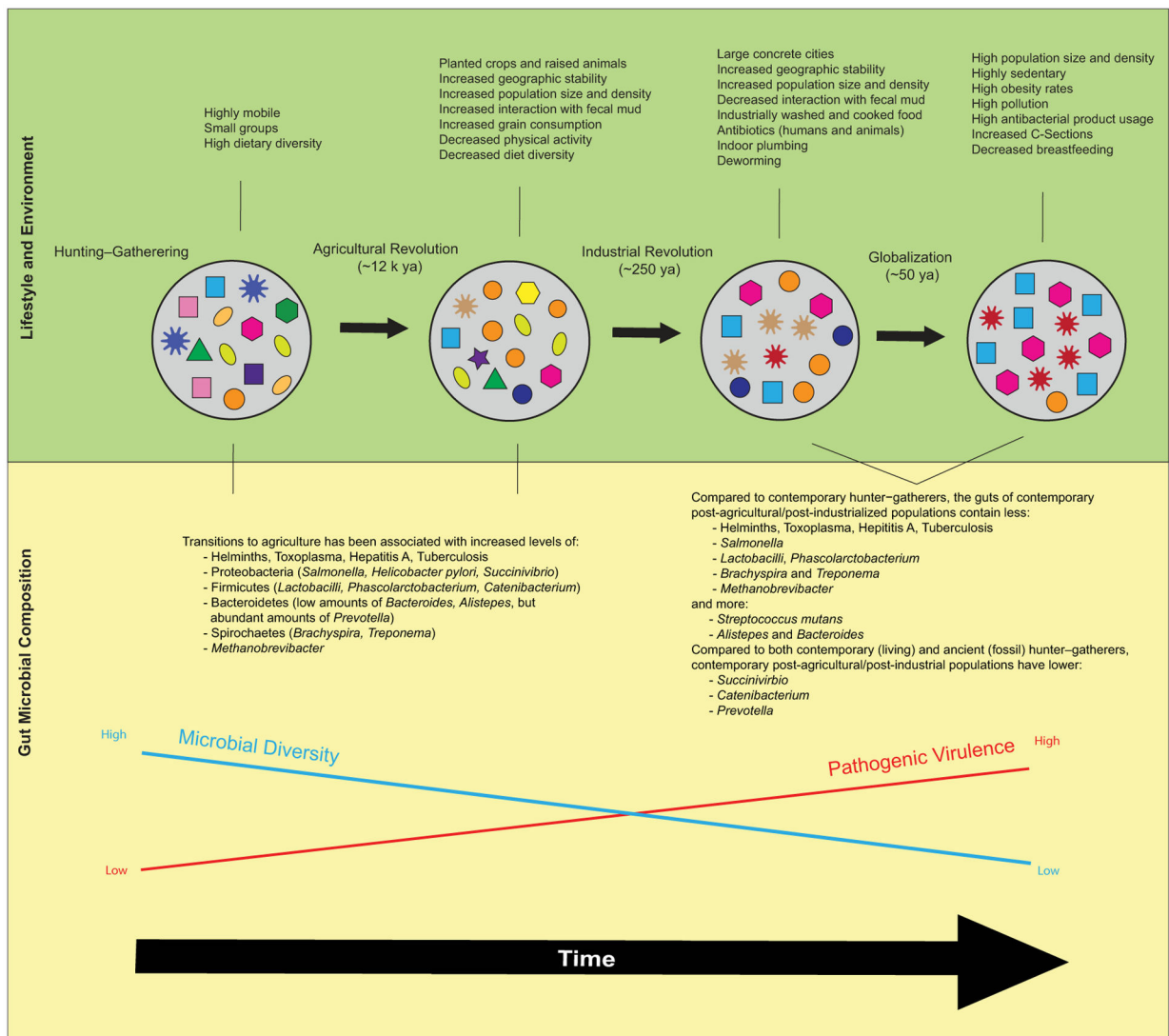
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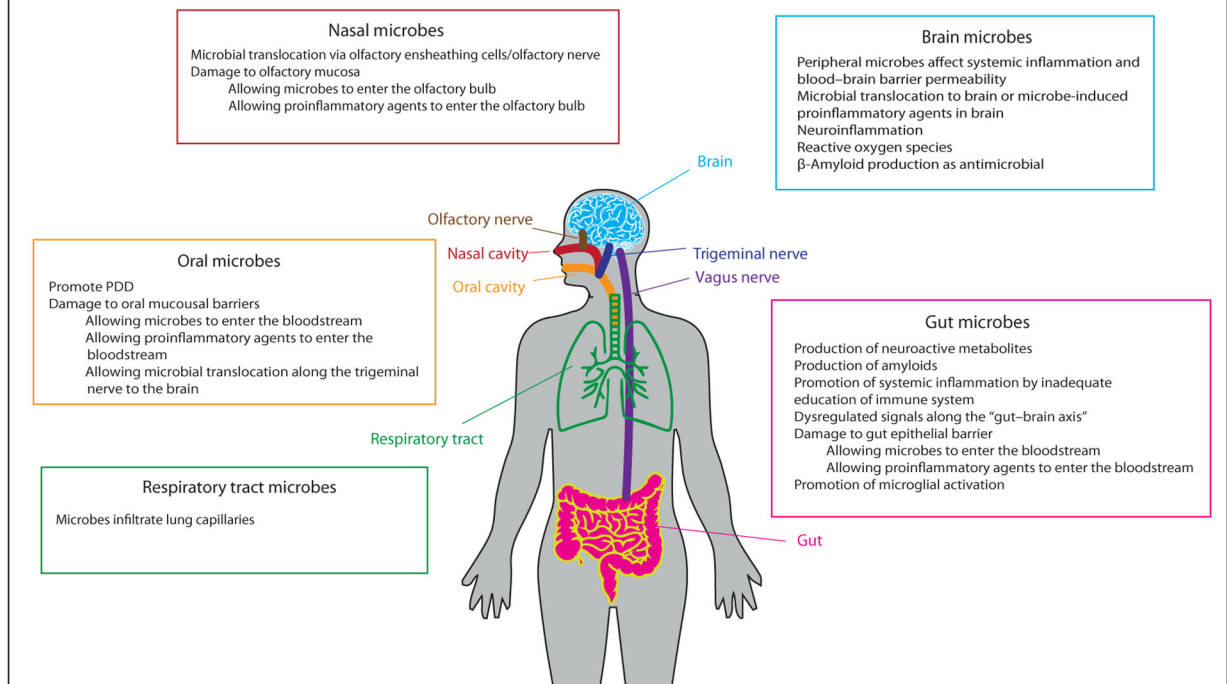
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**Figure 1.**

Over the past 15,000 years of human history, there have been a series of major lifestyle transitions that comprised changes in demography, environments, subsistence, and epidemiology. These transitions also likely brought about major changes in the composition of symbiotic microbiota, including generally reduced diversity and enhanced pathogenic virulence. Suppositions regarding pre-Agricultural Revolution gut flora are based on analyses comparing the gut microbial compositions of contemporary people who practice hunting–gathering subsistence strategies in nonindustrialized communities in Tanzania (Hadza), Peru (Matses),<sup>97</sup> Malawi, and Venezuela,<sup>232</sup> and fossil assemblages of Neanderthals (compilation from Spain, Croatia, Germany, and Russia), Denisovans (from Siberia<sup>233</sup>), and other early hominins (from Spain<sup>234</sup>) with those of contemporary industrialized populations in Europe, North America, Asia, and Oceania.<sup>97</sup> We note that contemporary hunter–gatherers offer an imperfect proxy for premodern gut microbiomes.<sup>235</sup>

## How might microbiota in various body regions affect Alzheimer's risk or etiology?



**Figure 2.** Biomechanisms by which symbiotic microbiota in various regions of the human body may affect Alzheimer's disease pathogenic processes.