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Review article

Metabolome informs about the chemical exposome and links to brain health

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ABSTRACT

The metabolome is an intermediate phenotype, summarizing the profile of all small molecules (<1.5 kDa) in biospecimens. The metabolome provides a readout for the net influence of the chemical exposome, diet, gut microbiome, and genome on human health. Metabolic changes observed in exposome studies may thus provide clues about adverse outcome pathways related to cancer, diabetes, heart disease, cognitive impairment and other neurological conditions such as Alzheimer's disease (AD). Whilst the number of human cohort studies including both metabolomic and exposomic profiles is increasing, they are particularly limited in the domain of neurological conditions. Environmental exposures and chemical toxicants are known to have significant effects on the brain, gut microbiome, and gut-brain axis. Environmental chemicals of greatest interest include bisphenols, phthalates, persistent organic pollutants such as polychlorinated biphenyls (PCBs) and per- and poly-fluoroalkyl substances (PFAS), heavy metals, chemicals from household products and pesticides/herbicides; all of which may increase the risk of AD as they impact relevant biochemical mechanisms, especially with chronic exposure. In this review we describe how the chemical exposome can be assessed, including the approach our consortium is taking in the context of AD. Further, we review the current evidence about the impact of the chemical exposome on cognition as well as its influence on the risk and pathogenesis of AD. Finally, we highlight our approach to study the exposome in AD as part of large national and international collaborative efforts on the topic.

1. Introductions

The exposome comprises the totality of environmental exposures, including exogenous chemicals and other external factors, that an individual experiences over their lifetime. In combination with the host genome, the exposome generates additional molecular products inside the body, some of which contribute to the pathogenesis of various diseases (Rappaport, 2011; Rappaport et al., 2014; Wheelock and

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Rappaport, 2020; Vermeulen et al., 2020). The exposome typically includes three kinds of exposures: internal (*e.g.*; metabolism, gut microbiome, immune system), specific external (*e.g.*, environmental pollutants, diet, drugs, stress, occupational), and general external (*e.g.*, socioeconomic status, education, climate) (Vermeulen et al., 2020; Spada et al., 1990). The ability to measure the internal environmental chemical space is a valuable tool to evaluate health risks of exposures over an individual's lifespan. The 'exposomics' approach to identifying disease risks differs from traditional epidemiological approaches because it includes significantly expanded exposure assessments. Exposomics also integrates dynamic data on both exposure and response, spanning both time and space while making extensive use of omics data (*e.g.*, metabolomics) to discover exposure–disease associations (Nabi and Tabassum, 2022; Oresic et al., 2020). Exposomics often incorporates both geospatial and social environment data to study more subtle outcomes (*e.g.*; early signs of disease) by employing internal (metabolic) markers of exposure and response. By using internal biomarkers of exposure and connecting these to disease risk, exposomics studies can be readily integrated with the toxicological concept of "adverse outcome pathways" or AOPs (Ankley et al., 2010). AOPs help to create an exposure model that, after exposure to a (toxic) substance, identifies the sequence of molecular and cellular events that lead to the observed adverse effects. With the growing availability of data on environmental factors and the continued maturation of analytical techniques for assessing the exposome, there is increasing interest in understanding how the exposome contributes to the pathogenesis of many conditions such as cancer, diabetes, heart disease and neurodegenerative disorders such as Alzheimer's disease (AD).

The metabolome serves as an intermediate phenotype, capturing the profile of all small molecules (<1.5 kDa) in biospecimens. It reflects the cumulative effects of the chemical exposome, diet, gut microbiome, and genome on human health (Oresic et al., 2020; Walker et al., 2019; Zhang et al., 2021). Changes in metabolism identified through exposome studies can offer insights into AOPs associated with cognitive decline and AD. Although the number of human cohort studies integrating metabolomic profiles with environmental exposures is growing, such studies remain particularly scarce in the context of neurological conditions. Environmental exposures and chemical toxicants are known to have significant effects on the brain (Nabi and Tabassum, 2022), gut microbiome (Chiu et al., 2020), and gut-brain axis (Zheng et al., 2021). Environmental chemicals of greatest interest include bisphenols, phthalates, persistent organic pollutants such as polychlorinated biphenyls (PCBs) and per- and polyfluoroalkyl substances (PFAS), heavy metals (Wang et al., 2016; Bakulski et al., 2020; Alasfar and Isaifan, 2021), chemicals from household products (Zheng et al., 2021; Hrubec et al., 2021), and pesticides/herbicides; all of which may increase the risk of AD as they impact relevant biochemical mechanisms, especially with chronic exposure (Nabi and Tabassum, 2022; Wang et al., 2016; Agin et al., 2020; Mesnil et al., 2020; Park et al., 2021). For example, chronic exposure to pesticides increases AD risk by 35–50 % (*57*), while higher blood/brain levels of heavy metals (*e.g.*, lead, cadmium, manganese, iron, aluminum) can increase AD risk up to three-fold (Bakulski et al., 2020). Many of these compounds are neurotoxic, but their mechanisms of action vary, including blood–brain barrier disruption, competing with essential metals, altering protein signaling, or inducing amyloidosis (Nabi and Tabassum, 2022; Bakulski et al., 2020).

In this review we described how the chemical exposome can be assessed, including the approach our consortium has adopted in the context of AD. Further, we review the current evidence about the impact of the chemical exposome on cognition as well as its influence on the risk and pathogenesis of AD. Finally, we highlight our approach to study exposome in AD as part of large national and international collaborative efforts on the topic.

2. The chemical exposome

Currently, the analytical evaluation of chemical exposures remains quite constrained. This is because the majority of documented exposome studies address only a fraction of the chemicals encountered by humans. While the precise global count of chemicals is uncertain, Europe has officially registered over 140,000 synthetic chemicals while the United States has registered 86,000 chemicals for industrial or commercial use. The number of synthetic or anthropogenic chemicals has grown rapidly over the past 75 years. Indeed, there has been a 50-fold increase in the number of synthetic industrial chemicals produced since 1950, with over 350,000 different chemicals now produced globally. This number is projected to triple again by 2050 (European Chemicals Agency, 2017; Naidu et al., 2021).

Due to the widespread use of anthropogenic or synthetic chemicals, humans are exposed to a vast array of potentially harmful compounds, including pollutants, food additives, personal care products and chemical contaminants. A significant portion of these exposure chemicals lack sufficient data for thorough risk assessment. Given the broad chemical diversity and the wide range of concentrations that can be found in the human body, analyzing the chemical exposome necessitates employing a diverse set of analytical techniques (Andra et al., 2017; Athersuch, 2016; Athersuch and Keun, 2015; Warth et al., 2017; Escher et al., 2020).

2.1. Technologies to capture the chemical exposom

Comprehensive characterization of the human exposome requires sophisticated analytical methods that cover both endogenous compounds (metabolites) and exogenous anthropogenic chemicals (Vermeulen et al., 2020; Balcells et al., 2024; David et al., 2021). Exposure chemicals also show a very wide concentration range. For example, food-derived substances can have significantly higher concentrations than classic environmental pollutants of concern (Fig. 1). Most common analytical techniques for the analysis of exposome compounds and their metabolites use liquid or gas chromatography (LC, GC), combined with mass spectrometry (MS). Particularly, high-resolution mass spectrometers (HRMS), characterized by high mass accuracy and resolution, and broad mass ranges, can provide precise mass measurements and distinguish between compounds with minimal mass differences. This capability makes them ideal for the simultaneous detection of thousands of substances, including both metabolites and other chemicals. For LC-based approaches, ion mobility spectrometry (IMS) can be integrated with the MS instruments (Chappel et al., 2024; Delvaux et al., 2022; Metz et al., 2017). This approach adds an additional separation dimension that is based on the shape, size, and charge of ions, rather than just their mass-to-charge ratio (m/z). This added separation offers several advantages particularly in distinguishing between different isomers or conformers.

MS-based exposome analysis can involve targeted analysis, untargeted analysis, suspect screening or any combination of these three approaches (Andra et al., 2017; Manz et al., 2023; Musatadi et al., 2023). The targeted analyses are usually quantitative, very sensitive and suitable particularly for those compounds present at low concentrations. However, they typically involve more tedious sample preparation and are limited to those compounds that are in the target list, thus not allowing for comprehensive chemical characterization of the samples. Untargeted and suspect screening approaches utilize typically a very simple sample preparation methodology that can cover large range of chemically diverse compounds. These methods can detect large number of compounds, and they allow also for the identification of previously unknown chemicals. However, they are typically not accurately quantitative and it is not possible to optimize the methodology to be optimal for all analytes detected, causing more analytical variation in the results. In metabolomics, untargeted analysis or a combination of targeted and untargeted analysis are the most commonly applied approaches

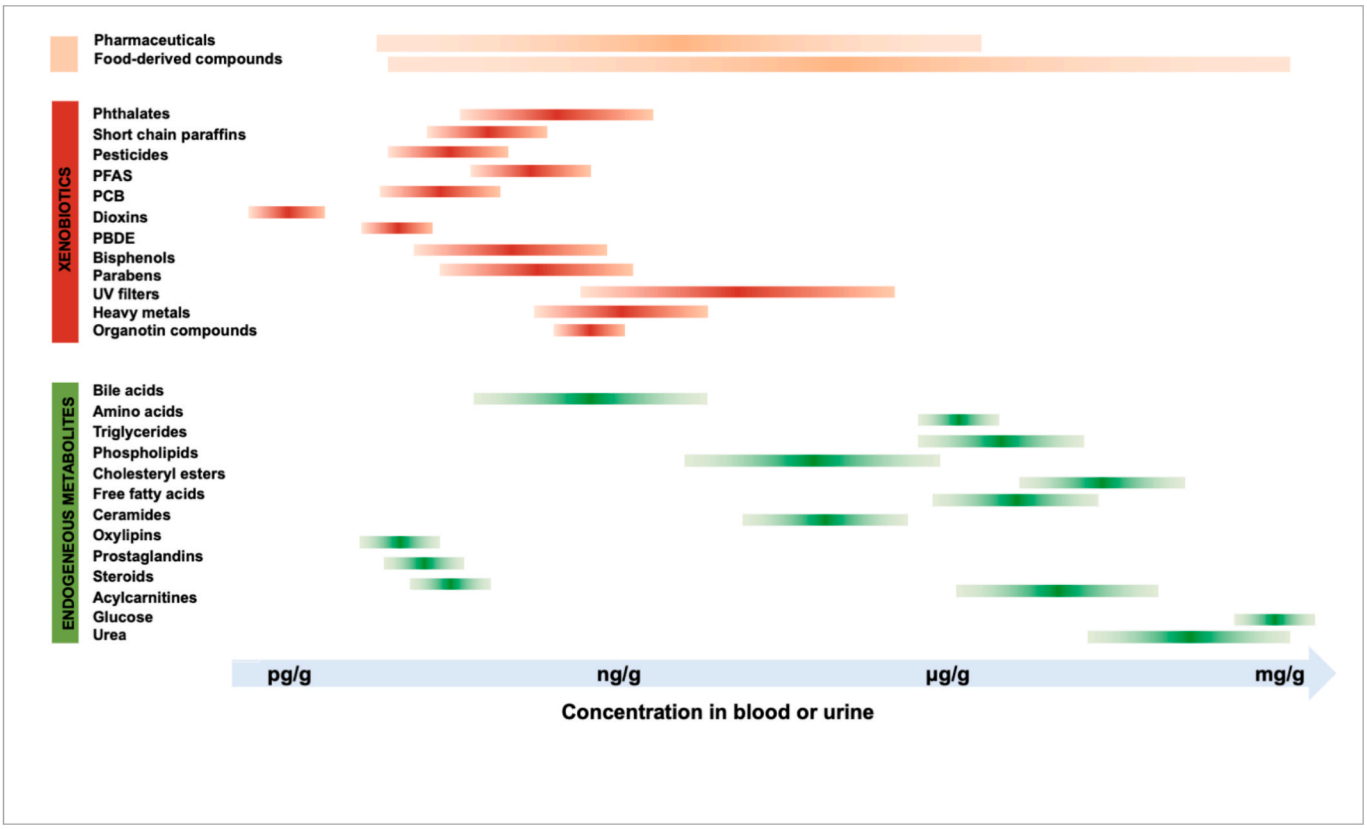

Fig. 1. Blood (plasma, serum) concentrations of the common persistent organic pollutants and metabolites. Concentration range of phthalates is shown for urine.

(Gonzalez-Dominguez et al., 2020; Lai et al., 2024), while in the analysis of environmental chemicals, targeted and suspect screening modes are more commonly used (Hollender et al., 2023). Specific metabolites may, however, require targeted strategies, either due to their low levels or their instability. HRMS systems that combine either with LC or GC are usually applied in the analysis of metabolites and environmental chemicals. The most common HRMS systems are Orbitrap and quadrupole-time-of-flight (QTOF) MS, the latter sometimes can be combined with IMS. In targeted MS analysis, both triple quadrupole analyzers (QqQ) or quadrupole-ion traps (QTRAP) are often used. With LC-MS based methods, soft ionization techniques such as electrospray ionization (ESI) or in some cases, atmospheric pressure chemical ionization (APCI) are used. However, in GC–MS, both hard (electron impact or EI) as well as soft ionization such as chemical ionization (CI) or APCI are typically utilized. For data acquisition, multiple options, such as data-dependent acquisition (DDA), data independent acquisition (DIA) and all-ion fragmentation (MS^{all}) are available (Defossez et al., 2023; Rudt et al., 2023).

Currently, the analysis of the endogenous metabolome and exogenous xenobiotics is often done separately, due to chemical complexity and the wide concentration range. However, to reduce the sample amounts required, improve the throughput and reduce the analytical costs, the current trend, especially in the case of large cohort studies, is to combine the methodologies and analyze both compound classes simultaneously. This is typically done for those compounds that have sufficiently similar concentration range and can be analyzed with similar methodologies. For example, it is very feasible to analyze several pharmaceuticals, PFAS, phthalates and parabens while analyzing most endogenous metabolites (Sen et al., 2024; Sen et al., 2022). For untargeted metabolomics and exposome analysis, a variety of established workflows have been described. The first step of the analysis is sample preparation which in most cases is liquid extraction. To comprehensively cover both highly hydrophilic compounds and lipophilic compounds, two separate methods are usually required, or if not, some compromises in sample coverage or recovery may be needed. Nonselective sample preparation methods, based on simple protein precipitation or liquid extraction for plasma and serum samples, combined with LC-HRMS or GC-HRMS, are the most common methods used in metabolomics (Athersuch and Keun, 2015; Hartonen et al., 2013; Hyotylainen and Oresic, 2015; Heli Nygren and Castillo, 2011; Hyotylainen and Oresic, 2015; Klavus et al., 2020). More selective methods and/or larger sample amounts are needed for low-abundance metabolites or low abundance environmental chemicals. In particular, methods that use sample clean-up (*e.g.*, *via* solid-phase extraction and phospholipid depletion) are typically required for the characterization of environmental pollutants due to their very low concentrations (Sdougkou et al., 2023; Hajeb et al., 2022). These clean-up methods are used to remove compounds such as lipids that can interfere with the detection of target compounds. Co-elution of such matrix components can lead to ion suppression in the mass spectrometer, reducing the detector's sensitivity and making it more difficult to accurately detect and quantify lower abundance chemicals. However, these methods also remove other compounds, as the phospholipid removal is not a highly selective methodology. In addition, to obtain sufficient sensitivity in the analysis of environmental pollutants, larger sample quantities (more than used in metabolomics) are often needed. The traditional methods used for the analysis of small numbers (<10) of environmental pollutants have been based on GC–MS and LC-MS/MS. However, for more comprehensive characterization (dozens to hundreds of compounds) the preference in environmental analysis or exposomics is to utilize untargeted analysis and suspect screening approaches (Wang et al., 2020; Li et al., 2020; Wang et al., 2018; Hollender et al., 2017; Gerona et al., 2018).

The key challenge in suspect screening and non-target analysis is the reliability of the identification. For identification, MS/MS spectra are required. This can be obtained by HRMS instruments (Q-Orbitrap and Q-TOF) using DDA mode, where after a full scan, the mass analyzer

selectively fragments ions from a predefined *m/z* list, usually selected based on abundance. In iterative tandem MS (MS/MS) cycles, samples get re-injected and DDA lists get updated to improve coverage of low abundant (exposome) compounds. Alternatively, all-ion fragmentation (AIF) on Orbitrap or "all ion MS/MS" on QTOF MS can be used after a full scan to fragment all ions entering the collision cell. However, linking precursor and product ions in this mode is challenging due to the high number of fragmented ions, which can reduce sensitivity and selectivity of the analysis.

2.2. Our approach to cover the chemical exposome

Our Alzheimer Gut Microbiome Project (AGMP), The Alzheimer Disease Metabolomics Consortium (ADMC) and the recently U01 funded "The Role of Chemical Exposures in Alzheimer's Disease and its Trajectory" initiatives funded by the National Institute on Aging (NIA) aim to provide the broadest possible coverage of the chemical exposome including in the blood and brain as part of the metabolome. Five metabolomic centers of excellence (exposomics ADMC labs) have completed a ring study to identify environmental chemical exposures, dietary components, and drug signatures that when linked to gut microbiome and metabolomic data will define exposome profiles associated with AD and cognitive changes (Fig. 2). With the analytical approach using parallel analysis across multiple participating centers, a broad range of chemical classes of pollutants can be covered. The feasibility of the approach has already been tested in the above-mentioned ring study, in a series of 465 patient plasma samples. The

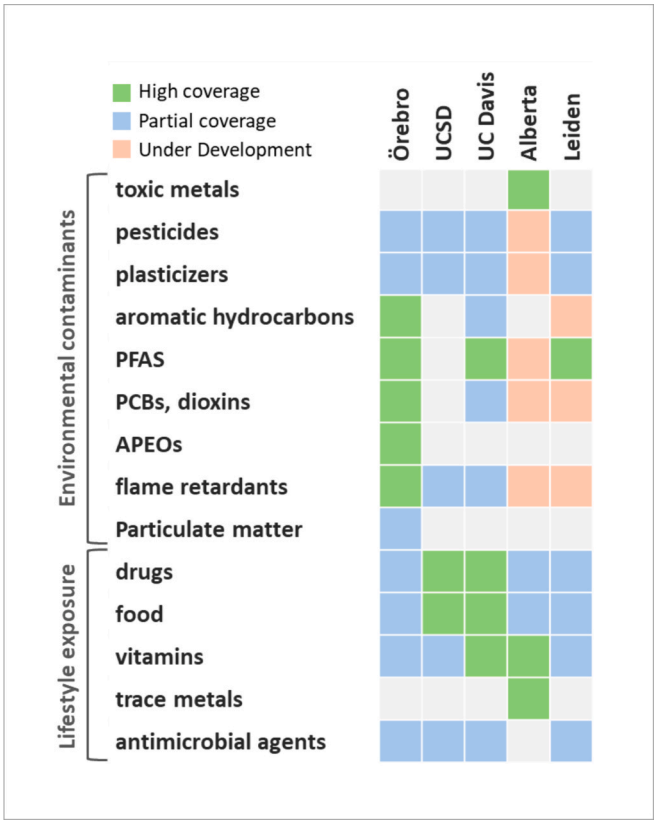

Fig. 2. Coverage of exposure chemicals by the exposomics ADMC labs. For each chemical / exposure class, current coverage by existing analytical platforms is indicated in green (high coverage) or blue (partial coverage). In pink are classes that will be covered by platforms which are under development. For most classes the platforms provide complementary or even overlapping coverage, enhancing the analytical quality and reliability. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

depth of chemical coverage does ultimately depend also on sample amounts being available, as some of the classes or compounds covered require large amounts of samples to assure reliable detection and quantitation.

In the U01 project, we will leverage a large NIA-funded collaborative infrastructure with connections to 10 Alzheimer Disease Research Centers (ADRCs), and access to unique community-based longitudinal cohort studies and biobanks (FHS, ROSMAP, Rotterdam Study, UK Biobank). This will allow our team to: (i) expand coverage of the chemical exposome in the blood and brain, (ii) link identified signatures to brain aging, incident dementia, and AD and (iii) through long-standing partnership with Sage Bionetworks, enable rapid sharing of exposome data collected under this application through the AD Knowledge Portal. Human data generated in this project will inform and be informed by results from complementary preclinical exposome studies in AD mouse models (AG-24–023) and cell-based systems (AG-24–021). We will leverage the data generated under these large NIA initiatives to enable data harmonization and data integration of complex exposure data across multiple cohorts and with other types of omics data. Below we summarize the analytical approaches pursued by the participating metabolic centers of excellence.

The Fiehn laboratory at University of California, Davis, specializes in standardized, robust and automated nontargeted analyses of metabolites, lipids and exposome compounds. These three types of chemicals are screened *via* three LC-high resolution MS/MS assays. The first two assays use classic biphasic extractions with a methyl tert-butyl ether (MTBE)/methanol/water ternary extraction solvent (50:1, v/v) including 76 internal standards for lipids and 43 internal standards for the hydrophilic phase. Using 2.1 mm i.d. Waters Bridged Ethylene Hybrid (BEH) amide and BEH C18 columns with 1.7 um particles, the internal standards are used for both quantitative purposes and to form a grid to normalize absolute retention times between laboratories and studies to standardized retention indices (Bonini et al., 2020; Cajka and Fiehn, 2016). All runs are performed in data dependent MS/MS to capture abundant metabolites and chemicals, in addition to five rounds of iterative exclusion MS/MS to define the complement of chemicals in pool quality control samples (Koelmel et al., 2017). Pooled quality control (QC) samples and method blank samples are utilized after each set of 10 cohort samples. In a third assay, specifically for exposome analyses, we use 100 µl plasma samples and first remove acyl-based lipids like di- and triacylglycerols, phospholipids and sphingolipids via commercial lipid removal kits. Eluates are concentrated to dryness and data are acquired on reversed phase (RP)LC-HRMS/MS with internal standards as above. Datasets are automatically processed *via* the new LC-BinBase database that builds on 20 + years of experience with our classic GC-BinBase database (Bremer et al., 2023). LC-BinBase has been developed at UC Davis over the past 5 years and uses Amazon Web Services (AWS) to guarantee scalability and 24/7 access. The LC-BinBase modular architecture enables improvements for better peak picking or data normalization over time. LC-BinBase generates unique '*accurate mass_MS/MS_retention time*' triplets (Bins) that are acquired from LC-MS/MS assays of biological samples. The database uses a PostgreSQL/Aurora Amazon relational database service (RDS) for storing computational data and compounds, combined with a DynamoDB key-value storage for metadata and tracking information. Python language was picked for rapid prototyping and visualization, and to query the system *via* REST APIs. We have rewritten the code for the main MS-DIAL data processing algorithms to enable their use on AWS. LC-BinBase converts all vendor-specific data formats into mzML open data formats and has been successfully tested for all major high-resolution mass spectrometer platforms. Data processing is executed on a AWS Fargate cluster to process hundreds of samples simultaneously. Using Docker images enables quick transitioning from processing data in the AWS cloud environment to a local system and back, for example, for developing and testing database functionalities or data processing parameters. Once all files of a specific biological study have been acquired, processed and exported, the

EventBridge system automatically detects completion and starts an aggregation task in ECS/Fargate to fetch all study metadata data from the DynamoDB Key/Value store. The modular architecture of LC-BinBase and Mass.Wiki, especially the API Gateway and its associated lambdas, are used to improve data quality and data usefulness for biomedical scientists and downstream informatics analyses. Datasets are exported and curated, and quantitative values are normalized by Systematic Error Removal by Random Forest (SERRF) (Fan et al., 2019).

The methods used in the Wishart lab at the University of Alberta (Edmonton, Canada) include both a targeted, absolutely quantitative LC-MS/MS assay for the measurement of nearly 1300 organic compounds and a targeted, absolutely quantitative inductively coupled plasma (ICP)-MS assay for the measurement of nearly 40 metals. Both assays require the use of solvent extraction and protein precipitation steps and both can use as little as 50 μL of plasma, serum or urine, or 20 mg of tissue or stool – or as much as 4X these amounts (followed by a concentration step). For the LC-MS/MS assay, internal isotopic standards are added and 7-point internal calibration curves are used to help with quantification, as described for our previously developed LC-MS/MS assays (Weissman et al., 1988; Zhang et al., 2024). The ICP-MS assay, which has been described in detail previously (Foroutan et al., 2019), uses a 6-point external calibration curve to quantify the metals. The LC-MS/MS assay, which has been adapted to run in a 96-well format, employs chemical derivatization to simplify the LC separation process and enhance detection. Specifically, amine-containing compounds are derivatized with phenylisothiocyanate (PITC) and organic acids are derivatized with 3-nitrophenylhydrazine (3-NPH). After derivatization, analyte extraction is performed followed by LC separation, then selective MS detection using multiple reaction monitoring (MRM) to identify and quantify metabolites. The LC-MS/MS assay requires 3 separate injections, one for 3-NPH derivatized metabolites, one for PITC-derivatized metabolites and one for lipids or lipid-like molecules (*via* direct flow injection). The data generated by the LC-MS/MS assay is processed by an in-house software package called LC-AutoFit, which can perform automated calibration, peak picking and peak integration, is able to process 96 samples in less than 30 min. The LC-MS/MS assay is capable of detecting and quantifying more than 350 water-soluble metabolites/exposure compounds and more than 900 lipids or lipid derivatives of which 620 are known disease or health biomarkers, 155 are microbially derived, 90 are biomarkers of food intake (BFIs), 50 are lifestyle/workplace exposure compounds (bisphenol A [BPA], cotinine, PFAS, antibiotics, ochratoxins, *etc.*), and 30 are essential nutrients.

The approach in the Dorrestein lab at UC-San Diego uses LC-MS/MS untargeted metabolomics combined with data science to generate potential exposures information, leveraging curated metadata associated with reference LC-MS/MS files or reference MS/MS libraries. This enables valuable insights into exposure source, occurrence profiles and provide the ability to provide insight into lifestyles. As a fundamental proof-of-concept, reference LC-MS/MS data of personal care products, cultured human cell lines, and 34 microbial monocultures were used to identify the most likely exposure source for a subset of the detectable ions of molecules, even if they were not yet annotated, from human samples *via* co-analysis using molecular networking (Bouslimani et al., 2019; Bouslimani et al., 2015). To enhance the ability to use reference LC-MS/MS data we set out to demonstrate that when well-curated ontologies with controlled vocabularies for food source data, which enables improved data science and reusability of the reference data (Gauglitz et al., 2022). The second overarching strategy is through the curation of knowledge associated with reference MS/MS spectra. We originally demonstrated this concept by producing a "lifestyle sketch" of an individual for forensic purposes (Bouslimani et al., 2016). A recent application of this concept, for clinical studies, is to enable medication readout directly from untargeted metabolomics data. We recently developed the GNPS Drug Library that integrates MS/MS reference spectra of drugs with controlled-vocabulary pharmacologic ontology on source of the medication, therapeutic indication, and mechanism of action (Zhao et al., 2024).

One of the most powerful strategies in the Dorrestein lab to understand exposures builds on the development of the mass spectrometry search tool (MASST) to query MS/MS spectra across the entire public metabolomics repositories. There are now roughly a million LC-MS/MS files available across Metabolights (Yurekten et al., 2024), National Metabolomics Data Repository (NMDR) /Metabolomics Workbench (Powell and Moseley, 2023; Sud et al., 2016), and GNPS/MassIVE (Wang et al., 2016) repositories. To facilitate the intepretation of the spectral matching results and enabling data science, the Dorrestein lab has developed ReDU, a platform that standardizes vocabularies for the metadata of data deposited in the public domain (El Abiead et al., 2025; Jarmusch et al., 2020). Such controlled vocabularies have enabled reverse metabolomics. Although the concept was demonstrated in 2020, reverse metabolomics was not formalized until 2024 (Gentry et al., 2024; Mohanty et al., 2024; Quinn et al., 2020). In reverse metabolomics, MS/MS can be searched against the repository to discover species distributions, health phenotype associations, organ/biofluid distributions and other information of the known or unknown molecules (Mohanty et al., 2024; Quinn et al., 2020). For domain-specific applications, we have also created MASST platforms with specialized controlled vocabularies, including FoodMASST (~3,600 files curate) (West et al., 2022), MicrobeMASST (~60,000 files curated) (Zuffa et al., 2024), PlantMASST (~20,000 files curated) (Gomes et al., 2024), with other domain specific MASSTs in developement to facilitate new discoveries in multiple fields. These domain-specific MASSTs rely on community efforts to curate metadata and link them to LC-MS/MS raw data files, generating detailed reports that answer questions such aswhether the detected molecules originate from food, plant, or microbes, and provide specific contextual information such as their specific food sources or microbial produces.

The approach at the Örebro University (Hyötyläinen, Orešič) is based on combined target analysis, suspect screening and non-target (untargeted) screening using both LC and GC-based methods, combined with HRMS (QTOF and Orbitrap MS), with LC based methods utilizing RPLC, HILIC and mixed-separation modes. The general workflow for sample preparation is based on non-selective liquid extraction and the with a large number of internal standards for both metabolites and environmental chemicals that has a good coverage of the metabolome and environmental chemicals using 40–60 μL of plasma or serum, or 20 mg of tissue. Most of the workflows are based on LC-QTOFMS, with two main platforms, one dedicated for comprehensive lipidomics determination and the other for polar and semipolar metabolites and environmental chemicals. The MS/MS data are acquired using both data independent and data dependent acquisition strategies. For verification of the identification, we have in-house compound library of ca. 1,800 metabolites and contaminants. When increased sensitivity is needed, we have also targeted methods based on UHPLC-QqQMS (bile acids, oxylipins, PFAS) and GC-Orbitrap and GC-QqQMS for persistent organic pollutants such as dioxins, flame retardants, specific pesticides, polycyclic aromatic hydrocarbons (PAHs), and other lipophilic pollutants. For the latter, the sample amount needed is 100–150 μl (serum or plasma), and the sample preparation includes clean-up by SPE. The methods are available for a variety of sample matrices, including plasma, urine, feces, tissue biopsies as well as cell and plant samples. The QC analysis is based on a set of quality control samples, including pooled samples, in-house QC for different sample matrices, NIST reference samples, extraction and solvent blanks, standards and calibration standards, with the latter allowing quantitation of the target analytes. Datasets are processed using MZmine software which provides a range of normalization and scaling methods to account for variations in data quality between samples (Schmid et al., 2023; Pluskal et al., 2010; Heuckeroth et al., 2024). MZmine also has advanced data filtering and annotation features, including spectral and retention time filtering, adduct and isotope annotation, and improved automatic peak

annotation using public databases. MZmine can be integrated with other open-source software tools and resources such as MetaboAnalyst (Pang et al., 2024) and GNPS (Aron et al., 2020) as well as with in-house libraries.

Leiden University has established the Exposome-Scan Facility (www.exposomescan.nl) led by Thomas Hankemeier and co-workers together with Utrecht University for exposome studies. The facility supports the analysis of small molecules in human samples like plasma and urine, or tissue samples, using complementary LC-QTOFMS methods with RPLC and/or HILIC separations, and GC-Orbitrap MS. The LC-QTOFMS method acquires HRMS scans and data independent MS/HRMS data to confirm or characterize the molecules detected and then uses MS/MS data to resolve isomers where necessary. The MS/MS data are acquired using Sequential Window Acquisition of all Theoretical Mass Spectra (SWATH-MS) to have enough MS and MS/MS data along an eluting peak (van der Laan et al., 2020). The data are processed using a combined targeted and untargeted analysis of the data using a home-built data preprocessing pipeline. The GC-Orbitrap MS analysis focuses on the analysis of semi-volatile environmental chemicals including pesticides, flame retardants, PCBs. To study the effect of environmental factors, additional methods are available including a HILIC-MS/MS method to analyze medium and apolar lipids covering more than 1200 lipids and more than 19 lipid classes (Zhang et al., 2023) and a targeted signaling lipid RPLC-MS/MS method covering more than 300 bioactive lipids such as oxylipins, isoprostanes, eicosanoids *etc.*, informing about inflammation and immune response (Yang et al., 2024). The methods are being continuously developed, with a focus on extending compound coverage, improving throughput, and delivering accurate concentrations where authentic standards are available. In addition to human tissue and biofluid samples, sampling devices such as wristbands are also analyzed in the facility. The data generated in the facility is made as Findable, Accessible, Interoperable, Reusable (FAIR) as possible so that they can be combined for federated data analysis using, *e.g.*, digital twinning (Schultes et al., 2022) with other FAIR data points such as high-resolution environmental maps established at Utrecht University. The Digital Twins are created for an abstraction called "molecule", which is a class entity, not an instance. The definition of molecule assumes that any collection of atoms with the same covalent bonding configurations will have identical (average) properties. Another focus is to understand the effects of hazardous chemicals on *in-vitro* human models using organ-on-chip models or organoids. The most important models are liver and kidney models, and various advanced microscopy techniques are used to study the effect combined with MS analysis. MS analysis can be performed on collected cell medium samples, such as using perfusate through blood vessels, (Pandian et al., 2024) cell content after cell lysis, (Jiang et al., 2021) or using single cell MS analysis (Zhang et al., 2023).

2.3. Databases for exposome research

The main bottlenecks in both suspect screening and untargeted analysis is the identification of unknown compounds. In recent years, significant emphasis has been placed on the development of identification protocols for LC-MS-based methods. These include the compilation of experimentally collected LC-MS-based reference spectral libraries including open spectral libraries such as those found in the Human Metabolome Database (HMDB) (Wishart et al., 2022), GNPS/MassIVE (Wang et al., 2016; Choi et al., 2020), and MassBank (Elapavalore et al., 2023; Horai et al., 2010). Although the original METLIN was accessible for free, it has since grown to become a large library of non-disclosed composition and is now only accessible by payment (Baker et al., 2023; Xue et al., 2020). To enable discovery of related analogs of molecules, a large neutral loss library is also accessible in METLIN *via* payment (Aisporna et al., 2022), however such neutral loss information is just a subset of what could be obtained using molecular networking for free (Bittremieux et al., 2022). Several MS instrument vendors also offer their own commercial spectral databases, but these resources are usually limited to vendor-specific instruments. Unfortunately, the majority of detected compounds or features in HRMS workflows cannot be found in today's spectral databases. Thus, *in silico* methods and MS/MS prediction tools have been developed, including MetFrag (Schymanski et al., 2021; Ruttkies et al., 2019), CFM-ID (Wang et al., 2021), CSI Finger-ID (Duhrkop et al., 2015), as well as methods that encompass H-donor rearrangements (Tsugawa et al., 2016), and quantum-chemistry based approaches (Lee et al., 2024). One recent example of the application of these *in silico* methods to exposome research and novel compound identification involved the use of CFM-ID and generative compound modeling to precisely determine the structure of novel or never-before-seen psychoactive drugs in various matrices (Wang et al., 2023). While the field of *in silico* compound identification in exposomics is still under development, many of the available tools employ similar concepts or ideas. MS2Analyzer, for example, uses an unsupervised classification algorithm and combines structural information characteristic to product ions and their fragments, neutral losses and isotopic ratios, with literature-derived neutral loss/substructure pairs to detect the presence of related substructures (Ma et al., 2014). Supervised machine learning classification methods, on the other hand, can be utilized in the detection of specific substructures or structural neighbors and thus, for the assignment of unknowns to specific chemical classes (Ma et al., 2014; Aguilar-Mogas et al., 2017; Treutler et al., 2016). Direct structure elucidation approaches using general fragmentation rules are also available *via* tools such as MS-FINDER (Tsugawa et al., 2016). It should be noted, however, that MS fragmentation patterns are notoriously hard to predict, and even structurally similar compounds do not always produce similar MS fragments. Several methodologies that utilize indirect structure elucidation workflows, in combination with *in silico* spectral prediction have also been developed (Cheng et al., 2020; Rogers et al., 2019; Qiu et al., 2018; Ljoncheva et al., 2020; McEachran et al., 2018). It is worth noting that certain types of commonly encountered compounds in exposomics studies have very unique mass spectral features, *e.g.*, halogenated compounds, which enables their facile screening *via* untargeted analyses. In GC–MS based methods, the assignment of unknowns to chemical classes can be done *via* comparisons to predicted EI-MS fragmentation patterns as has been demonstrated both for exposomics as well as for metabolomics studies (Koelmel et al., 2017; Schnelle-Kreis et al., 2005; Hummel et al., 2010).

As mentioned earlier, metadata-driven metabolomics provides new possibilities for tracking the sources of exposure molecules without the need to identify their chemical structures. For instance, exposures originating from food and medication can be directly identified by comparing MS/MS spectra to Foodomics databases (raw MS/MS data of over 3,600 foods linked to their ontology) (Gauglitz et al., 2022; West et al., 2022), as well as databases like MicrobeMASST, FoodMASST, and DrugMASST (currently in development – expected to contain over 100,000 MS/MS spectra of approximately 5,000 drugs, eventually 15,000 drugs, and their metabolites). This approach for finding exposures is now becoming possible because faster databases searches are becoming possible (Li et al., 2021; Wang et al., 2020). Up to 1 billion MS/MS spectra can be directly compared in detail using the Flash Entropy algorithm, even on personal computers without supercomputing resources (Li and Fiehn, 2023).

In addition to the MS/MS spectral databases just described, there are a number of other databases that provide reference information (structure, nomenclature, physical properties, descriptions, health effects, ontologies, pathways, source or origin, reference concentrations) for a large number of exposome compounds including food-derived chemicals, drugs, chemical exposures and microbial metabolites. The utility of these reference databases lies in the rich meta-data provided which gives both biological and chemical context to any compound identified *via* MS spectral database matching. Examples of these reference databases include FooDB (https://www.foodb.ca/), which has data on over 70,000 food-derived compounds, DrugBank (Knox et al., 2024) which has data on over 3,200 approved and illicit small molecule drugs (along

with over 3,100 drug metabolites), ExposomeExplorer (Neveu et al., 2020) which has data on over 1,200 chemical exposure biomarkers, T3DB (Wishart et al., 2015) which has data on over 2,900 small molecule toxins, herbicides, pesticides and contaminants, MiMeDB (Wishart et al., 2023) which has data on over 25,000 microbially derived compounds, and the NORMAN Suspect List Exchange (Mohammed Taha et al., 2022) which has data on over 100,000 chemical substances of environmental concern. Some of these databases (FooDB, HMDB, DrugBank) also contain reference MS/MS, EI-MS and/or NMR spectra.

3. Impact of chemical exposures on cognition and AD

The potential involvement of environmental contaminants and the "neural exposome" in neurodegenerative conditions is currently of very high interest, and detailed in several review and perspective articles, including Lefèvre-Arbogast *et al.* (Lefevre-Arbogast et al., 2024), Sakowski *et al.* (Sakowski et al., 2024), and others (Granov et al., 2024; Ibanez et al., 2024; Tsalenchuk et al., 2023). Fig. 3 depicts the various chemical classes, their exposure origins, and brain effects linked to AD and dementia, with evidence gathered from epidemiological studies, animal models, and *in-vitro* studies. A large number of studies have established associations between specific chemical exposures and the 'internal exposome' (Kajta et al., 2019) (*e.g.*; metabolome) or specific adverse health outcomes (*e.g.*, AD and dementia) (Oresic et al., 2020). However, in most cases, the question remains as to whether these are true, causal relationships or associations confounded by other factors. The epidemiological studies may provide evidence about potential links between specific exposures and disease risk at a population scale, but they are inherently associative and thus may not be able to disentangle various confounding factors such as socioeconomic status and exposures. Understanding the link between the specific exposures and AD thus requires a comprehensive exposomic approach, combining epidemiological studies and functional/toxicological studies in experimental models (*in vivo*, *in vitro*).

Below we provide a non-exhaustive summary of the suggested links between each chemical class and relevant aspects of neurological health. The selected information originates in reviews in the field, in addition to research publications found via PubMed and Google Scholar searches using keywords including each environmental chemical class AND (cogniti* OR neuro* OR alzheimer OR dementia OR brain). Supplementary Table 1 provides details of original research sources utilized in this section.

3.1. Halogenated and phenolic industrial pollutants

PFAS are extremely persistent environmental pollutants originating in a wide array of products that require waterproofing or surfactant action (non-stick cookware, food packaging, water-repellent clothes, stain-resistant textiles and carpets, firefighting foam, cleaning products). Drinking water contamination is a major contributor to higher blood levels in the population, but not the only source (Ingelido et al., 2018; Stubleski et al., 2017). Reviews of epidemiological and animal model studies have associated PFAS, mainly perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) with lipid and insulin dysregulation, liver disease, kidney disease, altered immune and thyroid function, cancer, along with adverse reproductive and developmental outcomes (Fenton et al., 2021; Blake and Fenton, 2020; Cao and Ng, 2021; Coperchini et al., 2020; Costello et al., 2022; Steenland and Winquist, 2021; Wang et al., 2021). A review also examined the evidence of PFAS accumulation and distribution in human and animal

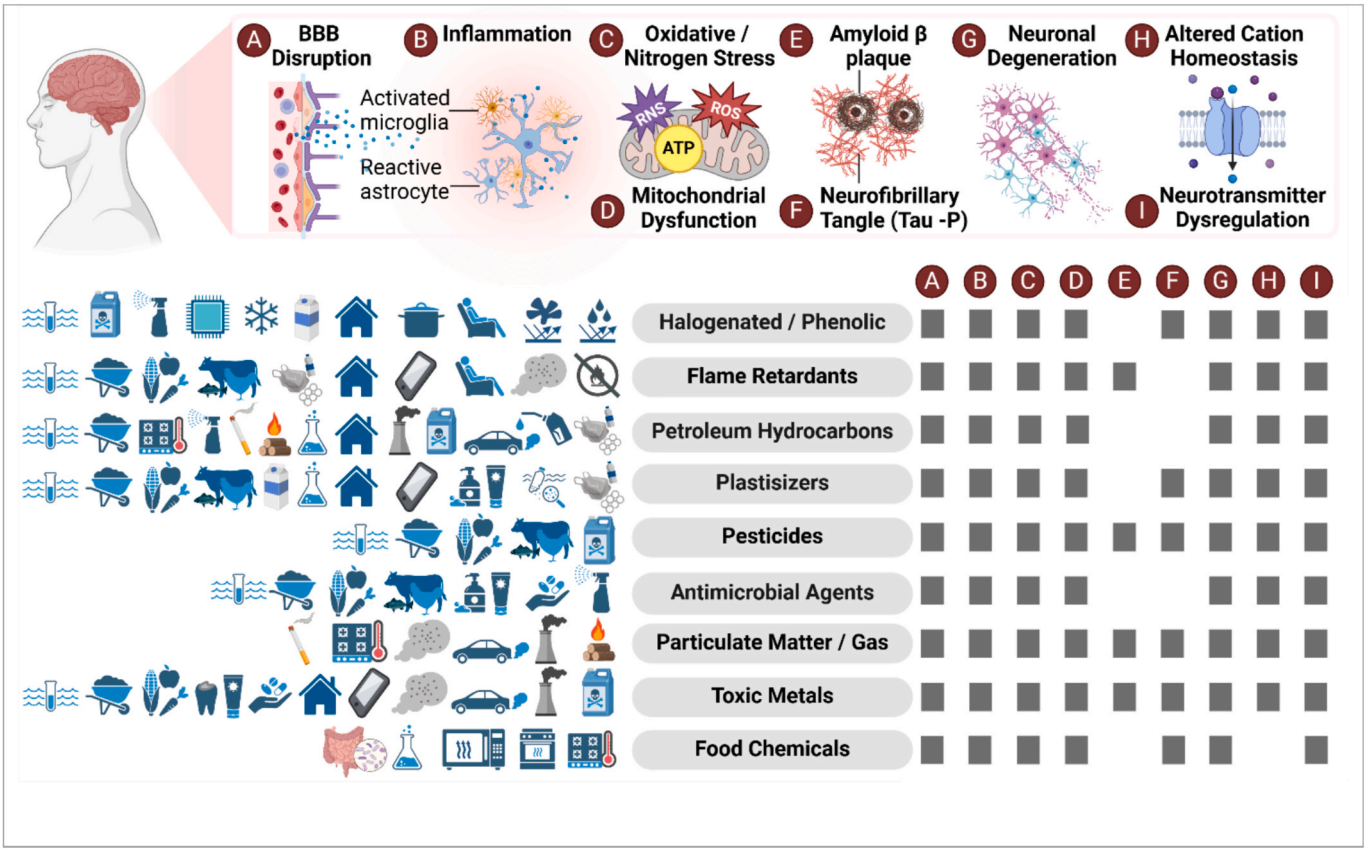

Fig. 3. AD-related brain processes (A-I), affected by classes of environmental contaminants as suggested based on epidemiological studies, animal models, and *in-vitro* studies. The main potential sources of environmental exposure to each contaminant class are indicated by icons. Note that additional secondary exposure is common *via* soil, water, plant- and animal-based food. Figure created with BioRender.com.

brains (Cao and Ng, 2021), however, the effects of PFAS on cognition, and specifically neurodevelopment are inconclusive according to a recent meta-review examining 21 PFAS/cognition studies (Liew et al., 2018). In 727 elderly participants in the NHANES study (US), serum levels of perfluorononanoic acid (PFNA) were associated with Z-scores of cognitive tests (Zuo et al., 2024). Prenatal exposure to PFOA, PFOS and perfluorohexane sulfonate (PFHxS) measured in umbilical cord blood, was linked to risk of lower cognition in children six years of age (Barrea et al., 2024). In mice, a single neonatal exposure to PFHxS induced memory and learning deficits in adults (Viberg et al., 2013), while other *in-vitro* studies have reported neurotoxicity of several PFAS compounds (Slotkin et al., 2008). PFAS may indeed contribute to cognitive disturbances, while their biochemical impact varies between different PFAS class members. These effects typically include mitochondrial dysfunction, oxidative stress, disruption of cell signaling, altered calcium homeostasis and possibly bile acid (BA) metabolism (Fenton et al., 2021; Slotkin et al., 2008). PFAS may interfere with microbially-regulated BA metabolism due to utilization of the same transporters as BA in the gut to re-enter enterohepatic circulation (Oresic et al., 2020; Zhao et al., 2015). The link between PFAS and bile acid metabolism was recently demonstrated in our work (Sen et al., 2024; Rotander et al., 2024) and is further relevant to cognition. We also showed that alteration in BA gut microbiome metabolism observed in mild cognitive impairment (MCI) and AD, was associated with cognitive and brain imaging changes (MahmoudianDehkordi et al., 2019; Nho et al., 2019).

Dioxins are byproducts of industrial manufacturing and combustion of PCBs, polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated benzofurans (PCDFs). According to reviews in the field, they are endocrine disruptors, and induce developmental neurotoxicity (Yegambaram et al., 2015). Mechanistically, they bind to aryl hydrocarbon receptor (AhR) and modulate oxidative balance, inflammation and also neuronal differentiation pathways (Yegambaram et al., 2015; Rajendran et al., 2022). Dioxins downregulate the Wnt/b-catenin pathway, promoting neuronal damage and apoptosis (Yegambaram et al., 2015).

Phenyl-based industrial pollutants, including PCBs, are used as coolants and insulators in capacitors and transformers (banned in 1977). They are by-products of industrial processes and can be released from existing products. hence are still common environmental and persistent pollutants. PCBs, their history, metabolism, and suggested neurotoxic effects and biochemical mechanisms were described in an early review by Fonnum and Mariussen (Fonnum and Mariussen, 2009). A later review by Rude *et al.* added an interesting link between PCBs neurotoxicity and the gut microbiome (Rude et al., 2019). Exposure in rodents induced intestinal inflammation, increased intestinal permeability, dysbiosis and changes in bile acid homeostasis (Rude et al., 2019). These were possibly mediated by activation of the NFκB pathway, in addition to oxidative stress and effects on calcium homeostasis (Fonnum and Mariussen, 2009). Such disruption may also negatively affect the integrity of the BBB allowing the circulation of toxic LPS, apart from a suggested direct impact of PCBs on the expression of tight junction proteins (Rude et al., 2019). Non-dioxin-like PCB mix exposure in lactating mice caused a decrease in synaptic proteins (synaptophysin, PSD95) and long-term memory impairment following Amyloid beta challenge at older age (Elnar et al., 2016). In humans, PCBs detected in umbilical cord blood were linked to risk of lower cognition in six years old boys (Barrea et al., 2024). Up to ten-year longitudinal studies in adults associated plasma concentrations of various PCBs with faster decline in cognitive performance (Medehouenou et al., 2019; Parada et al., 2024). In a NHANES study, levels of two PCBs in the serum of elderly people were associated with Z scores of cognitive tests (Zuo et al., 2024).

Alkyl-phenol polyethoxilates (APEOs) are used as non-ionic surfactants, defoaming agents and emulsifiers in a range of products (pesticides, detergents, paint, *etc.*) and industrial processes (paper and textile industry, for example) (Yegambaram et al., 2015; Mir et al., 2020). According to reviews, there is a persistent leaching into the environment of degradation products of APEOs, such as nonylphenol (NP) and octylphenol (OP). These chemicals accumulate in water and soil and penetrate the food chain, possibly causing endocrine disruption in animals (Yegambaram et al., 2015; Mir et al., 2020). OP exposure in an animal model was linked to AD *via* increased expression of the neurotoxic amyloid-precursor protein (APP) in the hypothalamus (Trudeau et al., 2002).

3.2. Flame retardants

Polybrominated diphenyl ethers (PBDEs) are the most common brominated combustion inhibitors (flame retardants) in a range of products and are suspected neurotoxins. Prenatal and childhood PBDE exposures were associated with poorer attention, reduced fine motor coordination, and lower levels of cognition in children (Eskenazi et al., 2013). A comprehensive review by Hendriks and Westerink summarized similar PBDE associations in additional epidemiological studies (Hendriks and Westerink, 2015). The summary also included exposure experiments in several rodent models, which affected behavior, reduced synaptic plasticity, and decreased neurotransmission systems (through GABA, Glu, n-ACh receptors) (Hendriks and Westerink, 2015). Neonatal mouse exposure to two PBDEs resulted in increased hippocampal proteins (CaMKII and synaptophysin) involved in brain maturation (Viberg, 2009), and perinatal rat exposure resulted in neurobehavioral impairments and reduced glucose metabolism in the brains of adult rats (Sun et al., 2025). The review of *in vitro* studies showed that various neuronal cells exposed to 1–50 μM of common congeners of PBDEs exhibited decreased cell viability, increased ROS production, MAPK activation (inflammatory cascades), disrupted calcium homeostasis (Hendriks and Westerink, 2015), and amyloid-beta peptide release (Al-Mousa and Michelangeli, 2012).

Organophosphate-esters (OPEs) flame retardants (OPFRs) are used as substitutes to PBDE flame retardants for textiles, furniture, building materials, plastic products, and electronics. Exposure to OPFRs and their degradation molecules is *via* the skin, inhalation (air and dust), and ingestion of contaminated food or water. Reviews on various OPFRs suggested adverse health effects in children, (Doherty et al., 2019) and a range of potential neurotoxicity levels (Hendriks and Westerink, 2015). Exposure to the OPFR tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) inhibited oligodendrocyte maturation *in-vitro* (Cohn et al., 2024). Prolonged exposure of mice led to hippocampus neuronal inflammation and apoptosis, with *in vitro* exposure demonstrating microglial activation and increased gene expression of pro-inflammatory cytokines (Cohn et al., 2024; Zhong et al., 2020). In young children, lower cognitive performance was associated with prenatal exposure to OPEs (measured in maternal urine as the metabolite isopropyl-phenyl phenyl phosphate) (Doherty et al., 2019). A scoping review incorporating nine studies worldwide, associated early life exposure to OPFRs with lower childhood intelligence and higher externalizing behavior (Zhao et al., 2022). A Chinese study in older people correlated lower cognitive function with higher urine concentrations of two OPFR metabolites (out of eight measured) (Zhao et al., 2022).

3.3. Petroleum hydrocarbons

Petroleum hydrocarbons can cross the BBB, inhibit acetylcholinesterase (AChE), alter ion channels, induce oxidative stress and activate microglia and astrocytes (Rajendran et al., 2022). Aromatic hydrocarbons include benzene, toluene, ethylbenzene, and xylene. They are used as petrol, and in the production of many industrial chemicals and products including polymers, insecticides, detergents, and dyes. As summarized in a review, they cause cognitive dysfunction and dementia in the long term; hallucination, reduced impulsive control and reduced motor function in the short term (Rajendran et al., 2022). A review of 30 studies on chronic toluene abusers found consistent abnormal white

matter in brain MRIs, correlating with the level of neuropsychological impairment (Yucel et al., 2008). Past occupational exposure to petroleum hydrocarbons and similar solvents was associated with AD onset (Kukull et al., 1995). In a French study, history of occupational exposure to turpentine and heavy fuels was associated with AD or dementia (Helou and Jaecker, 2014). Similar associations with development of Parkinson's disease (PD) are conflicting (Tsalenchuk et al., 2023).

PAHs are formed by the incomplete combustion of organic matter such as barbeque meat, tobacco, wood, coal, oil, and petrol. Reviews suggest that they promote inflammatory and oxidative stress responses (Pardo et al., 2020; Pardo et al., 2024), mitochondrial dysfunction and epigenetic changes, and are harmful to the nervous system at all stages of life (Xu et al., 2024). They were directly linked to cognitive dysfunction, attention-deficit disorder, olfactory impairment and are associated with decreased cortical thickness (Cho et al., 2023) and reduction in caudate nucleus volume (Rajendran et al., 2022). Longitudinal levels of the urinary PAH metabolites 1-hydroxypyrene, 2-naphthol, and 2-hydroxyfluorene (2-FLUO) correlated with decreased brain cortical thickness, in a pattern that resembles AD-specific cortical atrophy (Cho et al., 2023). Urinary 2- or 3-hydroxyfluorene, and 2-hydroxynaphthalene associated with reduced cognitive performance in older adults (Guan et al., 2024). PHAs can be also inhaled through active and passive smoking. Cigarette smoking is suggested to increase the risk for cognitive impairment and dementia (Livingston et al., 2020; Middleton et al., 2025), and large epidemiological studies associated cigarette smoking markers in urine and serum with decreased performance in cognitive tests (Middleton et al., 2025). Environmental exposure to tobacco smoke (mainly at home) was also associated with a higher risk of dementia and AD in older people who never smoked (Chen, 2012).

3.4. Plasticizers

Plasticizers have been a continuous source of environmental contamination for more than 50 years and have been accumulating in human biofluids and tissues for several years. Awareness is growing about their toxic effects (such as endocrine disruption), and as some plasticizers are phased out of production, the level of exposure is decreasing.

BPA is a precursor for plastic products and can cross the BBB. Reviews in the field suggest that prenatal exposure in animal models affected the developing brain, and triggered AD-related epigenetic changes, hippocampal neuroinflammation and increased NF-κB (Gauvrit et al., 2022). Apart from inducing oxidative stress (Gassman, 2017), BPA also disrupted the dopaminergic neurotransmission *via* pseudo-estrogenic action and epigenetically altered Kcc (K+/Cl cotransporter) gene expression (Rajendran et al., 2022). Such effects may explain observations of behavioral problems in children exposed to BPA earlier in life (Roen et al., 2015; Lim et al., 2017).

Phthalates are plasticizers and known contaminants in food, cosmetics, oils, building materials (vinyl flooring), flexible plastics *etc*. A review on neurotoxicity suggested that they can affect human health *via* brain development, cognitive function, and energy metabolism, while also inhibiting AChE (Yegambaram et al., 2015). Rat exposure to di(2-ethylhexyl)phthalate (DEHP) during gestation and lactation increased Tau phosphorylation and was associated with cognitive dysfunction when the rats aged (Sun et al., 2014). In a similar manner to BPA, prenatal exposure to phthalates was associated with neonatal behavior and children's psychosocial deficits, (Miodovnik et al., 2011; Engel et al., 2009) as well as cognitive development (Berezovsky et al., 2024). Moreover, DEHP metabolites and mono-2-heptyl phthalate (MHPP) detected in the urine of young children correlated with various symptoms of ADHD, most likely driven by children with autism spectrum disorder (ASD) (Oh et al., 2024). In the large American cohort NHANES, DEHP was the leading phthalate associated with insulin resistance (Bai et al., 2022). In the same cohort, lower cognitive performance in people aged 60 and over, was associated with exposure to various phthalates (MECPP, MnBP, MBzP, MCOP, MCPP) (Middleton et al., 2025; Weng et al., 2022).

OPEs are also used as plasticizers and considered serious environmental contaminants that can alter neurodevelopmental processes by inducing lipid peroxidation (Yao et al., 2021) and interfering with noncholinergic pathways at environmentally relevant doses (Patisaul et al., 2021).

3.5. Pesticides

Exposure to pesticides occurs mainly *via* the food chain, dietary ingestion and occupational exposure. The synthetic organic pesticides carbamates, pyrethroids, organophosphates (OP), and organochlorines (OC) are neurotoxic and are associated with cognitive decline, according to multiple reviews. They alter calcium homeostasis, increase oxidative stress and tau phosphorylation (Yegambaram et al., 2015; Torres-Sánchez et al., 2023; Agrawal and Sharma, 2010; Costas-Ferreira and Faro, 2021; Sule et al., 2022) *via* inhibition of protein phosphatase 2A and activation of phospho-glycogen synthase kinase-3β (Yegambaram et al., 2015). In addition to induced CNS damage *via* increased oxidative stress, carbamates and the dipyridyl herbicide paraquat also affect energy metabolism and mitochondrial function (Rajendran et al., 2022; Sule et al., 2022). Paraquat is a persistent soil contaminant that is further utilized by microorganisms as a nitrogen source (Jayaraj et al., 2016). It can also inhibit AChE, induce amyloid beta accumulation (Yegambaram et al., 2015), and is debatably linked to PD (Berry et al., 2010; Tanner et al., 2011; Weed, 2021).

Reviews show that OP pesticides exhibit delayed neurotoxic effects after acute exposure, and potentially contribute to chronic nervous system diseases following prolonged low-level exposure (Sánchez-Santed et al., 2016). Their mechanism of action involves the inhibition of AChE (Singh et al., 2013), in addition to lipid peroxidation (Rajendran et al., 2022) and modulation of inflammation, effects on neurotransmitters, neurotrophic factors, hormones, and amyloid-beta related enzymes (Sánchez-Santed et al., 2016). OCs such as dieldrin (now banned) may cross the BBB owing to their hydrophobicity, inhibit GABA(A) receptors in the brain, inducing hyperexcitation and influx of calcium *via* glutamate receptor channels, exacerbating oxidative and nitrogen stress in the brain (Sule et al., 2022). Postmortem studies found elevated levels of dieldrin in the brains of people with PD, compared to none in controls (Kanthasamy et al., 2005). The OC DDE detected in umbilical cord blood, was linked to risk of lower cognition in 6 year old boys (Barrea et al., 2024). A few epidemiological studies associated occupational/regional exposure to pesticides with risk of cognitive impairment and neurodegenerative conditions (Baldi et al., 2011; Baldi et al., 2003; Dardiotis et al., 2019; Parrón et al., 2011; Singh et al., 2013). A study in older people showed increased risks for all-cause dementia among individuals who reported occupational pesticide-exposure, and associated the risk of AD with OP exposure (Hayden et al., 2010). A Swedish study in older people linked plasma levels of three OCs to the risk of development of cognitive impairment (Lee et al., 2016). A 10-year Canadian study associated the plasma concentrations of two OCs (p,p'-DDT and its metabolite p,p'-DDE) with cognitive decline, but found no association between OCs and their metabolites and the risk of dementia and AD (Medehouenou et al., 2019).

Beyond the direct biochemical and neurological effects of pesticides, a review suggested that their ingestion also modifies the gut microbiota and expands their health impact, with specific implications for neurodegenerative diseases (Ghosh et al., 2024).

The plant-based glyphosate herbicides are an emerging health concern. Like other pesticides, a review suggests that they may induce oxidative stress, promote inflammation and cellular damage, potentially *via* disruption of ion channel activity (de Batista et al., 2023). A scoping review, utilizing mainly animal studies, associated exposure with alteration in gut microbiota, and with neurological disorders (AD, PD, ASD, seizures) (Hutchins and Compton, 2024).

3.6. Antimicrobial agents

The exposure to antimicrobial agents occurs mainly *via* the skin and through ingestion.

Para-hydroxy benzoic acid esters (Parabens) are used as antimicrobial preservatives in a wide range of personal hygiene products, cosmetics, pharmaceuticals and also in food. Besides their potential for endocrine disruption, environmental concerns about parabens are partly due to the potency of their toxic degradation products in wastewater (chlorinated parabens; para-hydroxybenzoic acid). In a rat model of autism, butylparaben exposure caused disturbed energy production, mitochondrial dysfunction, neuroinflammation and oxidative stress (Hegazy et al., 2015). In a Chinese study, prenatal exposure to benzophenones and parabens (measured as metabolites in mothers' urine) was associated with lower neurodevelopment in two-year-old children, in a sex-dependent manner (Jiang et al., 2019).

Triclocarban (TCC) and triclosan (TCS) are antimicrobial agents used in personal hygiene products and recognized as contaminants of emerging concern. They are structurally similar to PCBs. They are also endocrine-disrupting, and may affect fatty acid synthesis (Yegambaram et al., 2015) and neurodevelopment (Jackson-Browne et al., 2018). A recent review describes their distribution, activity and epidemiological outcomes (Zhang and Lu, 2023). Epigenetic alterations were recorded in mice and neuron cells exposed to TCC (Kajta et al., 2020; Kajta et al., 2019; Wnuk et al., 2021). Reviews on TCS detail its numerous biological effects (Yueh and Tukey, 2016), while its suspected neurotoxicity (Ruszkiewicz et al., 2017) was linked to induced oxidative stress and disruption of an array of relevant genes (Pullaguri et al., 2023). TCS inhibited AChE *in vitro* by direct binding, (Pullaguri et al., 2023) and disrupted calcium homeostasis (Alfhili and Lee, 2019) via its effect on ryanodine receptors (RyRs) (Yegambaram et al., 2015). Perinatal mice exposure to TCS resulted in compromised neurodevelopment, expressed as cognitive impairment and abnormal social behaviors (Pullaguri et al., 2023). In humans, TCS levels in mother's urine at delivery (but not earlier) were associated with child's lower cognitive performance at age 8 (Jackson-Browne et al., 2018; Jackson-Browne et al., 2020); gestational and childhood urinary triclosan associated with behavioral symptoms at age 8 in boys only (Jackson-Browne et al., 2019).

Quaternary ammonium and phosphonium compounds are used as antimicrobials in disinfecting products and personal care products. *In vitro*, they showed selective cytotoxicity to developing oligodendrocytes (Cohn et al., 2024).

3.7. Airborne particulate matter and inorganic gases

Air pollution contains particulate matter (PM) composed of chemical and biological elements, originating in various emissions such as biomass burning and combustion (that produces PAHs *etc.*), and friction-derived nanoparticles (Arias-Pérez et al., 2020; Calderón-Garcidueñas et al., 2019). PM can reach the brain *via* the olfactory system or *via* the blood and BBB following systemic absorption (You et al., 2022). Biomass burning, for example, also releases gas consisting of nitrogen oxides, sulfur dioxide, ammonia and ozone, apart from carbon oxides and methane (Pardo et al., 2024). A systematic review investigating 13 longitudinal studies on air pollutants found consistent associations between cognitive decline and exposure to particulate matter (PM up to 2.5 μm or 10 μm), nitrogen dioxide, and ozone (Peters et al., 2019). For the latter gasses, however, there are conflicting results with brain MRI measurements (UK Biobank, US ARIC, and other large cohorts) (Lynch et al., 2024). Exposure to airborne particulate matter (up to 2.5 μm) was associated with higher risk of dementia and AD in meta-analysis of four large cohorts (Taiwan (Jung et al., 2015), Canada (Chen et al., 2017), US (Kioumourtzoglou et al., 2016), UK (Carey et al., 2018); total $n > 12$ million) (Tsai et al., 2019). High exposure to PM2.5 in air pollution was also associated with increased amyloid-beta brain deposits in older people with MCI or dementia (Iaccarino et al., 2021). PM and industrial nanoparticles were linked to brain pathology and increased risk of neurodegenerative diseases in children and young adults living in air-polluted urban areas (Calderón-Garcidueñas et al., 2019; Calderon-Garciduenas and de la Monte, 2017; Calderón-Garcidueñas et al., 2024). According to reviews of the knowledge in the field, PM may promote AD *via* oxidative stress, microglial activation and inflammation, mitochondrial damage, disrupted BBB, increased cellular calcium levels, enhanced excitatory synaptic transmission, alteration in neurotransmitters, dysbiosis, reduction of DNA methylation (Sakowski et al., 2024; Yegambaram et al., 2015; Arias-Pérez et al., 2020; You et al., 2022; Calderon-Garciduenas et al., 2020; Calderon-Garciduenas et al., 2008; Hou et al., 2010; Shou et al., 2019), and possibly through the suppression of glymphatic waste clearance (Hussain et al., 2023.1.). The similarity to the neurotoxic effects of chemically-varied industrial pollutants and pesticides has led some researchers to suggest that the accumulated exposure (rather than a specific chemical effect) dictates the extent of neuroinflammation and the deleterious effects on the brain (Sarrouilhe et al., 2021). Causality, however, is still to be proven beyond mere association.

3.8. Metals

Environmental exposure to various metals can originate in industry, transportation, waste *etc.* and is delivered *via* the air, water, transported from soil into plants and the rest of the food chain (Babić Leko et al., 2023). Metals can also appear at trace levels in highly regulated products such as pharmaceuticals and dental fillings (mercury) (Huat et al., 2019), or (partially regulated) personal care products. The metals can be absorbed and reach the bloodstream *via* ingestion, inhalation or skin exposure (Bakulski et al., 2020). Multiple reviews indicate that in the gut, they can cause dysbiosis due to their toxicity to beneficial microbes and reduction in diversity (Bist and Choudhary, 2022; Duan et al., 2020; Kaur and Rawal, 2023; Porru et al., 2024; Tizabi et al., 2023). While lead, cadmium, arsenic, and mercury are carried in the blood (*e.g.*, bound to erythrocytes) and cross the BBB, they can also reach the brain directly *via* the olfactory system. Aluminum is possibly able to cross bound to blood carriers such as citrate and transferrin (Van Ginkel et al., 1990). Metallic nanoparticles have even higher odds to cross the BBB (Lyon et al., 2024). Generally, non-essential metals compete with essential trace metals (Zn, Mn, Fe, Cu, Ca, *etc.*) for their binding sites on proteins, thus altering the physiological activity of these proteins (Huat et al., 2019; Hille, 2002). According to reviews in the field, heavy metals are carcinogenic and detrimental to neurodevelopment, inducing epigenetic alterations *via* disruption of DNA or RNA methylation, and histone modification (Porru et al., 2024; Yu et al., 2024). The leading toxic metals investigated in relation to neurodegenerative diseases are lead, cadmium, mercury, arsenic and aluminium (Babić Leko et al., 2023; Bakulski et al., 2020; Schymanski et al., 2019; Frisardi et al., 2010; Flaten, 2001). These toxic metals have been implicated, to varying degrees, with AD pathogenesis including amyloid beta accumulation, tau pathology, oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity endothelial and BBB damage, and neuronal apoptosis (Gauvrit et al., 2022; Babić Leko et al., 2023; Huat et al., 2019; Yu et al., 2024; Paglia et al., 2016; Breijyeh and Karaman, 2020; Colomina and Peris-Sampedro, 2017; Ariafar et al., 2023; Deng et al., 2023; Mutter et al., 2004; Rahman et al., 2020; Zheng et al., 2003). Toxic metals were also linked to hyperhomocysteinemia, a known biomarker for the risk of dementia (Lyon et al., 2024). In addition to the above damaging processes, reviews mention that lead modifies neuronal differentiation, myelination and synaptogenesis, and affects neurotransmitters (Huat et al., 2019). Cadmium replaces zinc in enzymes, it disrupts the cation homeostasis in cells (Babić Leko et al., 2023). Aluminum affects the expression of iron-binding proteins, dysregulates iron-modulated signaling pathways and increases oxidative stress *via* iron lipid peroxidation (Huat et al., 2019). The drug Deferoxamine, an aluminum chelator, attenuates cognitive decline in AD patients (Yokel,

1994). Associations between toxic metals and cognitive impairment or increased risk of AD are mostly based on studies in aging populations (Wang et al., 2022; Min and Min, 2016; Peng et al., 2017; Yang et al., 2018), chronic exposure in the workplace (Viaene et al., 2000; Schwartz et al., 2000; Jordan et al., 1990), or animal models (Porru et al., 2024) utilizing acute or chronic exposure.

Many studies on environmental pollutants focus on neurodevelopment, and some suggest that exposure to toxic metals in early life (Gauvrit et al., 2022) or even in adulthood contributes to cognitive decline and neurodegenerative diseases later in life (Huat et al., 2019). Epidemiological studies in the NHANES cohort have associated higher blood cadmium levels with lower cognitive function (Min and Min, 2016; Wu et al., 2024) and an elevated risk of AD mortality within 7–13 years. This has been partly replicated utilizing urine measurements (Peng et al., 2017), although with a higher (occupational) exposure, urine levels associated with worse cognitive function (Viaene et al., 2000). Tungsten, a less-toxic yet still bioactive metal, was linked not only to memory deficits following chronic work-exposure (Jordan et al., 1990), but in the NHANES study, urinary levels correlated with lower cognition (Middleton et al., 2025). A recent systematic review examined the potential link between AD, exposure to heavy metals and disturbed homeostasis of essential trace metals (Babić Leko et al., 2023). This review revealed a high degree of variability between studies, thus recommending further research in diverse large cohorts, employing advanced analytical approaches on various biospecimens. Negative confounders may explain some of the mixed results. For example, better cognition despite the exposure to metal contaminants through the consumption of fish, may be explained by the fact that fish contain neuro-protecting compounds such as omega-3 PUFA (Sasaki et al., 2024).

The essential trace metals, including copper, iron, zinc, molybdenum and manganese, are involved in biochemical regulation (also of neurotransmitter receptors), act as cofactors and are bound to many enzymes. As such, they are part of the dietary and nutraceuticals recommended for general well-being and for improved cognition. However, it is not rare to see excessive levels in the circulation, for example copper and iron in people with MCI and dementia (Lyon et al., 2024). Unabsorbed iron in the gut causes inflammation and dysbiosis (Stoffel et al., 2020) as it supports iron-scavenging pathogenic bacteria (Zmora et al., 2019). Despite their role in homeostatic control, reviews point out that excessive levels of essential metals in the brain can induce misfolding of proteins, oxidative stress (lipid peroxidation) and activation of pro-inflammatory agents. These can affect mitochondrial function and neurotransmitter metabolism, leading to cognitive disturbances (Yu et al., 2024; Brewer, 2009; Altamura and Muckenthaler, 2009). More specifically, copper, which has two binding sites in the amyloid precursor protein (APP) (Huat et al., 2019), was shown to exacerbate amyloid beta-induced neurotoxicity in a mouse model, *via* enhanced TNF-mediated inflammation (Lu et al., 2009). In brains of people with AD compared to control, total copper content was not elevated, however the redox-active exchangeable copper was proportionally higher and correlated with increased oxidative damage and with AD neuropathology (James et al., 2012). Conflicting evidence also link copper exposure to higher risk of developing PD (Tsalenchuk et al., 2023). Zinc, having its highest body content in the brain, can at excess be neurotoxic based on animal models, promoting amyloid beta aggregation, Tau phosphorylation and neurofibrillary tangles (NFTs) (Huat et al., 2019). Excessive manganese is considered neurotoxic potentially *via* epigenetic mechanisms (Yu et al., 2024), and was linked to developmental as well as neurodegenerative disorders involving basal ganglia dysfunction, such as PD and Huntington's disease (Tsalenchuk et al., 2023; Huat et al., 2019; Kwakye et al., 2015). Nevertheless, circulating manganese levels were decreased in the serum of people with AD compared to healthy people, while molybdenum levels were higher in AD (Paglia et al., 2016).

3.9. Food chemicals and drugs

Apart from the plethora of natural products in food, an array of potentially harmful compounds are formed during food preparation, especially under high temperature and in processed food. During baking, roasting or frying of high-fat and high-sugar foods, excessive heat induces a series of non-enzymatic reactions between reducing sugars, proteins (specifically Lys or Arg residues), lipids, or DNA (Stinghen et al., 2016). The resulting compounds, either in freshly cooked food or in packaged food (Khan et al., 2023), are called advanced glycation end-products (AGEs). AGEs can also be formed endogenously or even by gut microbiota. These metabolites affect the gut microbial profile, induce oxidative stress, promote inflammation, accumulate in the blood of people with kidney disease (Stinghen et al., 2016), increase with aging, and are linked to various health conditions (Twarda-Clapa et al., 2022). Higher dietary intake of AGEs in non-demented older people was associated with accelerated cognitive decline (Schnaider Beeri et al., 2022; Cai et al., 2014). An example of an AGE is N6-carboxymethyllysine (CML), which weakens the intestinal barrier, its deposition causes dysbiosis and increases oxidative stress. In reviews, animal models of dietary CML and other AGEs showed association with inflammatory response, however there is less evidence in humans (Kellow and Coughlan, 2015; Uribarri et al., Jun 2005). In a mice model, CML crossed the BBB, accumulated in microglia from the brains of aged mice, mediated increased ROS and mitochondrial dysfunction (Mossad et al., 2022). Another common AGE product is acrylamide, which acts as a neurotoxin possibly due to several activities. Exposure in rats impaired the blood-CSF barrier function, and such reduced transport and secretion can lead to neuropathy (Yao et al., 2014). Reviews also suggest that acrylamide impacts nerve terminals and may inhibit neurotransmission *via* disruption of the presynaptic nitric oxide signaling (Lopachin and Gavin, 2008). As neuronal oxidative stress is one factor in neurodegenerative diseases, acrylamide may contribute to AD (LoPachin and Gavin, 2012). Other intermediates in the heat-derived oxidation of sugar and lipid (specifically PUFA), are reactive carbonyls such as glyoxal, malondialdehyde, acrolein, hydroxynonenal, deoxyglucosone, and glyceraldehyde, which can also be formed endogenously *via* glycolysis (Twarda-Clapa et al., 2022; Negre-Salvayre et al., 2008). The reactive carbonyls increase the "carbonyl stress", bind to proteins and nucleic acids with detrimental cell and tissue effects. A review highlights malondialdehyde and 4-hydroxynonenal as especially potent, implicated with aging-related disorders and neurodegeneration (Barrera et al., 2018). Reactive carbonyls that react with free amino acids or proteins yield advanced lipid-peroxidation end-products (ALEs), which are also suggested to be involved in inflammation and neurodegeneration (Negre-Salvayre et al., 2008).

A systematic scoping review about alcohol and dementia linked higher risk of dementia and cognitive decline to high chronic consumption of alcoholic beverages (over 14 drinks per week) (Rehm et al., 2019). In contrast, meta analysis of 13 studies concluded that low-to-moderate consumption (especially of wine) is associated with lower risk of AD, likely owing to the content of beneficial natural products in wine (Rehm et al., 2019; Xie and Feng, 2022). The negative health effects of ethanol include oxidative and nitrogen stress. Ethanol also affects the vascular actions of nitrogen oxide derived from endothelial and neuronal NOS activity (Toda and Ayajiki, 2010). *In vitro*, ethanol exposure enhanced amyloid beta-induced neuronal cell death by increasing ROS and mitochondrial dysfunction (Lee et al., 2008). Similar neurotoxic effects were recorded in chronic use of recreational drugs such as the potent CNS stimulant methamphetamine (also used as a second-line treatment for attention deficit hyperactivity disorder, depression and obesity). Despite this link to premature AD and neurodegeneration following chronic abuse, reviews mentioned methamphetamine as a potential therapeutic drug for AD, providing it involved a personalized and well-controlled treatment plan (Shrestha et al., 2022; Shukla and Vincent, 2020).

Exposure to non-psychoactive or neurological pharmaceuticals may also affect the risk of dementia and AD. An example of a potentially harmful drug is methotrexate (MTX), a folic acid antagonist that inhibits the synthesis of nucleic acids methionine, and used in chemotherapy and as an immuno-suppressant drug in auto-immune diseases. Probably since folate and methionine are essential for sphingomyelin synthesis and myelination of neurons, treatment of primary CNS lymphoma patients with MTX-based chemotherapy increased the risk of changes in CNS white matter and death from leukoencephalopathy (Lai et al., 2004; Linnebank et al., 2005).

Analysis of records from over 100000 people with rheumatoid arthritis, revealed that treatment with hydroxychloroquine associated with lower risk of incident AD compared to treatment with MTX (Varma et al., 2023). In a mouse model of AD, hydroxychloroquine reversed impaired synaptic plasticity (Varma et al., 2023). In cell culture, the same drug prevented common AD phenotypes (neuroinflammation, tau phosphorylation, amyloid beta proliferation) (Varma et al., 2023). In AD-relevant cell lines, hydroxychloroquine blocked the phosphorylation of STAT3, preventing its activation which is associated with neuroinflammation and AD (Varma et al., 2023).

The search for neurodegenerative disease drug targets is an ongoing effort and its review is not within the scope of this paper.

4. Collaborative initiatives in AD exposomics

It has become increasingly clear that the genome, gut microbiome, diet, lifestyle, socioeconomic status, and environmental exposures all affect an individual's metabolic state, contributing to brain health and brain disease. Our Alzheimer's Disease Metabolomics Consortium (ADMC), part of the Accelerating Medicines Partnership for AD (AMP-AD) and in partnership with AD Neuroimaging Initiative (ADNI), has applied state-of-the-art metabolomics and lipidomics technologies along with genomic and imaging data to map metabolic failures across the trajectory of the disease (MahmoudianDehkordi et al., 2019; Nho et al., 2019; Arnold et al., 2024; Arnold et al., 2020; Baloni et al., 2022; Baloni et al., 2020; Barupal et al., 2019; Batra et al., 2023; Batra et al., 2023; Bernath et al., 2020; Horgusluoglu et al., 2022; Huynh et al., 2020; Kling et al., 2020; Nho et al., 2019; St John-Williams et al., 2017; Toledo et al., 2017; Liu et al., 2022). Our studies confirmed that peripheral metabolic changes influenced by the exposome inform about cognitive changes, brain imaging changes, and Amyloid-Tau-Neurodegeneration (ATN) markers for disease. These data have confirmed that peripheral and central changes in the brain are connected, in part through the metabolome. We replicated ADNI findings in Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL), Rotterdam Study, and UK Biobank studies, defined metabolic differences between men and women with AD, (Arnold et al., 2020) developed an initial brain metabolome for AD (Batra et al., 2023) and defined lipidomic signatures that off insights about the mechanism of APOE ε2 resilience for AD (Wang et al., 2022). This rich metabolomics data generated all pointed to an important role for the exposome in AD pathogenesis. In addition, a major role for the exposome was noted in the development of neuropsychiatric symptoms, including depression and anxiety which are commonly noted in AD patients. The exposome could regulate common biochemical processes implicated in cognition and in mood changes. The Alzheimer Gut Microbiome Project that we lead in partnership with ten ADRCs and multiple diet and lifestyle intervention studies (POINTER, MIND, BEAT-AD, BEAM, TDAD) aims to define the influences of gut microbiome and the gut-brain axis in AD adding influences of diet chemical exposome, drugs as other components of the exposome including socioeconomic influences. In addition, and along with five centers of excellence in metabolomics we have started to build research infrastructure that will lead to the creation of a first molecular atlas for AD that captures influences of the exposome with the metabolome as a readout enabled through a partnership with Sage Bionetworks, for secure and rapid sharing of all exposome data collected. Big data from AD and community studies including ADNI AIBL Rotterdam, Framingham Heart Study (FHS) and the UK Biobank will be used to define the interconnected influences of chemical exposome on brain metabolic health and cognitive function.

Our team has built the most comprehensive national databases for exposome influences to date, including the Human Metabolome Database (HMDB), the Food Components Database (FooDB), the Drug Components Database (DrugBank), the Gut Microbiome Metabolome Database (MiMeDB), and other databases linking dietary exposures with AD signatures using metadata-driven reference data analysis from over 3,600 foods (FoodOmics). This is the first time these databases will be used in combination, on a specific study. Through our NIA initiatives, we have made thousands of metabolomics measurements from AD patients publicly available through an open science model and collaboration with Sage Bionetworks under the AMP-AD program. Our AD metabolic signatures will be linked to the large databases we are building to learn about influences of chemical exposures, diet and lifestyle as well as the genome on these metabolic changes. Specifically, we intend to identify chemical exposure signatures in the blood and target brain regions that correlate with cognitive changes and AD biomarkers (blood, CSF, neuroimaging ATN) across an existing collaborative network of large AD-relevant cohort studies. By leveraging targeted and untargeted metabolomic and lipidomic platforms, this project will provide the first comprehensive metabolomic profile of exposome factors linked to AD. The significance of this work is being enhanced by leveraging big data from a number of large established clinical cohorts (10 ADRCs, ADNI) and epidemiological and community-based studies (FHS, ROSMAP, UK Biobank). With an experienced team and unparalleled resources, this project is well positioned to provide the AD research community with publicly available big data resources needed to evaluate exposome effects on brain metabolic health and dysfunctions relevant to AD.

5. NIA funded initiatives with major focus on the exposome and brain health

The NIA seeks to expand our understanding of how comprehensive set of exposures across domains (*e.g.*, physical, chemical, social, psychological, economic) that constitute the "exposome" shape health and risk for disease, especially AD and Alzheimer's disease-related dementias (ADRD). The NIA has a growing grant portfolio on environmental health and is conducting research to address disparities in AD/ADRD research, including the social and contextual factors that contribute to increased AD risk, as well as to understand the underlying mechanisms linking exposures and AD risk by using experimental models. In 2022, the NIA issued a NOT-AG-22–022: *Notice of Special Interest (NOSI) for Administrative* Supp*lements to Support Research Infrastructure on Exposome Studies in Alzheimer's Disease (AD) and AD-Related Dementias (ADRD)*. Sixteen projects were funded under this NOSI, some of which are highlighted below.

1. Enhance research on air pollution and AD/ADRD.
2. Establish infrastructure to study the effect of life-course exposures such as residential histories on AD/ADRD health outcomes (Expo-AD).
3. Increase the usability of exposome-related data from the Framingham Heart Study (FHS) such as diet, exercise, and medication use for research on brain aging and dementia.
4. Enhance the data infrastructure for understanding connections between the exposome, gut microbiome, and metabolome.
5. Add exposome measures to large, population-based longitudinal studies such as the Health and Retirement Study (HRS) and international family of studies, National Longitudinal Study of Adolescent to Adult Health, as well as other NIA-supported studies.

New funding within the NIA portfolio will highlight NIA's strategic research framework for addressing the burden of AD/ADRD, including

health disparities in AD/ADRD, centered around a precision medicine approach to treatment and prevention. To this end, the NIA developed a series of funding initiatives that aim to enable a precision environmental health approach to AD/ADRD risk reduction and disease prevention. These new programs leverage the NIA's long-standing investment in population studies, social and behavioral sciences, genetics, epigenomics, metabolomics, systems biology, and translational/data infrastructure, and expand the NIA's collaboration with the National Institute on Environmental Health Sciences (NIEHS). The programs will operate under open-science principles, to maximize their translational impact.

Three components enable this rich exposome initiative under NIA-with complimentary focus areas on human studies, animal models and model systems and invitro. These include:

RFA-AG-24–011: Research Coordinating Center on the Exposome and Alzheimer's Disease and Related Dementias: Elucidating the Role of Social and Behavioral Determinants of Health. This initiative seeks to establish a national coordination network to act as a centralized hub for accessing, harmonizing, linking, and sharing environmental contextual data and individual exposure data with NIA/NIH-funded projects that hold potential for advancing our understanding of the links between life course exposures and Alzheimer's and related dementias risk and resilience, and disparities across populations.

RFA-AG-24–021: Understanding Gene-Environment Interactions in Brain Aging and AD/ADRD. The objective of this initiative is to stimulate research to gain mechanistic insights into GxE interactions in response to environmental toxicants using human cell-based models.

RFA-AG-24–022: Quantifying the Impact of Environmental Toxicants on Alzheimer's Disease and Related Dementias Risk in Cohort Studies. This initiative aims to aims to do the following:

Enrich existing longitudinal cohorts with measures of exposures to individual toxicants or combinations of toxicants and/or multi-omics molecular profiling that reflects the body's response to exposure(s); Support the development of multi-disciplinary teams needed for the rigorous measurement and assessment of environmental exposures at the population level; Create an environmental epidemiology consortium to facilitate rapid and broad data sharing, harmonization, and integration of complex exposure data across multiple studies to enhance the opportunity for data pooling and data integration for various meta-analyses and/or comparative analyses.

RFA-AG-24–023: Preclinical Studies to Characterize the Impact of Toxicants on Brain Aging and AD/ADRD. The goal of this initiative is to examine the consequences of early and mid-life exposure on late life brain health, including the impact of genetic diversity and sex differences on exposure-related AD/ADRD outcomes across brain and peripheral tissues.

Taken together, these collaborative teams and their adoption of an open science model where data is shared in real time will accelerate our understanding of the role of exposome in AD.

6. Conclusions

While most studies to date have focused on the brain and cerebrospinal fluid to define mechanisms of CNS diseases, it has become increasingly clear that the genome, gut microbiome, diet, lifestyle, socioeconomic status, and environmental exposures affect an individual's metabolic state, including the brain, contributing to the development of neuropsychiatric diseases. The molecular mapping of these influences and their interconnections and the creation of powerful databases and atlases that captures their effects brings the promise to transform our understanding of these brain diseases along with novel therapeutic approaches to treat them.

CRediT authorship contribution statement

Matej Orešič: Writing – review & editing, Writing – original draft, Conceptualization. **Naama Karu:** Writing – review & editing, Writing – original draft, Visualization. **Haoqi Nina Zhao:** Writing – review & editing, Writing – original draft. **Arthur Moseley:** Writing – review & editing. **Thomas Hankemeier:** Writing – review & editing. **David S. Wishart:** Writing – review & editing, Writing – original draft. **Pieter C. Dorrestein:** Writing – review & editing, Writing – original draft. **Oliver Fiehn:** Writing – review & editing, Writing – original draft. **Tuulia Hyötyläinen:** Writing – review & editing, Writing – original draft, Visualization. **Rima Kaddurah Daouk:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rima Kaddurah-Daouk reports financial support was provided by National Institutes of Health. Rima Kaddurah-Daouk reports a relationship with Metabolon Inc that includes: equity or stocks. Rima Kaddurah-Daouk reports a relationship with Chymia LLC that includes: equity or stocks. Pieter C. Dorrestein reports a relationship with Cybele that includes: equity or stocks. Pieter C. Dorrestein reports a relationship with Sirenas that includes: equity or stocks. Pieter C. Dorrestein reports a relationship with Ometa that includes: equity or stocks. Pieter C. Dorrestein reports a relationship with Enveda that includes: equity or stocks. Pieter C. Dorrestein reports a relationship with Arome that includes: equity or stocks. Pieter C. Dorrestein reports a relationship with DSM animal health that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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A listing of AGMP Investigators can be found at https://alzheimergut.org/meet-the-team/.

A complete listing of ADMC investigators can be found at: https://sites.duke.edu/adnimetab/team/.

Declaration of conflicts of interest.

Dr. Kaddurah-Daouk in an inventor on a series of patents on use of metabolomics for the diagnosis and treatment of CNS diseases and holds equity in Metabolon Inc., Chymia LLC and PsyProtix. PCD is an advisor and holds equity in Cybele and Sirenas and a Scientific co-founder, advisor and holds equity to Ometa, Enveda, and Arome with prior approval by UC-San Diego. PCD also consulted for DSM animal health in 2023.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109741.

Data availability

No data was used for the research described in the article.

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