HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2020 September 10.

Published in final edited form as:

Alzheimers Dement. 2019 September ; 15(9): 1123–1132. doi:10.1016/j.jalz.2019.06.3914.

The AD Exposome

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Abstract

Environmental factors are poorly understood in the etiology of Alzheimer's Disease and related dementias (AD). 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. 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.

Keywords

Alzheimer's disease; environment; exposome; GxE; toxins; infections

We propose the 'AD Exposome' to address major gaps in understanding environmental contributions to the genetic and non-genetic risk of AD and related dementias. Studies of Swedish twins 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, e.g. 'psychiatric enviromics' [2] and the 'envirome' [3], but were not a main agenda of Alzheimer researchers. While the heterogeneity of cognitive aging and dementia is mainly attributable to gene variants ([4]; www.alzforum.org), little is known about their GxE interactions.

The exposome was first conceptualized for cancer [5, 6], 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 The exposome concept is now mainstream and has superseded the characterization of environmental factors "one by one"

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[7]. Studies for GxE include the Exposome-Genome-paradigm [8]; multi-generational GxE interactions of toxins and behavioral influences [9–11]; and the Cancer Exposome [12].

The AD Exposome concept extends and leverages the NIA-AA Research Framework developed by the Alzheimer Disease Neuroimaging Network (ADNI) [13]. This US-wide consortium longitudinally follows clinical cohorts by brain imaging for amyloid aggregates and pathologic tau to assess neurodegeneration (ATN). 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, 14].

A systems approach is needed to understand the multiple brain-body interactions during neurodegenerative aging. Moreover, we must expand beyond clinical studies to diverse populations for lifestyles, socio-economic status (SES), and gender differences [15]. The AD Exposome extends the ADNI Framework to include GxE across individual age and duration of exposure (GxExT), which may extend from pre-fertilization gametes into later life [16]. The AD exposome could benefit later brain health by optimizing GxE. The recent decreases of AD incidence and prevalence in the U.S. and other populations [17–19] anticipates further improvements in AD from health and behavioral management [20, 21].

Three domains of the AD Exposome

The AD Exposome considers three domains of Wild [6]. The *Exogenous AD-Exposome* includes *macrolevel* factors (rural vs urban, pollutants, SES) in distinction to *individual* exogenous factors (diet, infections, etc.) (Figure 1, Table 1). The *Endogenous AD-Exposome* includes individual biomes, fat depots, hormones, 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, e.g. 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 axis may have different GxE for each AD-risk gene. Currently, 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 mutant (PSEN1 *E28A* mutant) [22]. In this under-appreciated example, the onset of dementia was accelerated a decade or more by urban vs rural residence, and by low education levels (SES, Exogenous Domain). ApoE4 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, ApoE4 carriers with less education had more cognitive decline (Wisconsin Longitudinal Study) [23] and higher mortality (New Mexico Aging Process Study) [24]. Two other AD-risk genes (MEF2C and SLC24A4), were associated with SES-life-style factors of alcohol, smoking, physical activity, or social support, among 27 AD-risk genes considered in the Taiwan BioBank [25].

The *Exogenous individual AD-Exposome* includes diet and life-style; see Table for an expanded list. Excess consumption of fat and sugars above energy requirements and sedentary lifestyles promotes 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 disease (see below). ApoE alleles modify nutrient clearance and uptake: ApoE4 carriers had greater postprandial lipedema after a fatty meal [26] and more brain uptake of docosahexanoic acid (DHA) [27].

Dietary intake of omega-3 fatty acids and physical activity may influence the AD impact of ApoE4 [28]. While ApoE4 is associated with AD risk and accelerated neurodegeneration in many populations, some ApoE4 homozygotes retain cognitive health at extreme old ages [29]. The conditionality of ApoE4 shows GxG interactions with TOMM40 and other genes in the ApoE gene cluster on Chromosome 19q13.3 [30, 31]. Sex chromosome genes also interact with ApoE alleles, with time dependence (GxT): after age 75, ApoE3/E4 women had 50% higher AD risk than E3/E4 men at ages 65-75 years old (meta-analysis) [32], while prospective data showed declining ApoE4 hazards for women at age 75 and 80 for men [33]. Changes in the Body Mass Index (BMI) during middle age differed by ApoE alleles in a 37 year study of Swedish women [34]. ApoE4 interactions with age for BMI are independent of TOMM40 variants [35].

Exogenous-endogenous interactions are illustrated by blood amino acid metabolite responses to vehicular exhaust exposure [36] and adducts of albumin-Cys34 from maternal smoking [37, 38]. Organ-specificity is shown by detoxifying responses to inhaled or ingested toxins that differed between lung and brain [39]. GxE and GxGxE interactions are anticipated in pathway crosstalk between immune and neuroendocrine modules of 430 AD-related genes [40]. We do not know the specificity of these individual and macrolevel factors for AD pathogenesis as distinct from influences on general processes of aging.

TBI, Air Pollution, and Cigarette Smoke: Risk Factors enhanced by ApoE4

TBI was the first recognized ‘environmental’ risk factor for long-term cognitive impairments associated with ApoE4 in professional boxers [41]. Subsequent studies showed neurodegenerative and cognitive changes in up to 65% of moderate to severe TBI [42], with amyloid deposits [43] and Lewy body pathology [44]. The variable ApoE4 association with cognitive impairments from TBI [45] may involve GxG in the ApoE gene cluster on Chromosome 19 (see above). We expect ApoE alleles will influence cognitive declines from anesthesia [46] and microembolisms after aortic valve replacement [47].

Air pollution ozone was the first common airborne toxicant associated with dementia risk [48] and with accelerated cognitive decline [49]. In the Women’s Health Initiative Memory Study (WHIMS), women exposed to air pollution PM2.5 above EPA standards had 2-fold higher risk of dementia, further compounded for ApoE4/E4 homozygotes [50]. Cigarette smoke has strong association with faster cortical amyloid deposition and higher AD risk [51], but has not shown significant ApoE4 associations [52]. The population attributable fraction (PAF) of AD is more than 10% for both air pollution [50] and cigarette smoke [53], separately considered.

AD and cardiovascular disease share major risk factors of hypertension, obesity, and sedentary lifestyle, summarized in "*Getting to the Heart of Alzheimer Disease*" [54]. Atheromas and senile plaques share many inflammatory proteins that are produced within each tissue [55, 56]. 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 [55, 57, 58]. During middle-age, basilar and middle cerebral arteries accumulate lipids exponentially, while carotid lipid accumulation is more linear [57].

Blood-brain barrier disruption begins in healthy adults by age 40 and is accelerated in ApoE4 carriers [59, 60]. These findings expand the role of ischemic changes in Aβ accumulation [61] and show the importance of brain vascular imaging biomarkers [62]. The burden of vascular disease lowers the threshold for clinically overt dementia [63]. Moreover, atrial fibrillation is associated with cerebrovascular hypoperfusion and accelerated brain amyloid deposition [60]. Common variants of presenilins PSEN1 and PSEN2 are associated with cardiomyopathies [54]. Heart disease accelerated cognitive aging by 6 months in the Health and Retirement Study [20].

Cardiovascular ischemic risk is increased by both air pollution [64] and cigarette smoking [65]. These airborne toxins have super-additive synergies for cardiovascular mortality [66] 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 [67, 68]. Cognitive decline also showed synergy of air pollution and cigarette smoking [69].

Environmental factors may explain AD-discordant twins which differed in DNA methylation of the whole genome [70] and in the ApoE promoter [71]. Altered DNA methylation from gestational exposure to urban air pollution was associated in children with higher systolic blood pressure and carotid thickening, for particular DNA methylation genotypes [72]. At the next epigenetic level of chromatin proteins, seasonal rhythms of histone acetylation were disrupted in AD [73].

Mechanisms

Age remains the main risk factor in AD. The exponentially increasing incidence of AD after age 60 [74, 75] is paralleled by exponential increases in mortality from many chronic diseases [76, 77]. By age 40 in healthy middle-age, cerebral cortex synapse density shows linear decreases [78] that are concurrent with increased astrocyte volume in the same brain set [79]. Aging rodents show reciprocal trends for synapse atrophy and astrocyte activation [80]. Brain imaging in ADNI cohorts shows regional differences for cerebral cortex grey matter atrophy that differ by amyloid load [81]. Air pollution [82] and cigarette smoke [83] are also associated with grey 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 [84], 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 [85]. Caloric restriction of mouse models attenuated astrocyte activation during aging (Morgan *et al.* 1999) and brain amyloid deposition in AD transgenic mice [86]. The AD associations with blood leukocyte DNA methylation [87] and telomere length [88] also implicate system-level innate immunity.

Obesity, a risk factor for AD, itself contributes to systemic inflammation, based on two lines of evidence [89, 90]. *First*, fat tissues secrete inflammatory factors directly into the blood. In obese persons, the venous blood effluent from visceral and subcutaneous fat depots is higher than from arterial blood for several acute phase inflammatory proteins including IL-6 and C-reactive protein (CRP) [91–93]. *Second*, macrophage cells accumulate around adipocytes during obesity [90]. Air pollution exposure is obesogenic in adults [94, 95], consistent with increased children's BMI by air pollution and cigarette smoke [67], see above. 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. Postmortem, most elderly brains harbor diverse species of viruses and bacteria [96]. Amyloid Aβ deposits can be nucleated by microbes and viruses from brain [97, 98] and oral gingiva [99]. The human Aβ peptide itself has extensive anti-microbial activities [98]. In mouse AD models, antibiotic perturbations of the gut biome accelerated deposition of Aβ plaque [100]. AD-relevant infections are modulated by ApoE alleles. Vulnerability to HIV and HSV1- and −2 in increased by ApoE4 [101]. In contrast, ApoE4 is neuro-protective in populations with high infectious loads [102], shown for Brazilian slum children with diarrhea [103] and adult Amazonian Tsimane with parasitemia [104]. 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 [105]. 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 NFkB and Nrf2 [106]. In vitro, cells with NFkB reporters respond to PM0.2 [107], while adipocyte PPARγ and other transcription factors mediated responses to obesogenic xenobiotics [108]. Other mouse brain genomic responses to PM0.2 are shared with longevity genes in elderly cigarette survivors [109]: ApoE, FOXO3, and mTOR [110].

The time depth of toxins may extend to prenatal influences from the grand-maternal uterus, when our maternal oocytes had formed [111]. Multi-generational 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 [112]. The role of epigenetics in environmental responses is consistent with evolutionary perspectives on the genetic architecture of age-related diseases [113, 114].

Further Development of the AD exposome

Methodology for environment-wide association studies (EWAS) was developed by HEALS (Health and Environment-wide Associations based on Large Population Surveys) [105]. Sixty-four stressors were categorized for biological, chemical, physical, psychological and social environmental 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 (HELIX) project [115] is assessing exposures with biomarkers following [6]: general (e.g., climate, SES) and individual (e.g., smoking, diet, physical activity) external domains and specific internal domain with omics biomarkers from early ages.

Next generation sequencing and omics technologies are complimented by genomic information in single cells [116]. Recent single-cell transcriptomic analysis linked AD with transcriptionally-distinct subpopulations across different major brain cell-types [117]. Examining regulatory activity at a cell type and 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, e.g. animal feeding operations, coal burning power plants, and pollen concentrations. Relationships to dementia risk can be assessed by sophisticated geographic information system (GIS) technologies [118, 119]. Fuzzy logic for GIS for quantification of exposure impact allows finer rankings of exposure factors than binary (yes/no) characterization [119].

Large datasets with longitudinally collected information are available. The UK Biobank, which anticipates 30,000 AD cases by 2027 [120] is complemented by the Healthy Cognitive Aging Project [121] (https://www.nia.nih.gov/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 (HRS) with the Harmonized Cognitive Assessment Protocol (HCAP) that is widely used to assess dementia. HRS sister studies in Mexico, England, and China are using translated and adapted versions of HCAP. The Alzheimer's Disease Neuroimaging Initiative (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 [122].

Machine-learning methods are applicable to genetic and non-genetic factors, and should improve accuracies of regression models, e.g., LASSO [123], and classification of variables (e.g., Random Forest [124]). Generalization of machine-learning techniques is statistically and computationally demanding for high-order interactions involving multiple factors [125], 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 [126]. 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 [127]. These effects can be additive [128, 129] or represent non-additive 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 [30].

Temporal component in the AD exposome and genome interactions is a challenging problem even when the respective data are available [16]. One approach is to average the effects of exposures over time, enabling widely used techniques, e.g., 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 [130]. Multi-dimensionality 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 [131, 132] and for deviations from norm for indices of physiological dysregulation [133]. Stochastic process models, a subclass of joint models [134], can evaluate dynamic component in the AD risk together with age-related meta-processes, such as allostasis [135] and homeostenosis [136, 137].

Challenges and Limitations

The ambitious NIH goal to treat or prevent AD by 2025 [138] 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, epi-genomic, and other omics. Relating this large-scale diversity to individualized risk trajectories driven by GxExT requires large-scale initiatives and rigorous methods.

Recommendations

The AD Exposome proposes to address contributions to AD from multiple genetic and non-genetic factors across the full life history in diverse populations for multi-generational 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 policy makers for large scale, multi-national 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. Multi-generational 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.

Lastly, to offset discouragement from the failed AD drug interventions [15], we suggest funding agencies and policy makers promote better public understanding of modifiable risk factors in AD shared with cardiovascular health.

Acknowledgements:

These studies are supported by the National Institute on Aging: CEF (R01-AG051521, P50-AG05142, P01-AG055367) and AMK (P01-AG043352, R01-AG047310, R01-AG061853). We are grateful for comments by Harvey Cohen (Duke), Rob McConnell (USC) and Judy Pa (USC). The figure was developed with Troy Palmer.

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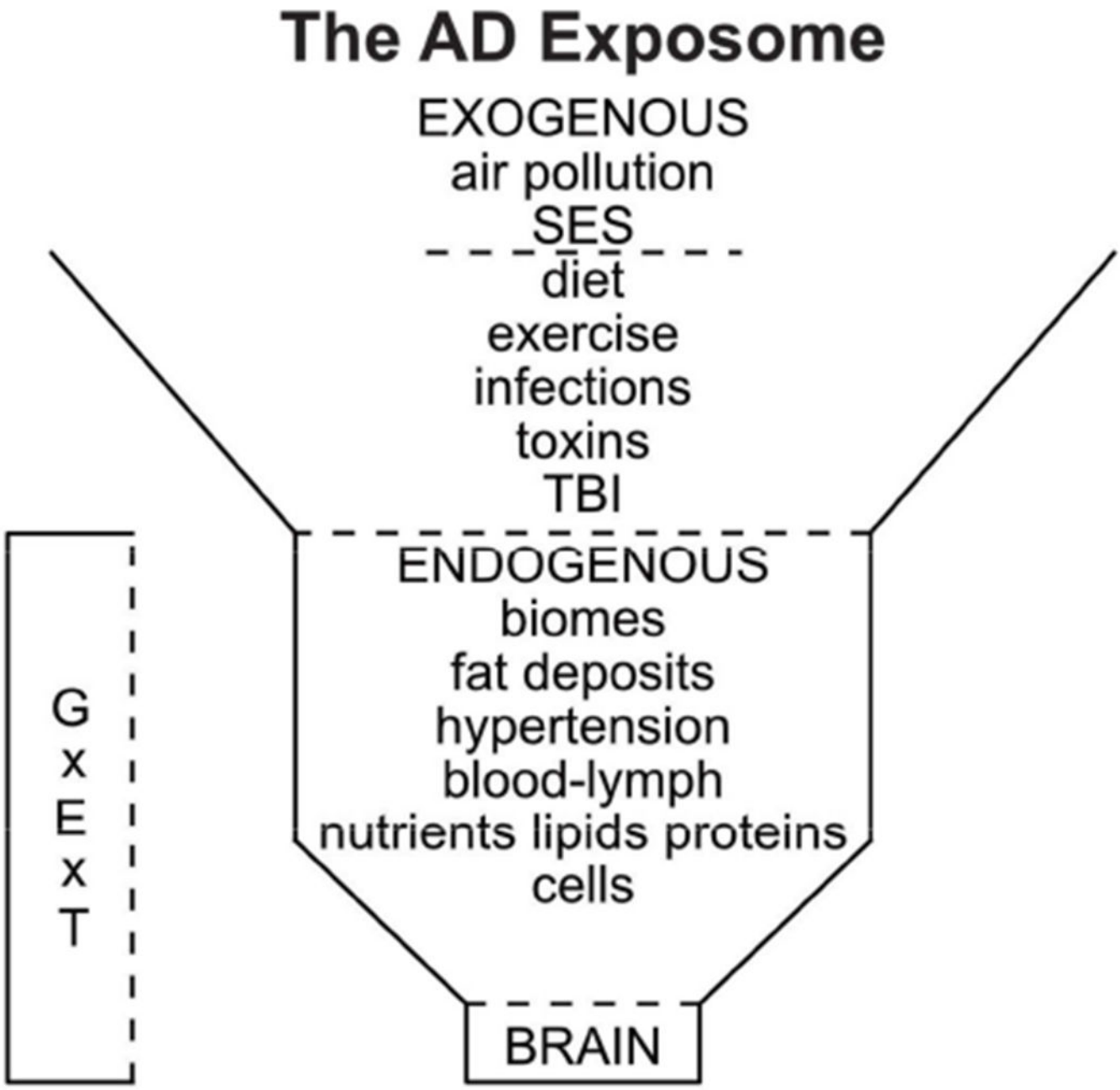

Figure.

Schema of the Exposome for Alzheimers Disease and related dementias (AD-Exposome) with exogenous and endogenous components. See Table for details and references; GxExT, interactions of gene by environment over age and time.

Table:

Domains of the AD Exposome

Domain/exposures		[6]
Exogenous macrolevel		
Air pollution		[50, 139]
Rural vs urban		[140]
Socioeconomic status (SES)		[15, 141, 142]
Exogenous individual		
Cigarette smoke		[53, 143]
Diet		[144, 145]
Exercise		[146, 147]
Infections		[42, 148]
Surgery and anesthesia		[46, 47]
Endogenous individual		
Biome	gut	[100, 149]
	periodontal gingiva	[99, 150]
Blood	cells: mast cells, monocytes, T-lymphocytes	[151–153]
	glucose	[154]
	hypertension	[155, 156]
	inflammatory factors	[148, 157]
	lipids and other metabolites	[158]
	sex steroids	[159–161]
Fat deposits		[91–93, 162, 163]
Gender		[32, 164]
Traumatic brain injury (TBI)		[42]

These exposome domains are based on Chris Wild's pioneering concept [5, 6]. The cited references are illustrative and cannot fairly represent the bodies of excellent work on many of these topics.