

Featured Article

# The Alzheimer's Disease Exposome

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## Abstract

**Introduction:** Environmental factors are poorly understood in the etiology of Alzheimer's disease (AD) and related dementias. The importance of environmental factors in gene environment interactions (GxE) is suggested by wide individual differences in cognitive loss, even for carriers of AD-risk genetic variants.

**Results and Discussion:** We propose the “AD exposome” to comprehensively assess the modifiable environmental factors relevant to genetic underpinnings of cognitive aging and AD. Analysis of endogenous and exogenous environmental factors requires multi-generational consideration of these interactions over age and time (GxExT). New computational approaches to the multi-level complexities may identify accessible interventions for individual brain aging. International collaborations on diverse populations are needed to identify the most relevant exposures over the life course for GxE interactions.

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We propose the “Alzheimer's disease (AD) exposome” to address the major gaps in understanding environmental contributions to the genetic and nongenetic risk of AD and related dementias. Studies of Swedish twins [1] suggest that half of individual differences in AD risk may be environmental, with 45% heritability for women and 58% for men [1]. Gene-environment (GxE) interactions were recognized in early studies in mental health, for example, “psychiatric environments” [2] and the “envirome” [3] but were not a main agenda of AD researchers. While the heterogeneity of cognitive aging and dementia is mainly attributable to gene variants ([4]; [www.alzforum.org](http://www.alzforum.org)), little is known about their GxE interactions. What are the “smoking guns” of the AD exposome [5]?

The exposome was first conceptualized for cancer [6,7] as lifetime exposure to environmental carcinogens to

match the expanding genomics. The exposome concept is now mainstream and has superseded the characterization of environmental factors “one by one” [8]. Studies for GxE include the exposome-genome paradigm [9]; multigenerational GxE interactions of toxins and behavioral influences [10–12]; and the cancer exposome [13].

The AD exposome concept extends and leverages the National Institute on Aging–Alzheimer's Association Research Framework developed by a work group led by the two organizations [14]. This US-wide consortium longitudinally follows clinical cohorts by brain imaging for ATN biomarkers of amyloid aggregates (A) and pathologic tau (T) to assess neurodegeneration (N). The ADNI studies discuss potential mechanisms of cognitive degeneration and recognize the major importance of arterial degeneration to ATN from cardiovascular disease, cerebral infarcts, and blood-brain barrier leakage [4]. Another ADNI study showed how declining renal function contributes directly to the vascular burden and indirectly to brain amyloid load and hippocampal shrinkage [4,15].

A systems approach is needed to understand the multiple brain-body interactions during neurodegenerative aging.

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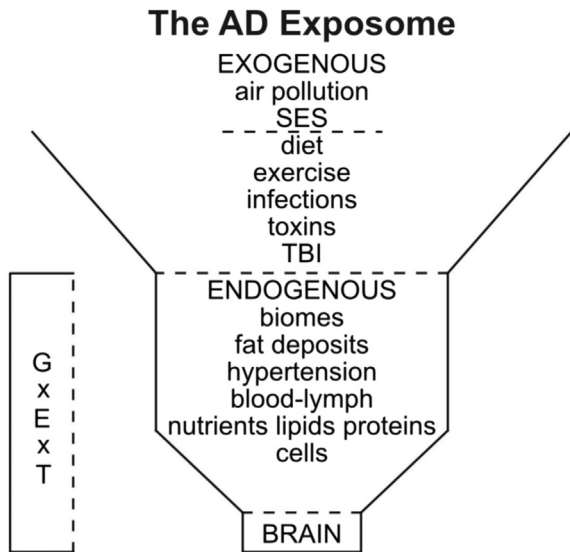


Fig. 1. Schema of the exposome for Alzheimer's disease and related dementias (AD exposome) with exogenous and endogenous components; see Table for details and references. Abbreviations: GxExT, Interactions of gene by environment over age and time; SES, socioeconomic status; TBI, traumatic brain injury.

Moreover, we must expand beyond clinical studies to diverse populations for lifestyles, socioeconomic status (SES), and gender differences [16]. The AD exposome extends the ADNI Framework to include GxE interactions across individual age and duration of exposure (GxExT), which may extend from prefertilization gametes into later life [17]. The AD exposome could benefit later brain health by optimizing GxE. The recent decreases in AD incidence and prevalence in the U.S. and other populations [18–20] anticipate further improvements in AD from health and behavioral management [21,22].

### 1. Three domains of the AD exposome

The AD exposome considers the three domains mentioned in the study by Wild [7]. The exogenous AD exposome includes macrolevel factors (rural vs. urban, pollutants, SES) in distinction to individual exogenous factors (diet, infections, and so forth) (Fig. 1, Table 1). The endogenous AD exposome includes individual biomes, fat depots, hormones, and traumatic brain injury (TBI). These domains are overlapping and interactive. We assume that systemic interactions mediate particular factors of the AD exposome by different inputs, for example, a “lung-brain axis” for inhaled neurotoxicants of air pollution and cigarette smoke, and a “renal-CVD-brain axis” for diet- and hypertension-driven renal aging. Each of these axes may have different GxE for each AD risk gene. Currently, apolipoprotein E (APOE) alleles provide most examples of GxE for cognitive outcomes.

Exogenous macrolevel GxE interactions for AD genes were first shown for the familial dominant presenilin 1

Table 1  
Domains of the AD exposome

Domain/exposures	[7]
Exogenous macrolevel	
Air pollution	[23,24,25,26]
Rural versus urban	[27,28]
Socioeconomic status (SES)	[16,29,30,31]
Exogenous individual	
Cigarette smoking	[32,33]
Diet	[34,35]
Exercise	[36,37]
Infections	[38–43]
Surgery and anesthesia	[44,45]
Endogenous individual	
Biome	
Gut	[42,46,47]
Periodontal gingiva	[41]
Blood	
Cells: mast cells, monocytes, T-lymphocytes	[48–50]
Glucose	[51]
Hypertension	[52,53]
Inflammatory factors	[54,55]
Lipids and other metabolites	[56]
Sex steroids	[57]
Fat deposits	[58–60,61]
Stress	[62]
Gender	[63,64,65,66]
Thyroid	[67]
Traumatic brain injury (TBI)	[68,69]

NOTE: These exposome domains are based on Chris Wild's pioneering concept [7]. The cited references are illustrative and cannot fairly represent the bodies of excellent work on many of these topics.

mutant (PSEN1 E28 A mutant) [27]. In this underappreciated example, the onset of dementia was accelerated a decade or more by urban versus rural residence and by low education levels (SES, exogenous domain). APOE  $\epsilon$ 4 accelerated dementia onset in PSEN1 carriers in this study; the sample may have been too small to evaluate interaction of both genes with environment (GxGxE). Elsewhere, APOE  $\epsilon$ 4 carriers with less education had more cognitive decline (Wisconsin Longitudinal Study) [70] and higher mortality (New Mexico Aging Process Study) [71]. Two other AD risk genes (MEF2C and SLC24A4) were associated with SES lifestyle factors such as alcohol, smoking, physical activity, or social support, among the 27 AD risk genes considered in the Taiwan BioBank [72].

The exogenous individual AD exposome includes diet and lifestyle (see Table 1 for an expanded list). Excess consumption of fat and sugars above energy requirements and sedentary lifestyles promote obesity, diabetes mellitus, hyperlipidemia, hypertension, and systemic inflammatory responses. Each of these are risk factors for AD and accelerated brain aging, as well as for cardiovascular diseases, discussed below. APOE alleles modify nutrient clearance and uptake: APOE  $\epsilon$ 4 carriers had greater postprandial lipedema after a fatty meal [73] and more brain uptake of docosahexaenoic acid [74].

Dietary intake of omega-3 fatty acids and physical activity may influence the AD impact of APOE4 [75]. Although

APOE  $\epsilon 4$  is associated with AD risk and accelerated neurodegeneration in many populations, some APOE  $\epsilon 4$  homozygotes retain cognitive health at extreme old ages [76]. The conditionality of APOE  $\epsilon 4$  shows GxG interactions with TOMM40 and other genes in the APOE gene cluster on chromosome 19q13.3 [77,78]. Sex chromosome genes also interact with APOE alleles, with time dependence (GxT): after age 75 years, APOE  $\epsilon 3/\epsilon 4$  women had 50% higher AD risk than  $\epsilon 3/\epsilon 4$  men at ages 65-75 years (meta-analysis) [63], while prospective data showed declining APOE  $\epsilon 4$  hazards for women at age 75 and 80 years for men [64]. Changes in the body mass index (BMI) during middle age differed by APOE alleles in a 37-year study of Swedish women [79]. APOE  $\epsilon 4$  interactions with age for BMI are independent of TOMM40 variants [80].

Exogenous-endogenous interactions are illustrated by blood amino acid metabolite responses to vehicular exhaust exposure [81] and adducts of albumin-Cys34 from maternal smoking [82,83]. Organ specificity is shown by detoxifying responses to inhaled or ingested toxins that differed between the lungs and brain [84]. GxE and GxGxE interactions are anticipated in pathway crosstalk between immune and neuroendocrine modules of 430 AD-related genes [85]. We do not know the specificity of these individual and macrolevel factors for AD pathogenesis as distinct from influences on general processes of aging.

## 2. TBI, air pollution, and cigarette smoke: risk factors enhanced by APOE $\epsilon 4$

TBI was the first recognized “environmental” risk factor for long-term cognitive impairments associated with APOE  $\epsilon 4$  in professional boxers [86]. Subsequent studies showed neurodegenerative and cognitive changes in up to 65% of moderate to severe TBI [68], with amyloid deposits [69] and Lewy body pathology [87]. The variable APOE  $\epsilon 4$  association with cognitive impairments from TBI [88] may involve GxG in the APOE gene cluster on chromosome 19 (as mentioned previously). We expect APOE alleles will influence cognitive declines from anesthesia [44] and microembolisms after aortic valve replacement [45].

Air pollution ozone was the first common airborne toxicant associated with dementia risk [89] and with accelerated cognitive decline [23]. In the Women’s Health Initiative Memory Study, women exposed to air pollution PM<sub>2.5</sub> above 12  $\mu\text{g}/\text{m}^3$ , the 2012 standard of the Environmental Protection Administration, had 2-fold higher risk of dementia, further compounded for APOE  $\epsilon 4/\epsilon 4$  homozygotes [24]. Cigarette smoke also has strong association with faster cortical amyloid deposition and higher AD risk [90] but has not shown significant APOE  $\epsilon 4$  associations [91]. The population attributable fraction of AD is more than 10% for both air pollution [24] and cigarette smoke [32], considered separately.

AD and cardiovascular disease share major risk factors of hypertension, obesity, and sedentary lifestyles, summarized

in “*Getting to the Heart of Alzheimer Disease*” [92]. Atheromas and senile plaques share many inflammatory proteins that are produced within each tissue [93,94]. Cardiovascular and cerebrovascular changes begin early in life. Even healthy children have low-grade arterial inflammatory foci with oxidized lipids that may be seeds of adult plaques [93,95,96]. During middle age, basilar and middle cerebral arteries accumulate lipids exponentially, while carotid lipid accumulation is more linear [95].

Blood-brain barrier disruption begins in healthy adults by age 40 and is accelerated in APOE  $\epsilon 4$  carriers [97,98]. These findings expand the role of ischemic changes in amyloid  $\beta$  (A $\beta$ ) accumulation [99] and show the importance of brain vascular imaging biomarkers [100]. The burden of vascular disease lowers the threshold for clinically overt dementia [101]. Moreover, atrial fibrillation is associated with cerebrovascular hypoperfusion and accelerated brain amyloid deposition [98]. Common variants of presenilins PSEN1 and PSEN2 are associated with cardiomyopathies [92]. Heart disease accelerated cognitive aging by 6 months in the Health and Retirement Study [21].

Cardiovascular ischemic risk is increased by both air pollution [102] and cigarette smoking [103]. These airborne toxins have superadditive synergies for cardiovascular mortality [104] and with at least one AD risk factor, obesity. Childhood BMI was greater for those living near a freeway and for those living with adult smokers; the combined exposures more than doubled their independent impact [105,106]. Cognitive decline also showed synergy of air pollution and cigarette smoking [107].

Environmental factors may explain AD-discordant twins which differed in DNA methylation of the whole genome [108] and in the APOE promoter [109]. Altered DNA methylation from gestational exposure to urban air pollution was associated with higher systolic blood pressure and carotid thickening in children, for particular DNA methylation genotypes [110]. At the next epigenetic level of chromatin proteins, seasonal rhythms of histone acetylation were disrupted in AD [111].

## 3. Mechanisms

Age remains the main risk factor in AD. The exponentially increasing incidence of AD after age 60 [112,113] is paralleled by exponential increases in mortality from many chronic diseases [114,115]. By age 40, in healthy middle age, cerebral cortex synapse density shows linear decreases [116] that are concurrent with increased astrocyte volume in the same brain set [117]. Aging rodents show reciprocal trends for synapse atrophy and astrocyte activation [118]. Brain imaging in ADNI cohorts shows regional differences for cerebral cortex gray matter atrophy that differ by amyloid load [119]. Air pollution [120] and cigarette smoke [121] are also associated with gray matter atrophy during aging in overlapping cortical subregions. Histological studies are needed to identify

cellular differences in neurons, glia, and vasculature that underlie these divergences.

Because astrocytes from aging mice have less neurotrophic activity [122], we hypothesize that astrocyte activation is a driver of synaptic atrophy. Aging rodents do not accumulate brain amyloid and lack ischemic vascular disease, which complicate interpretations of human brain aging. We hypothesize a role for metabolically dependent systemic inflammatory processes in brain aging processes, beginning in middle age [123]. Caloric restriction of mouse models attenuated astrocyte activation during aging [124] and brain amyloid deposition in AD transgenic mice [125]. The AD associations with blood leukocyte DNA methylation [126] and telomere length [127] also implicate system-level innate immunity.

Obesity, a risk factor for AD, itself contributes to systemic inflammation, based on two lines of evidence [128,129]. First, fat tissues secrete inflammatory factors directly into the blood. In patients with obesity, the venous blood effluent from visceral and subcutaneous fat depots is higher than from the arterial blood for several acute phase inflammatory proteins including IL-6 and C-reactive protein [58–60]. Second, macrophage cells accumulate around adipocytes during obesity [129]. Air pollution exposure is obesogenic in adults [130,131], consistent with increased children's BMI by air pollution and cigarette smoke [105], as mentioned previously. Systemic inflammatory responses to air pollution may contribute to fat depots, directly or indirectly.

Infections are increasingly implicated in AD and include exogenous and endogenous microbiomes and viromes. Post-mortem, most elderly brains harbor diverse species of viruses and bacteria [38]. A $\beta$  deposits can be nucleated by microbes and viruses from brain [39,40] and oral gingiva [41]. The human A $\beta$  peptide itself has extensive antimicrobial activities [40]. In mouse AD models, antibiotic perturbations of the gut biome accelerated deposition of A $\beta$  plaque [42]. AD-relevant infections are modulated by APOE alleles. Vulnerability to HIV and herpes simplex viruses HSV-1 and HSV-2 is increased by APOE4 [43]. In contrast, APOE  $\epsilon$ 4 is neuroprotective in populations with high infectious loads [132], shown for Brazilian slum children with diarrhea [133] and adult Amazonian Tsimane with parasitemia [134]. We anticipate GxExT interactions of past infections with other AD risk genes.

Xenobiotic detoxification pathways are also relevant to the AD exposome. The European Human Biomonitoring Initiative recognizes thousands of potential neurotoxicants in the environment [135]. Genomic detoxification pathways can be assayed in cell-based transcriptomic models for particular neurotoxicants alone or in combination in natural samples. For example, air pollution ultrafine particles (PM0.2) activate detoxification and inflammatory pathways in mouse brain and lung via the transcription factors NF $\kappa$ B and Nrf2 [136]. In vitro, cells with NF $\kappa$ B reporters respond

to PM0.2 [137], while adipocyte PPAR $\gamma$  and other transcription factors mediated responses to obesogenic xenobiotics [138]. Other mouse brain genomic responses to PM0.2 are shared with longevity genes in elderly cigarette survivors [139]: APOE, FOXO3, and mTOR [140].

The time depth of toxins may extend to prenatal influences from the grandmaternal uterus, when our maternal oocytes had formed [141]. Multigenerational epigenetic effects of lead in Detroit drinking water were related to grandmaternal lead exposure: the ensuing DNA methylation changes persisted in six genes of the grandchildren [142]. The role of epigenetics in environmental responses is consistent with evolutionary perspectives on the genetic architecture of age-related diseases [143,144].

#### 4. Further development of the AD exposome

Methodology for environment-wide association studies was developed by Health and Environment-wide Associations based on Large Population Surveys [135]. Sixty-four stressors were categorized for biological, chemical, physical, psychological, and socioenvironmental hazards (e.g., noise, water and food contamination, smoking, air pollution) assessed by 135 biomarkers of exposure measured in blood/serum/plasma, breast milk, urine, and hair. The Human Early-Life Exposome project [145] is assessing exposures with biomarkers following the study by Wild [7]: general external domains (e.g., climate, SES), individual external domains (e.g., smoking, diet, physical activity), and specific internal domains with omics biomarkers from early ages.

Next-generation sequencing and omics technologies are complimented by genomic information in single cells [146]. Recent single-cell transcriptomic analysis linked AD with transcriptionally distinct subpopulations across different major brain cell types [147]. Examining regulatory activity in a cell type and at single-cell levels extends tissue-specific gene expression approach. This may identify AD-specific neurodegenerative pathways involving populations of specific minor cell types, distinguished from the relatively benign aging processes that cause slow synapse atrophy.

An underused resource is environment-related data collected by service agencies and industry for the spatial-temporal distribution of environmental hazards, for example, animal feeding operations, coal-burning power plants, and pollen concentrations. Relationships to dementia risk can be assessed by sophisticated geographic information system technologies [148,149]. Fuzzy logic for geographic information system for quantification of exposure impact allows finer rankings of exposure factors than binary (yes/no) characterization [149].

Large data sets with longitudinally collected information are available. The UK Biobank, which anticipates 30,000 AD cases by 2027 [150], is complemented by the Healthy Cognitive Aging Project [151] (<https://www.nia.nih.gov/>)



[research/blog/2019/05/healthy-cognitive-aging-project-major-data-resource-cognitive-epidemiology](https://www.alzdiscovery.com/research/blog/2019/05/healthy-cognitive-aging-project-major-data-resource-cognitive-epidemiology)). This new longitudinal US-wide study will augment the long-standing Health and Retirement Study with the Harmonized Cognitive Assessment Protocol that is widely used to assess dementia. The sister studies of the Health and Retirement Study in Mexico, England, and China are using translated and adapted versions of the Harmonized Cognitive Assessment Protocol. The ADNI is expanding cases and controls for individual trajectories of pathological amyloid and tau, and regional atrophy. We suggest that ADNI consider air pollution PM2.5 and ozone as part of the individual profile; this requires special effort to identify previous residential locations. The cumulative impact of environmental and endogenous chemicals can be assessed by blood adductome measured from dried blood spots [152].

Machine-learning methods are applicable to genetic and nongenetic factors and should improve accuracies of regression models (e.g., LASSO) [153] and classification of variables (e.g., random forest [154]). Generalization of machine-learning techniques is statistically and computationally demanding for high-order interactions involving multiple factors [155] and requires larger cohorts. Large-scale initiatives such as UK Biobank (<http://www.ukbiobank.ac.uk/>) and ALLofUS (<https://allofus.nih.gov/>) are generating megacohorts. These massive data will improve current methods and enable new methods to examine high-order interactions of multiple factors in the GxExT framework, such as factorial design [156]. In megasamples, data harmonization may be less critical because sample size mitigates heterogeneity.

Polygenic scores are increasingly used to evaluate combined effects of multiple variants (up to millions) on AD risk [157]. These effects can be additive [158,159] or represent nonadditive interactions between alleles (GxG). Polygenic scores can examine interactions between aggregate effect of alleles at different molecular “omics” levels. This approach essentially averages effects of alleles that may obscure critical stages of vulnerability and other GxE effects across the lifespan. Another approach is to personalize polygenic profiles via complex haplotypes, as the APOE gene cluster on chromosome 19.q3 suggests [77].

Temporal component in the AD Exposome and genome interactions is a challenging problem even when the respective data are available [17]. One approach is to average the effects of exposures over time, enabling widely used techniques, for example, mediation analyses, Mendelian randomization. Another approach is explicit modeling of temporal variations. “Joint models” and other approaches to time-varying risk outcomes can be used to analyze temporal components with missing observations and irregular schedules of data collection [160]. Multidimensionality can be reduced by aggregating exposures and genetic factors into cumulative measures. For

example, diet, infections, pollutants, and toxins can be aggregated by accounting for deviations from “normative” exposures. The aggregation approach was effective in developing frailty/deficit indices for cumulative characteristics of health [161,162] and for deviations from norm for indices of physiological dysregulation [163]. Stochastic process models, a subclass of joint models [164], can evaluate dynamic component in the AD risk together with age-related metaprocesses, such as allostasis [29] and homeostasis [165,166].

## 5. Challenges and limitations

The ambitious National Institutes of Health goal to treat or prevent AD by 2025 [167] requires a comprehensive assessment of individual GxExT that has eluded conventional reductionist approaches. Identifying molecular architecture for the AD exposome is challenging in three domains: (i) the expanding complexity of cell and physiological networks; (ii) the rapidly pending huge expansion of omics information; (iii) the expanding omics modifications that are environmentally modifiable. We anticipate a plethora of new variants from genomics, epigenomics, and other omics. Relating this large-scale diversity to individualized risk trajectories driven by GxExT requires large-scale initiatives and rigorous methods.

## 6. Recommendations

The AD Exposome proposes to address contributions to AD from multiple genetic and nongenetic factors across the full life history in diverse populations for multigenerational cohorts where possible. To develop an AD roadmap of modifiable factors in brain aging and dementia, we suggest four research targets for funding agencies and policymakers for large-scale, multinational collaborative initiatives.

- (1) Integrate environmental data from service agencies and industry with existing data. Expand exposure data to air pollution, cigarette smoke, and household toxins using personal monitors for multiple toxic chemicals and gases.
- (2) Expand studies of other age-related disorders and aging to include cognitive aging and dementia. Multigenerational cohorts with extensive genetic/omics and phenotypic information are available for the Framingham Heart Study and the Long-Life Family Study.
- (3) Identify multiple exposures alone or as GxExT with synergistic potential to reduce risk of AD.
- (4) Brain cell aging processes must be included in animal models of AD.

Finally, to offset discouragement from the failed AD drug interventions [16], we suggest funding agencies and

policymakers promote better public understanding of modifiable risk factors in AD shared with cardiovascular health.

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# Did you know?

The screenshot shows the homepage of the journal *Alzheimer's & Dementia*. At the top, there is a search bar with a dropdown menu set to 'This Periodical' and a search button. Below the search bar, there are navigation links for 'Advanced Search', 'MEDLINE', 'My Recent Searches', 'My Saved Searches', and 'Search Tips'. The main content area features the 'Current Issue' for November 2009, Vol. 5, No. 6, which is noted as 'Now Included on MEDLINE'. A 'Featured Articles' section lists several research papers, including one on cognitive performance in African Americans and another on cerebral blood flow in ischemic vascular dementia. On the left side, there is a sidebar with navigation links such as 'JOURNAL HOME', 'CURRENT ISSUE', 'BROWSE ALL ISSUES', 'ARTICLES IN PRESS', 'SEARCH THIS JOURNAL', 'JOURNAL INFORMATION', 'SUBSCRIBE TO JOURNAL', and 'ALZHEIMER'S ASSOCIATION'. At the bottom of the sidebar, there is a 'STAAART' logo and a 'JOIN' button. The footer of the page states: 'Alzheimer's & Dementia: The Journal of the Alzheimer's Association is published by Elsevier for the Alzheimer's Association.'

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