Received: 18 December 2024 | Revised: 31 March 2025 | Accepted: 7 April 2025

DOI: 10.1002/alz.70226

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

PERSPECTIVE

# The role of per- and polyfluoroalkyl substances in cognitive impairment and dementia

**Hannah Gardener**[1] | **Bonnie Levin**[1] | **Kurunthachalam Kannan**[2] | **Tatjana Rundek**[1]

[1]Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida, USA

[2]Wadsworth Center, New York State Department of Health, Empire State Plaza, Albany, New York, USA

**Correspondence**
Hannah Gardener, University of Miami Miller School of Medicine, Department of Neurology, 1120 NW 14th St, Miami, FL 33136, USA.
Email: hgardener@med.miami.edu

**Funding information**
National Institute on Aging, Grant/Award Number: R01AG086393

## Abstract

Per- and polyfluoroalkyl substances (PFAS) are ubiquitous persistent organic pollutants. The neurotoxic and cardiometabolic effects of PFAS are well documented, leading to the hypothesis that exposure increases dementia risk. However, empirical data on PFAS in relation to cognitive impairment and dementia are weak, limited, and inconsistent. This report reviews the literature on PFAS and cognitive impairment and provides a rationale and overview of the PFAS VascCog Longitudinal Study, a new study using the population-based Northern Manhattan Study cohort, to prospectively examine serum concentrations of 13 PFAS in relation to lipids, carotid atherosclerosis, cognitive impairment, and dementia. We hypothesize that PFAS deleteriously impact cognition through a pathway involving hyperlipidemia and atherosclerosis. Rigorous examination of PFAS exposure in relation to dementia is needed to inform public health policies on PFAS-containing products, support regulations to reduce community exposure, and provide new avenues to protect cognitive health and impact dementia at the individual and community levels.

**KEYWORDS**
cognitive impairment, cohort studies, dementia, environmental toxins, epidemiology, per- and polyfluoroalkyl substances, persistent organic pollutants

## Highlights

- PFAS exposure increases cardiometabolic risk factors and neurotoxicity.
- Data on PFAS in relation to cognitive health is limited, weak, and controversial.
- We hypothesize that PFAS exposure increases dementia risk.
- We hypothesize a mechanistic pathway involving hyperlipidemia and atherosclerosis.
- Rigorous study of PFAS exposure and dementia risk can inform public health policy.

## 1 | BACKGROUND

Lifestyle intervention strategies to prevent or delay cognitive decline have mainly focused on modifying cardiometabolic risk factors, which have demonstrated modest success, underscoring the need to identify more modifiable targets.[1] Examining causal environmental toxicants offers an opportunity to study a class of contaminants that have been linked to a host of negative health outcomes, which include cognition,

and offers an opportunity to inform effective interventions at the individual and community level.[2] Specifically, persistent organic pollutants (POPs) represent modifiable environmental toxicants, characterized by stability and persistence in the environment, bioaccumulation in living organisms, and expansive distribution.[3] A rapidly growing body of literature has shown that POPs exert broad adverse health impacts, including disrupted cardiometabolic function, delayed or abnormal neurodevelopment, and diminished childhood cognition.[4–6] Per- and polyfluoroalkyl substances (PFAS) are a class of artificial POPs, characterized by a backbone of a chain of carbon atoms bonded to fluorine atoms, sometimes with a functional group at the end of the carbon chain. The exceptional stability of PFAS is attributed to the strength of the carbon–fluorine bonds and makes PFAS resistant to heat, chemical, and biological degradation. It is for this reason that PFAS have become commonly referred to as forever chemicals, referring to their remarkable resistance to degradation in the environment. PFAS vary by the length of their carbon backbone, and non-polymeric PFAS have been commonly divided into categories based on chain length. Long-chain PFAS (e.g., perfluorooctane sulfonate [PFOS] and perfluorooctanoic acid [PFOA]) include perfluoroalkyl sulfonic acids with six or more carbon atoms and perfluoroalkyl carboxylic acids with seven or more carbon atoms, and are often referred to as legacy compounds. Short-chain PFAS (e.g., GenX) were largely developed as alternatives due to rising concerns about the environmental health impacts of the long-chain PFAS, although both are highly persistent in the environment. The goal of this manuscript is to review the current state of research exploring the potential deleterious impacts of PFAS exposure on cognitive health, a pressing environmental issue that has not received sufficient attention, and introduce a newly funded study that will address this looming health threat.

## 1.1 | PFAS: Environmental sources

PFAS were developed over 70 years ago and added to commercial products to make them stain, water, and grease/oil resistant. PFAS were intentionally added to a wide range of consumer products, including furniture, cookware, home décor, carpet, clothing, outdoor gear, personal care products, dental floss, contact lenses, medical devices, car interiors, stains/sealants, luggage, baby gear, sanitary products, cleaning products, pesticides, artificial turf, and food packaging/wrappers. PFAS are also intentionally added to certain types of firefighting foam (aqueous film-forming foam) commonly used to treat fires at military sites, airports, chemical plants, and other locations, resulting in widespread ground contamination near those sites. The persistent nature of PFAS, which are resistant to degradation, widely used in consumer products and firefighting foams, commonly produced and used, and discharged at industrial sites, has therefore resulted in significant pervasive PFAS contamination in soil, water, air, and food. PFAS can enter the environment through manufacturing, use, emissions, spills, and disposal, which then lead to contamination of soil, water, air, and uptake by plants, followed by consumption by animals and humans.[7] Soil contamination is particularly high around waste disposal sites, manufacturing facilities, military facilities, and airports. A recent study by the US Geological Survey National Water Quality Program predicted PFAS occurrence prior to treatment in groundwater at the depths of drinking-water supplies across the conterminous United States. Their model estimates that 71 to 95 million people in the United States use drinking water derived from groundwater with detectable concentrations of PFAS, corresponding to approximately 20% of the US population.[8] The concentrations of PFAS in groundwater and drinking water vary widely across the country. However, it is important to note that bottled water is also frequently and similarly contaminated with PFAS. Dietary sources of PFAS are many and varied, with seafood, animal products, and particularly processed foods contributing to PFAS exposure.[9,10]

## 1.2 | PFAS: Human exposure

Humans are exposed to PFAS through ingestion (e.g., through food, water, cookware coating, dental floss, dust, microplastics), inhalation, and dermal contact (e.g., personal care products, makeup, clothing, carpet, furniture, cars, artificial turf). PFAS are both hydrophilic and hydrophobic and, unlike some POPs, do not accumulate in adipose tissue, but instead bind to proteins and accumulate in other organs.[11] Following exposure, PFAS are distributed throughout the body, accumulating in the liver, brain, kidneys, blood, bones, and lungs. The liver is the organ with the most substantial burden of PFAS accumulation, but there is also experimental evidence for high levels of accumulation in the brain and, in particular, the brainstem, thalamus, cerebellum, and hypothalamus.[7] PFAS are not readily metabolized, with excretion through urine occurring at a very slow rate, and bioaccumulate and persist in human bodies, with typical half-lives of several years, but ranging from days to decades depending on the compound.[11] Notably, long-chain PFAS have reduced renal clearance and longer half-lives in the body, leading to greater concern about their health impacts. PFAS molecular weight and chain length and the presence of functional groups all play a role in the accumulation and excretion rate.[7]

US National Health and Nutrition Examination Survey (NHANES) data show that 100% of the US population has detectable levels of some PFAS in serum.[12] In fact, NHANES data show that detectable levels of multiple PFAS are pervasive in human serum, regardless of age, sex, race, and ethnicity. NHANES data have been used to evaluate trends in five of the most common PFAS (PFOS, PFOA, PFHxS, perfluorodecanoic acid [PFDA], and perfluorononanoic acid [PFNA]) since 1999 to estimate the distribution in the general population.[13] The two PFAS with the highest serum concentrations are the legacy compounds PFOA and PFOS, but they are also the two whose concentrations have markedly declined over time. PFOS levels dramatically declined between 1999 and 2013, as it was phased out of production and use in the United States in 2002. PFOA levels declined later, starting around 2008, as US manufacturers eliminated PFOA emissions and product content in 2015. These legacy PFAS have been primarily replaced with alternative PFAS, which have remained largely detectable in human

serum based on NHANES data from 1999 to 2018. In fact, since 2016, serum concentrations of PFDA, PFOA, and PFHxS have increased in at least one racial/ethnic group.[13] NHANES data have also shown some differences in PFAS concentrations across the population by age, sex, race, and ethnicity. Overall, PFAS concentrations were higher in adults compared to teenagers, and males compared to females.[13] Race and ethnic associations varied somewhat across specific PFAS and over time, but PFOA and PFOS concentrations in recent years have tended to be higher in Asian and non-Hispanic White populations, followed by non-Hispanic Black populations, compared to Hispanics.[13] PFAS exposure is a worldwide health threat, and data on exposure burden and associated health effects have also come from many regions outside of the United States.[14–16] Studies have shown both ubiquitous exposure and geographic variability in PFAS burden within the United States and globally.[15,17]

## 1.3 | PFAS: Health outcomes

The established health impacts of PFAS exposure are many. Increased PFAS exposure is associated with an increased risk of various cancers (including kidney, testicular and prostate cancers), liver damage (e.g., elevated liver enzymes and fatty liver disease), reproductive effects (e.g., decreased fertility and preeclampsia), immune system dysfunction (e.g., reduced vaccine response and higher infection rates), and developmental effects from in utero exposure (e.g., low birthweight, developmental delays, neurodevelopmental disorders, accelerated puberty, behavioral problems).[7,18] PFAS exposure has also been hypothesized to increase the risk of dementia, but the evidence is lacking.[19,20]

### 1.3.1 | Neurotoxicty

The molecular mechanisms of toxicity support both direct and indirect routes of PFAS neurotoxicity. PFAS are believed to cross and impair the blood–brain barrier and accumulate in the brain, where they can directly impact neuronal function, disrupting neurotransmitters, neural cell proliferation and differentiation, calcium homeostasis and signaling, synaptogenesis, and plasticity.[7] The neurotoxic effects of PFAS also involve neuroinflammation, oxidative stress, endocrine disruption (particularly thyroid effects), mitochondrial dysfunction, and, notably, the activation of peroxisome proliferator-activated receptor-alpha (PPAR$\alpha$).[21] Neurotransmitter disruption has been shown particularly in relation to the dopamine and glutamate systems, with PFAS exposure increasing glutamate levels in the hippocampus, increasing catecholamine levels in the hypothalamus, and decreasing dopamine levels throughout the brain.[22] Disruption of the gut–brain axis has also been hypothesized to play a role in the indirect neurotoxicity of PFAS.[7] In adult mice, PFOS exposure resulted in hippocampal cell apoptosis, increase in glutamate in the hippocampus and decrease in dopamine in the caudate putamen, and impaired spatial learning and memory.[23] In vitro data from mice have also shown that PFOS exposure altered the protein levels of Alzheimer's disease (AD)-related biomarkers, including both amyloid and tau pathways.[24]

### 1.3.2 | Cerebrovascular health

There is a compelling argument to be made for PFAS exerting a selective effect on vascular cognitive impairment. There is a growing body of evidence showing that higher PFAS exposure is associated with vascular health outcomes, including an increased risk of diabetes, insulin resistance, hypertension, obesity, and hyperlipidemia, across various study populations in many countries.[14,16,25–33] These health effects are noteworthy due to the broad impact of these vascular risk factors for both heart and brain health, including stroke, myocardial infarction, vascular death, and dementia. The frequency of vascular dementia has been estimated to include up to 85% of all dementia patients, which underscores that the majority of AD patients have not just a purely neurodegenerative form but also a substantial vascular involvement.[34] Vascular health risk factors, like hypertension, obesity, diabetes, and hypercholesterolemia, are well established strong modifiable predictors of dementia.[35–38] The unweighted population attributable fraction for dementia in relation to obesity has been estimated to be 3.8%, hypertension 5.9%, diabetes 6.4%, and high LDL cholesterol 18.7%, with relative risk estimates of 1.2 or higher.[39]

## 1.4 | PFAS and dementia: epidemiological evidence

Growing evidence of the effects of PFAS on vascular risk factors, neurotoxicity, and cognitive development collectively point to their potentially important role in dementia.[31–33,40–43] However, observational epidemiological data on the relationship between PFAS and cognitive health are limited, weak, and controversial. The lack of consensus likely stems from significant interstudy methodological shortcomings that prevent a meaningful interpretation of the existing data. Table S1 provides a description of the existing studies on the relationship between PFAS exposure and adult cognitive impairment in humans. Four cross-sectional studies showed *better* cognition with increased PFAS exposure,[44–47] an outcome hypothesized to result from the presumably anti-inflammatory effects of PFAS. Two studies employed only a single question as the primary outcome, in which participants self-rated (yes/no) whether they had experienced memory problems.[44,45] Only one study used a full neuropsychological battery, and only found better performance on 3/31 subtest scores, and did not control for multiple comparisons due to the small sample size.[46] Only one cross-sectional study of NHANES participants over age 60 looked at the mixed effects of PFAS and reported a protective association with a short cognitive battery, driven by PFOA.[47] Other important shortcomings that limit the interpretation and/or generalizability of the existing data include homogeneous populations, no control for key confounding variables including diet and kidney function, no consideration for non-monotonic dose–response relationships, no prospective data, and no analysis of composite PFAS burden. The unexpected findings from

these methodologically limited studies are hard to reconcile with the literature showing associations between increased PFAS exposure and an *increased* burden of vascular risk factors that are strong predictors of cognitive decline and dementia. Importantly, a recent analysis explored alternative explanations for the positive associations between PFAS and cognitive performance and examined four PFAS in relation to average cognitive *z*-scores among 903 adults from NHANES.[48] When some of the aforementioned concerns – for example, excluding participants with chronic kidney disease and adjusting for diet – were addressed, PFOS exhibited a non-monotonic dose–response relationship with worse composite cognition score, supporting the hypothesis that PFAS increase the risk of late-life cognitive decline. This study demonstrates the importance of employing methodological rigor.

An innovative analysis using data from the French Three-City cohort underscored the importance of incorporating diet data when studying the link between PFAS and dementia risk.[49] This study estimated the dietary intake of 167 contaminants, including PFAS, based on multiple diet behavior assessments and information about food chemical content from the French second Total Diet Study, and found that among cohort members with higher fat intake, increased PFAS consumption (as well as five additional contaminants) was associated with an increased risk of incident dementia during follow-up.

Data from Italy have also supported the hypothesis that PFAS exposure may increase AD risk. Higher mortality due to AD was observed in municipalities with known PFAS contamination of drinking water due to the emissions of a manufacturing company in the Veneto Region during 1980–2013, compared to uncontaminated municipalities.[50]

Most recently, a pilot study in France measured 18 PFAS in the cerebrospinal fluid (CSF) of eight hospitalized patients with suspected normal pressure hydrocephaly. This study provided preliminary evidence that PFAS, and PFOS specifically, was found in the CSF samples from all patients, but the concentrations were higher in patients with both AD biomarkers and cognitive impairment, compared to patients with only one or neither.[19] This novel finding suggests that central nervous system PFAS burden may impact both the clinical and biological hallmarks of AD and builds on emerging evidence that PFAS accumulate in CSF over time and associate with weakening of the blood–brain barrier. Another recent study using cerebral organoids showed that exposure to a mixture of three PFAS induced amyloid beta accumulation and tau phosphorylation, indicative of AD neurotoxicity, as well as lipid disturbances.[20]

## 1.5 | Mechanistic pathways linking PFASs and dementia

One mechanistic pathway through which PFAS may impact cognitive impairment and dementia involves dyslipidemia and atherosclerosis, as shown in Figure 1. Several studies have shown that higher PFAS exposure, particularly PFOA and PFOS, is associated with elevated serum lipid levels,[51–57] though the results across studies and across specific PFAS have not been entirely consistent,[58,59] and data on many prevalent PFAS (e.g., PFDA and PFNA), as well as non-traditional lipid parameters (e.g., high-density lipoprotein [HDL] subfractions, apolipoproteins) are lacking, underscoring the need for further research to better understand the impacts of total PFAS burden on the full spectrum of lipid metabolism.[60–62] Prospective data on the relationship between PFAS exposure and lipid markers are also limited, but changes in plasma PFAS over a decade have been positively associated with progression of plasma lipids.[31] The mechanisms through which PFAS impact lipid metabolism are not well understood. They include the activation of PPAR$\alpha$, disruption of the hepatocyte nuclear factor 4-alpha signaling pathway, and influences on the expression of hepatic genes that control lipid metabolism.[21,63]

Carotid atherosclerosis is considered a risk factor for cognitive impairment and dementia,[64] and PFAS exposure is hypothesized to impact the development of atherosclerosis, with dyslipidemia likely mediating these associations. One prospective cohort study showed that changes in the plasma levels of several PFAS over 10 years were associated with increased carotid intima-media thickness (IMT).[65] In a cross-sectional study, several PFAS were positively associated with carotid atherosclerosis in women, but not in men.[66] Higher serum concentrations of individual PFAS have been associated with increased IMT in adolescents and young adults.[67] There are limited data on the relationship between PFAS and carotid plaque. One study showed an association with an increased risk of carotid plaque in women, but not in men.[66] In addition, PFAS may be directly prothrombotic through platelet adhesion and aggregation.[33]

Hypertension and diabetes may also mediate impacts of PFAS exposure on both carotid atherosclerosis[68] as well as cognitive impairment.[39] A meta-analysis of 14 studies with over 71,000 participants showed that higher PFAS exposure, and particularly PFHxS and PFDA, was associated with an increased risk of hypertension.[69] A systematic review and meta-analysis including 22 studies concluded that the association between PFAS and incident type 2 diabetes mellitus was consistently significant in cohort studies, but not in case-control and cross-sectional studies.[70] In addition, though many studies have demonstrated significant associations between PFAS exposure and insulin resistance and glucose tolerance, the associations have also been highly inconsistent across studies and have mainly focused on the legacy PFAS (PFOA and PFOS).[32] Proposed mechanisms contributing to an effect of PFAS on hypertension have included thyroid hormone disruption and oxidative stress resulting in impaired vasodilation.[71,72] Similarly, thyroid hormone disruption, oxidative stress, altered lipid metabolism, nuclear receptor interference including activation of peroxisome proliferator-activating receptors, disrupted pancreatic beta-cell function, impaired insulin secretion and glucose homeostasis, and adipogenesis are also believed to underlie deleterious impacts of PFAS exposure on diabetes risk.[73–76] PFAS exposure has also been associated with both obesity and weight gain, though the evidence remains limited, and obesity has also been hypothesized to mediate the deleterious effects of PFAS on vascular health.[33] For example, elevated plasma PFAS concentrations were associated with greater weight gain following initial diet-induced weight loss.[77] PFAS have been associated with increased body weight, waist circumference, fat mass and proportion, and rates of increase in these measures over time.[78]

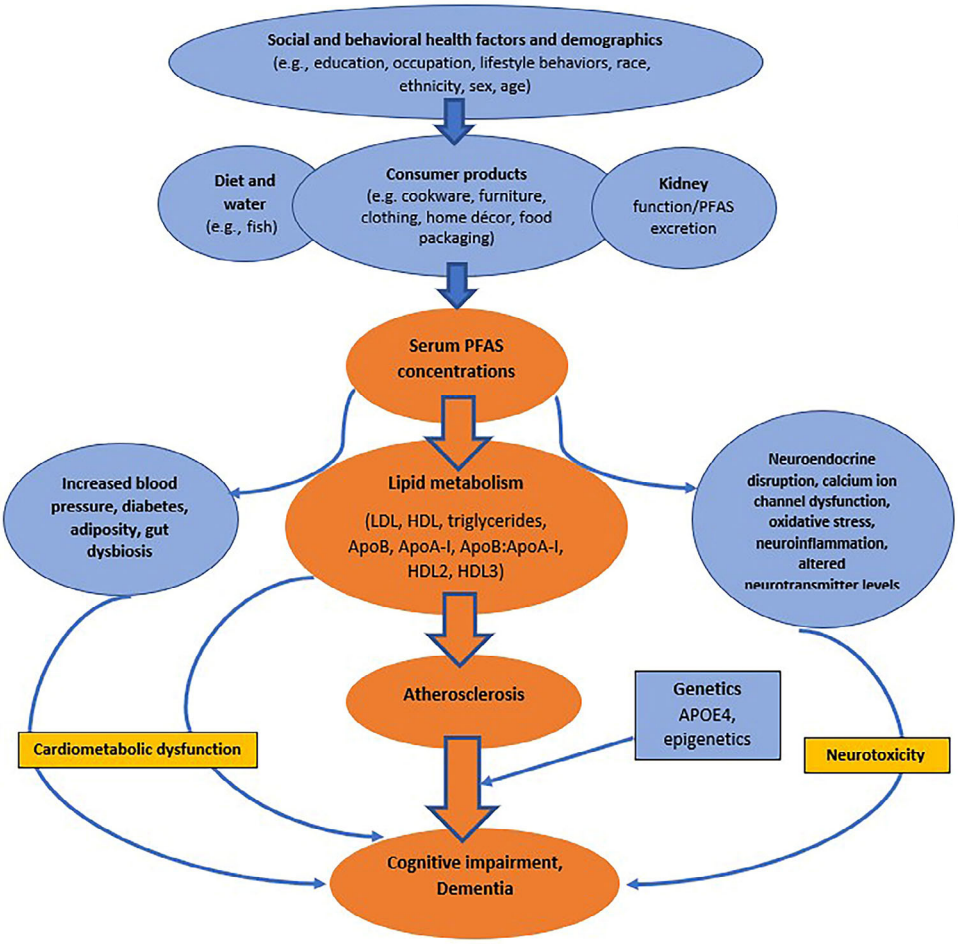


**FIGURE 1** Conceptual framework.

## 2 | METHODS

### 2.1 | PFAS VascCog longitudinal study

The public health burden of cognitive impairment and dementia is substantial. Among Americans aged 65 and older, the prevalence of AD is estimated to be 6.2 million and is expected to more than double over the next 40 years in the absence of significant scientific advancements in dementia prevention.[79] Further, mild cognitive impairment (MCI) has been observed in 15% to 20% of individuals over age 65.[80] Clearly, the preservation of cognitive health in adulthood is of paramount importance. The growing evidence of high-stakes health impacts of PFAS exposure underscores the urgent need to investigate their potential role in cognitive decline and dementia. Given the significant public health burden associated with dementia and its societal burden, it is crucial to examine how cumulative PFAS exposure contributes to the onset and progression of cognitive impairment, while accounting for key confounding factors such as diet, kidney function, and other vascular risk factors. To our knowledge, no prior studies have directly examined PFAS exposure and dementia, creating a critical gap in our understanding. The new PFAS VascCog Longitudinal Study, funded by the National Institute on Aging, is uniquely positioned to address this key knowledge gap and provide the basis for a thorough mechanistic analysis of the relationship between composite PFAS burden over time and incident dementia. Understanding this relationship is vital for informing public health policies and regulations regarding PFAS use, environmental remediation, and dementia prevention. Identifying modifiable environmental toxic exposures represents an opportunity to impact dementia at the individual and community levels.

### 2.2 | Overview and goals

The PFAS VascCog Longitudinal Study is a prospective cohort study whose overarching goal is to elucidate whether PFAS impact lipid profiles and consequently atherosclerosis and dementia risk in the Northern Manhattan Study (NOMAS). We will examine the causal mechanistic pathway through which PFAS exposure may increase dementia risk by increasing dyslipidemia and atherosclerosis. We will also examine the effect of apolipoprotein ε4 (APOE4) on these associations as APOE ε4 is a strong genetic risk factor for AD[43] and also associated with lipid metabolism and atherosclerosis.[81] APOE ε4 has been shown to modify vascular risk factors for dementia in previous studies,[82,83] underscoring the importance of examining its interactions

with PFAS to understand its potential causal mechanisms to dementia. One study also suggested that APOE ε4 might modify the association between PFOS (a specific type of PFAS) and carotid atherosclerosis.[67] Advancing the findings of previous studies, we will examine a comprehensive lipid profile, including HDL subfractions (HDL2 and HDL3), Apolipoprotein B (ApoB), Apolipoprotein A-I (ApoA-I), and lipoprotein(a) (lp(a)). These non-traditional lipid parameters have strong and distinct associations with carotid atherosclerosis phenotypes.[84–86]

This study will measure the serum concentrations of 13 distinct ubiquitous PFAS from the stored NOMAS blood samples at two time points, on average 6 years apart, and focus on a single measure representing composite PFAS exposure burden at each time point and the change in PFAS burden over time.[87] The following 13 PFAS will be measured: perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), PFOS, perfluorodecane sulfonate, perfluorohexanoic acid, perfluoroheptanoic acid, PFOA, PFNA, PFDA, perfluoroundecanoic acid, perfluorododecanoic acid, n-methylperfluoro-1-octanesulfonamidoacetic acid, and perfluorooctane sulfonamide. The legacy PFASs remain significant exposure sources despite regulations to restrict their production.[60] Though there are several thousand PFAS, most epidemiological studies have focused on three to six PFAS in relation to health outcomes. PFAS assessments at two time points, approximately 6 years apart, can be considered to represent long-term exposure due to the long half-lives (typically several years) of PFAS.[58]

Importantly, the PFAS VascCog Longitudinal Study will examine the relationship between PFAS and dementia risk using fully adjudicated cognitive and clinical outcomes.[88] We will also include adjudicated MCI in secondary analyses, as MCI can progress to dementia. In one longitudinal study of MCI cases, 65% progressed to dementia during the mean follow-up of 3.1 years and 24% died.[89]

## 2.3 | Study design

### 2.3.1 | Conceptual framework

Figure 1 depicts the overall conceptual framework, including the underlying causal mechanistic pathways and key variables influencing our hypothesized associations between PFAS with dementia and cognitive impairment. Shown in orange is the specific causal mechanism linking PFAS with dementia and cognitive impairment that will be initially scrutinized in the PFAS VascCog Longitudinal Study. It is important to note that the arrows included in Figure 1 are not a complete depiction of the hypothesized causal relationships between these variables, as many arrows have been intentionally excluded to improve readability. For example, health behaviors, demographic variables, diet, consumer product usage, and kidney function are understood to impact vascular, metabolic, and cognitive health through pathways that are independent of PFAS and can impact cognitive health independent of lipid metabolism and atherosclerosis. Sociodemographic variables may modify the associations between PFAS with lipid metabolism, atherosclerosis, cognitive impairment, and dementia, which will also be examined in the PFAS VascCog Longitudinal Study.

## 2.4 | The PFAS VascCog study population

NOMAS is a large longitudinal population-based cohort study investigating the incidence and risk factors for stroke, cognitive decline, and dementia in an urban population.[90,91] Northern Manhattan is a well-defined and predominantly low socioeconomic status area of New York City. From 1993 to 2001 participants were identified using random-digit dialing with the following inclusion criteria: (a) never diagnosed with a stroke, (b) at least 40 years old, and (c) resided in Northern Manhattan for ≥3 months in a household with a telephone. The participants had a baseline interview and assessments (enrollment response rate was 75%), with annual follow-up thereafter. Extensive health data were collected at baseline using structured interviews with trained bilingual research assistants in English or Spanish and physical examinations with study physicians and included lifetime smoking and alcohol use, physical activity, diet, medical history, medication use, blood pressure, and anthropometrics, as previously described.[88,91–95] The full, complete NOMAS sample size is 3497.

Figure 2 shows the NOMAS timeline. Between 2003 and 2008, a MRI subcohort was recruited during annual follow-up of NOMAS participants age ≥50 years who were clinically stroke-free with no contraindications to MRI ($N$ = 1290, median age 70 at MRI; 60% women, 15% non-Hispanic White, 17% non-Hispanic Black, 66% Hispanic, 2% other). Following an initial evaluation with a standardized brain MRI and cognitive battery, this subcohort has been prospectively followed with annual telephone contacts and up to three additional in-person cognitive assessments and thorough adjudication of dementia and MCI, and comprises the study population for the PFAS VascCog Longitudinal Study.[88,92,96] The NOMAS cohort is representative of an aging, urban, lower socioeconomic status (half are on Medicaid or uninsured) community with low educational attainment at increased risk of dementia.

## 2.5 | Analytic strategy

PFAS concentrations from serum collected at NOMAS baseline, PFAS concentrations from serum collected during follow-up (time of first comprehensive neuropsychological assessment), and the change in PFAS concentrations from baseline to follow-up will be examined as predictors of incident dementia (alone and dementia + MCI) using Cox proportional hazards models. A sequence of multivariable models will be constructed to adjust for confounding by sociodemographic variables, health behaviors (diet, physical activity, sleep, alcohol consumption, smoking), and kidney function. In addition to adjusting for APOE4, it will also be considered as a potential effect modifier. Diet, including fish, is one of many sources of PFAS exposure[97] and also associated with cognitive health.[98] Fish consumption is associated with *increased* PFAS exposure and fish consumption is also associated with a *decreased* risk of cognitive impairment and, therefore, acts as a *negative confounder*, biasing associations between PFAS and cognitive impairment toward the null when studies fail to account for fish intake. Therefore, it is important to take dietary habits into

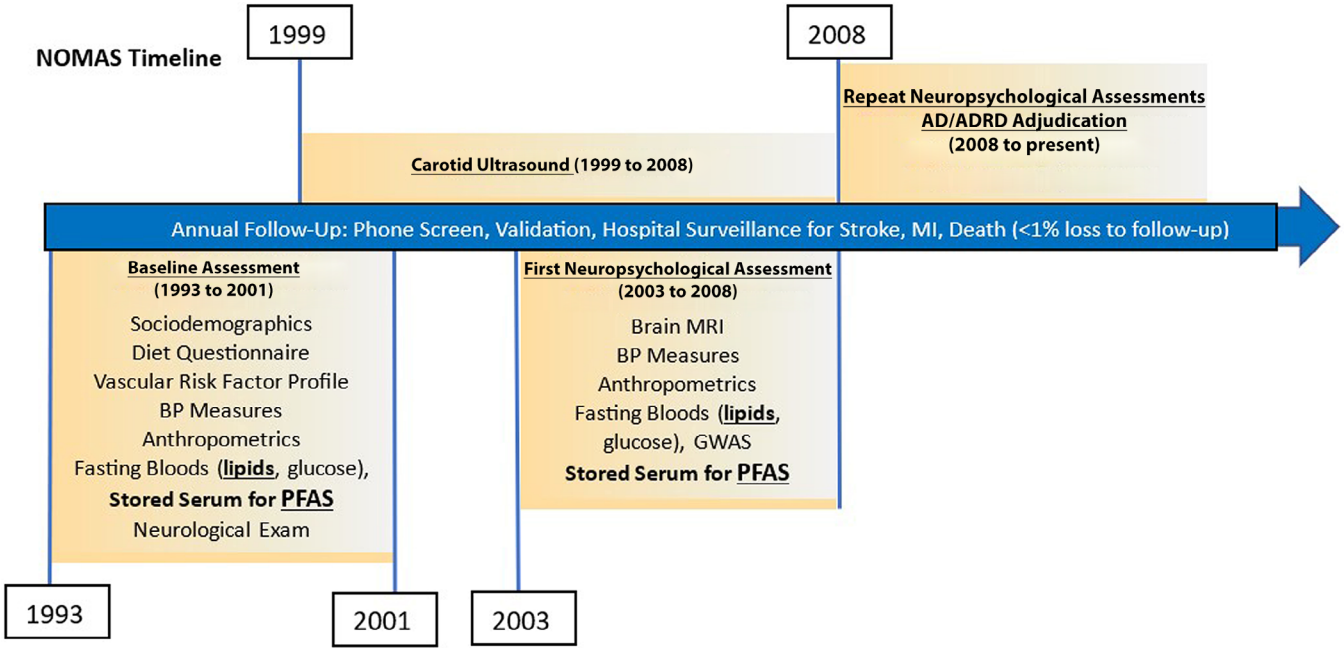


**FIGURE 2** Northern Manhattan Study timeline.

account when examining the health effects of PFAS. Though fish has been shown to be a type of food highly contaminated with PFAS, there are many dietary sources of PFAS, and therefore all major food groups will be investigated. Kidney function is another important confounder to include as chronic kidney disease can increase PFAS serum concentrations due to reduced excretion and has been associated with cognitive impairment.[99,100] Cognitive performance and decline over time across cognitive domains (episodic memory, semantic memory, executive function, processing speed) will also be examined as secondary outcomes.[92]

We are particularly interested in whether lipid profiles and atherosclerosis mediate effects of PFAS on the risk of dementia and MCI. This will be examined in the framework of natural-effects models, which express natural direct and indirect effects as a model for the nested counterfactual. Causal mediation pathway analyses will be used to fit models to identify potential mediation pathways linking PFAS to lipid profiles and subsequently carotid atherosclerosis and dementia/MCI. Independent mediation by additional vascular risk factors, including body mass index, waist circumference, hypertension, and diabetes, will also be examined.

Temporality: As shown in Figure 2, serum PFAS concentrations will be measured from stored samples collected at two time points, study baseline and on average 6 years later at the time of the first neuropsychological assessment, and lipids are measured at these same two time points. Incident dementia cases identified after these time points will be included, and prevalent cases will be excluded. Therefore, PFAS analyses in relation to lipid profiles and atherosclerosis in the PFAS VascCog Longitudinal Study will be both prospective and cross-sectional, and PFAS analyses in relation to dementia will be prospective.

## 3 | DISCUSSION

The pervasive population-wide exposure to PFAS has emerged as a public health priority over the past decade. The PFAS VascCog Longitudinal Study in NOMAS aims to provide new knowledge on the relationship between PFAS and risk of dementia and MCI in a high-risk population, which is critical to support community-wide interventions to reduce exposure to this class of POPs, particularly in vulnerable adult populations. The findings can inform environmental health policies and recommendations regarding the avoidance of PFAS-containing products, support regulatory efforts to reduce community-wide PFAS exposure, and identify communities at high risk of dementia. PFAS exposure levels vary substantially across communities, and many highly exposed counties throughout the United States have already been identified, with remediation efforts and health surveillance needed.[17] PFAS represent an environmental exposure category that can be modified in multiple ways, as the exposure routes are many and varied.[60] For example, in recent years there has been considerable controversy at the state and federal levels about the application of stringent regulatory limits for PFAS levels in municipal water supplies. On April 10, 2024, the EPA announced its final National Primary Drinking Water Regulation for six PFAS as a major progressive step to combat PFAS pollution.[101] The EPA leveraged the latest science to complement state efforts with legally enforceable Maximum Contaminant Levels (MCLs) for six individual PFAS known to contaminate US drinking water, as well as a Hazard Level MCL for PFAS mixtures containing at least two of four PFAS to reflect the increased risk of PFAS co-exposures. Water is only one of many major sources of PFAS (e.g., food packaging, textiles) that need strict regulations. States have recently started to initiate regulations about PFAS in consumer products, and

many states have started prohibiting the use of PFAS-based firefighting foams.

While regulatory efforts can take many years, public health campaigns can help people reduce PFAS exposures with lifestyle changes as well. A causal association between PFAS exposure and cognitive impairment and dementia could implicate many avenues for disease modification and the potential prevention of significant morbidity. A relationship between PFAS and cognitive health and dementia would also help elucidate etiological mechanisms involved in the epidemiology of cognitive impairment and dementia. Though the scrutiny on this class of endocrine disrupting compounds is ongoing, we are still at the beginning stage of elucidating the range and strength of PFAS effects, particularly in populations at high risk of dementia.

The PFAS VascCog Longitudinal Study will support future studies on the biological mechanisms through which PFAS may impact dementia and cognitive health, as well as the potential effect modifying roles of additional genetic factors, AD biomarkers, and structural and functional imaging markers of small vessel disease and neurodegeneration. Though the initial study focuses on vascular risk factors as potential mediators and will provide insight into how PFAS may impact dementia risk, PFAS are also believed to exert neurotoxic and inflammatory effects and disrupt endocrine function,[42,43] requiring future exploration. In addition, future research is needed to explore the potential interaction of multiple genetic factors with PFAS, including DNA methylation studies to examine PFAS in relation to epigenetic modification in a multi-omics integrated approach to cognitive function and dementia.

## 4 | CONCLUSIONS

The growing body of literature showing neurotoxic and cardiometabolic effects of PFAS exposure on a range of health outcomes underscores the importance of examining the impact of PFAS on cognitive impairment and dementia. To date, no rigorous prospective studies have investigated this critical issue, creating a knowledge gap in our understanding of a widespread environmental exposure that offers opportunities for intervention. This report describes the new PFAS VascCog Longitudinal Study, which will quantify the concentrations of 13 ubiquitous PFAS in archived serum samples from two time points and the total PFAS exposure burden in a well-established population-based longitudinal cohort to test the hypothesis that PFAS exposure increases the risk of cognitive impairment and dementia through a mechanistic pathway involving hyperlipidemia and atherosclerosis. The PFAS VascCog Longitudinal Study seeks to provide impactful mechanistic insight into the relationships between PFAS and dementia that will ultimately inform public health policies regarding PFAS use, remediation efforts to reduce community PFAS exposure, and dementia risk reduction. PFAS exposure occurs in the context of the broad chemical exposome that also includes polychlorinated biphenyls, flame retardants, phthalates, bisphenols, pesticides, heavy metals, organic solvents, particulate matter, and other toxic chemicals. The impacts of the chemical exposome overall on cognitive impairment, decline, and dementia risk, as well as the relative contributions of these different classes of chemicals and how they interact with each other and with genetics, remain largely unknown. Large multicohort and interdisciplinary collaborative efforts to systematically study the chemical exposome over the life course as a driver of brain health are of critical importance,[2,3,102] as is the characterization of the independent contributions of PFAS in the chemical exposome to dementia risk.

## ACKNOWLEDGMENTS

Funding was received from the National Institute on Aging (R01AG086393).

## CONFLICT OF INTEREST STATEMENT

H.G. has provided paid consulting regarding PFAS exposure avoidance to individuals. No additional disclosures are necessary. Author disclosures are available in the supporting information.

## CONSENT STATEMENT

All subjects provided written informed consent.

## REFERENCES

1. Castro CB, Costa LM, Dias CB, et al. Multi-domain interventions for dementia prevention—a systematic review. *J Nutr Health Aging*. 2023;27:1271-1280. doi:10.1007/s12603-023-2046-2
2. Sakowski SA, Koubek EJ, Chen KS, Goutman SA, Feldman EL. Role of the exposome in neurodegenerative disease: recent insights and future directions. *Ann Neurol*. 2024;95(4):635-652. doi:10.1002/ana.26897
3. Pan S, Li Z, Rubbo B, et al. Applications of mixture methods in epidemiological studies investigating the health impact of persistent organic pollutants exposures: a scoping review. *J Exposure Sci Environ Epidemiol*. 2024. doi:10.1038/s41370-024-00717-3
4. Park SH, Lim J, Park H, Jee SH. Body burden of persistent organic pollutants on hypertension: a meta-analysis. *Environ Sci Pollut Res*. 2016;23:14284-14293. doi:10.1007/s11356-016-6568-6
5. Gaston SA, Birnbaum LS, Jackson CL. Synthetic chemicals and cardiometabolic health across the life course among vulnerable populations: a review of the literature from 2018 to 2019. *Curr Environ Health Rep*. 2020;7:30-47. doi:10.1007/s40572-020-00265-6
6. Grova N, Schroeder H, Olivier J-L, Turner JD. Epigenetic and neurological impairments associated with early life exposure to persistent organic pollutants. *Int J Genomics*. 2019;2019:1-19. doi:10.1155/2019/2085496
7. Bharal B, Ruchitha C, Kumar P, et al. Neurotoxicity of per- and Polyfluoroalkyl substances: evidence and future directions. *Sci Total Environ*. 2024:176941-1. doi:10.1016/j.scitotenv.2024.176941
8. Tokranov AK, Ransom KM, Bexfield LM, et al. Predictions of groundwater PFAS occurrence at drinking water supply depths in the United States. *Science*. 2024;386(6723):748-755. doi:10.1126/science.ado6638
9. Langberg HA, Breedveld GD, Kallenborn R, et al. Human exposure to per- and polyfluoroalkyl substances (PFAS) via the consumption of fish leads to exceedance of safety thresholds. *Environ Int*. 2024;190:108844. doi:10.1016/j.envint.2024.108844
10. Fábelová L, Beneito A, Casas M, et al. PFAS levels and exposure determinants in sensitive population groups. *Chemosphere*. 2023;313:137530. doi:10.1016/j.chemosphere.2022.137530
11. Pérez F, Nadal M, Navarro-Ortega A, et al. Accumulation of perfluoroalkyl substances in human tissues. *Environ Int*. 2013;59:354-362. doi:10.1016/j.envint.2013.06.004

12. Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Tully JS, Needham LL. Serum concentrations of 11 polyfluoroalkyl compounds in the U.S. data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. *Environ Sci Technol*. 2007;41:2237-2242. doi:10.1021/es062686m
13. Khadgi Sonnenberg N, Ojewole AE, Ojewole CO, Lucky OP, Kusi J. Trends in serum per- and Polyfluoroalkyl Substance (PFAS) concentrations in teenagers and adults, 1999-2018 NHANES. *Int J Environ Res Public Health*. 2023;20:6984-6984. doi:10.3390/ijerph20216984
14. Xu Y, Jakobsson K, Harari F, Andersson EM, Li Y. Exposure to high levels of PFAS through drinking water is associated with increased risk of type 2 diabetes—findings from a register-based study in Ronneby, Sweden. *Environ Res*. 2023;225:115525. doi:10.1016/j.envres.2023.115525
15. Kuo K-Y, Chen Y, Chuang Y, Lin P, Lin Y-J. Worldwide serum concentration-based probabilistic mixture risk assessment of perfluoroalkyl substances among pregnant women, infants, and children. *Ecotoxicol Environ Saf*. 2023;268:115712. doi:10.1016/j.ecoenv.2023.115712
16. Averina M, Brox J, Huber S, Furberg A-S. Exposure to Perfluoroalkyl Substances (PFAS) and dyslipidemia, hypertension and obesity in adolescents. the fit futures study. *Environ Res*. 2021;195:110740. doi:10.1016/j.envres.2021.110740
17. Centers for Disease Control and Prevention. Fast Facts: PFAS in the U.S. Population. Per- and Polyfluoroalkyl Substances (PFAS) and Your Health. 2024. Accessed December 3, 2024. https://www.atsdr.cdc.gov/pfas/data-research/facts-stats/?CDC_AA
18. Fenton SE, Ducatman A, Boobis A, et al. Per- and polyfluoroalkyl substance toxicity and human health review: current state of knowledge and strategies for informing future research. *Environ Toxicol Chem*. 2020;40:606-630. doi:10.1002/etc.4890
19. Delcourt N, Pouget A-M, Grivaud A, et al. First observations of a potential association between accumulation of per- and polyfluoroalkyl substances in the central nervous system and markers of Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*. 2024;79:glad208. doi:10.1093/gerona/glad208
20. Lu S, Zhu X, Zeng P, et al. Exposure to PFOA, PFOS, and PFHxS induces Alzheimer's disease-like neuropathology in cerebral organoids. *Environ Pollut*. 2024;363(Pt 1):125098. doi:10.1016/j.envpol.2024.125098
21. Starnes HM, Rock KD, Jackson TW, Belcher SM. A critical review and meta-analysis of impacts of per- and polyfluorinated substances on the brain and behavior. *Front Toxicol*. 2022;4:881584. doi:10.3389/ftox.2022.881584
22. Brown-Leung JM, Cannon JR. Neurotransmission targets of per- and polyfluoroalkyl substance neurotoxicity: mechanisms and potential implications for adverse neurological outcomes. *Chem Res Toxicol*. 2022;35:1312-1333. doi:10.1021/acs.chemrestox.2c00072
23. Long Y, Wang Y, Ji G, Yan L, Hu F, Gu A. Neurotoxicity of perfluorooctane sulfonate to hippocampal cells in adult mice. *PLoS One*. 2013;8:e54176. doi:10.1371/journal.pone.0054176
24. Basaly V, Hill J, Bihaqi SW, Marques E, Slitt AL, Zawia NH. Developmental perfluorooctanesulfonic acid (PFOS) exposure as a potential risk factor for late-onset Alzheimer's disease in CD-1 mice and SH-SY5Y cells. *Neurotoxicology*. 2021;86:26-36. doi:10.1016/j.neuro.2021.06.008
25. Wu B, Pan Y, Li Z, et al. Serum per- and polyfluoroalkyl substances and abnormal lipid metabolism: a nationally representative cross-sectional Study. *Environ Int*. 2023;172:107779-9. doi:10.1016/j.envint.2023.107779
26. Knutsen HK, Alexander J, Barregård L, et al. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. *EFSA J*. 2018;16:e05194. doi:10.2903/j.efsa.2018.5194
27. Haug M, Dunder L, Lind PM, Lind L, Salihovic S. Associations of perfluoroalkyl substances (PFAS) with lipid and lipoprotein profiles. *J Exposure Sci Environ Epidemiol*. 2023;33(5):757-765. doi:10.1038/s41370-023-00545-x
28. Shin M-W, Kang H, Kim S-H. Concentrations of serum per- and polyfluoroalkyl substances and lipid health in adolescents: a cross-sectional study from the Korean National Environmental Health Survey 2018-2020. *Toxics*. 2025;13:91-91. doi:10.3390/toxics13020091
29. Batzella E, Fletcher T, Pitter G, et al. Decreases in serum PFAS are associated with decreases in serum lipids: a longitudinal study on a highly exposed population. *Sci Total Environ*. 2024;954:176227. doi:10.1016/j.scitotenv.2024.176227
30. Sharma A, Jorvekar SB, Bhowmik S, Mohapatra P, Borkar RM. Comprehensive assessment of per and polyfluoroalkyl substances contamination in groundwater of Kamrup, Assam, India: occurrence, health risks, and metabolomic insights. *Environ Sci Process Impacts*. 2024;26:1601-1617. doi:10.1039/d4em00159a
31. Dunder L, Lind PM, Salihovic S, Stubleski J, Kärrman A, Lind L. Changes in plasma levels of per- and polyfluoroalkyl substances (PFAS) are associated with changes in plasma lipids—a longitudinal study over 10 years. *Environ Res*. 2022;211:112903. doi:10.1016/j.envres.2022.112903
32. Margolis R, Sant KE. Associations between exposures to perfluoroalkyl substances and diabetes, hyperglycemia, or insulin resistance: a scoping review. *JoX*. 2021;11:115-129. doi:10.3390/jox11030008
33. Meneguzzi A, Fava C, Castelli M, Minuz P. Exposure to perfluoroalkyl chemicals and cardiovascular disease: experimental and epidemiological evidence. *Front Endocrinol*. 2021;12:706352. doi:10.3389/fendo.2021.706352
34. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward?. *Neurology*. 2009;72:368-374. doi:10.1212/01.wnl.0000341271.90478.8e
35. Theofilis P, Doumani G, Tsatsani G-C, et al. The role of hypertension in cognitive dysfunction. *J Clin Med*. 2024;13:5979. doi:10.3390/jcm13195979
36. Stephan BCM, Cochrane L, Kafadar AH, et al. Population attributable fractions of modifiable risk factors for dementia: a systematic review and meta-analysis. *Lancet Healthy Longev*. 2024;5:e406-21. doi:10.1016/s2666-7568(24)00061-8
37. Kciuk M, Kruczkowska W, Gałęziewska J, et al. Alzheimer's disease as type 3 diabetes: understanding the link and implications. *Int J Mol Sci*. 2024;25:11955. doi:10.3390/ijms252211955
38. Pappolla MA, Refolo L, Sambamurti K, Zambon D, Duff K. Hypercholesterolemia and Alzheimer's disease: unraveling the connection and assessing the efficacy of lipid-lowering therapies. *Alzheimers Disease*. 2024;101:S371-93. doi:10.3233/jad-240388
39. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 Report of the Lancet Standing Commission. *Lancet*. 2024;404:572-628. doi:10.1016/s0140-6736(24)01296-0
40. Rappazzo K, Coffman E, Hines E. Exposure to perfluorinated alkyl substances and health outcomes in children: a systematic review of the epidemiologic literature. *Int J Environ Res Public Health*. 2017;14:691. doi:10.3390/ijerph14070691
41. Lee YJ, Jung HW, Kim HY, Choi Y-J, Lee YA. Early-Life exposure to per- and poly-fluorinated alkyl substances and growth, adiposity, and puberty in children: a systematic review. *Front Endocrinol*. 2021;12. doi:10.3389/fendo.2021.683297
42. Zeng Z, Song B, Xiao R, et al. Assessing the human health risks of perfluorooctane sulfonate by in vivo and in vitro studies. *Environ Int*. 2019;126:598-610. doi:10.1016/j.envint.2019.03.002
43. Cao Y, Ng C. Absorption, distribution, and toxicity of per- and polyfluoroalkyl substances (PFAS) in the brain: a review. *Environ Sci Process Impacts*. 2021;23:1623-1640. doi:10.1039/d1em00228g

44. Power MC, Webster TF, Baccarelli AA, Weisskopf MG. Cross-sectional association between polyfluoroalkyl chemicals and cognitive limitation in the National Health and Nutrition Examination Survey. *Neuroepidemiology*. 2012;40:125-132. doi:10.1159/000342310
45. Gallo V, Leonardi G, Brayne C, Armstrong B, Fletcher T. Serum perfluoroalkyl acids concentrations and memory impairment in a large cross-sectional study. *BMJ Open*. 2013;3:e002414. doi:10.1136/bmjopen-2012-002414
46. Shrestha S, Bloom MS, Yucel R, et al. Perfluoroalkyl substances, thyroid hormones, and neuropsychological status in older adults. *Int J Hyg Environ Health*. 2017;220:679-685. doi:10.1016/j.ijheh.2016.12.013
47. Weng X, Liang H, Tan Y, et al. Mixed effects of perfluoroalkyl and polyfluoroalkyl substances exposure on cognitive function among people over 60 years old from NHANES. *Environ Sci Pollut Res*. 2022;29:32093-32104. doi:10.1007/s11356-021-17789-5
48. Park SK, Ding N, Han D. Perfluoroalkyl substances and cognitive function in older adults: should we consider non-monotonic dose-responses and chronic kidney disease?. *Environ Res*. 2021;192:110346. doi:10.1016/j.envres.2020.110346
49. Lefèvre-Arbogast S, Duquenne P, Helmer C, Auriacombe S, Sirot V, Samieri C. Association between dietary exposure to chemical contaminants and risk of dementia in older persons. *Environ Int*. 2024;192:109033. doi:10.1016/j.envint.2024.109033
50. Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P. Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto region, Italy. *Eur J Public Health*. 2017;28:180-185. doi:10.1093/eurpub/ckx066
51. Christensen KY, Raymond M, Thompson BA, Anderson HA. Perfluoroalkyl substances in older male anglers in Wisconsin. *Environ Int*. 2016;91:312-318. doi:10.1016/j.envint.2016.03.012
52. Costa G, Sartori S, Consonni D. Thirty years of medical surveillance in perfluorooctanoic acid production workers. *J Occup Environ Med*. 2009;51:364-372. doi:10.1097/jom.0b013e3181965d80
53. Sakr CJ, Kreckmann KH, Green JW, Gillies PJ, Reynolds JL, Leonard RC. Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonium perfluorooctanoate or APFO) as part of a general health survey in a cohort of occupationally exposed workers. *J Occup Environ Med*. 2007;49:1086-1096. doi:10.1097/JOM.0b013e318156eca3
54. Sakr CJ, Leonard RC, Kreckmann KH, Slade MD, Cullen MR. Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. *J Occup Environ Med*. 2007;49:872-879. doi:10.1097/jom.0b013e318124a93f
55. Frisbee SJ, Shankar A, Knox SS, et al. Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents. *Arch Pediatr Adolesc Med*. 2010;164:860-869. doi:10.1001/archpediatrics.2010.163
56. Nelson JW, Hatch EE, Webster TF. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. *Environ Health Perspect*. 2010;118:197-202. doi:10.1289/ehp.0901165
57. Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *Am J Epidemiol*. 2009;170:1268-1278. doi:10.1093/aje/kwp279
58. United States Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls. 2021. doi:10.15620/cdc:59198
59. He X, Liu Y, Xu B, Gu L, Tang W. PFOA is associated with diabetes and metabolic alteration in US men: National Health and Nutrition Examination Survey 2003-2012. *Sci Total Environ*. 2018;625:566-574. doi:10.1016/j.scitotenv.2017.12.186
60. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. *J Exposure Sci Environ Epidemiol*. 2019;29:131-147. doi:10.1038/s41370-018-0094-1
61. Winquist A, Steenland K. Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. *Environ Health Perspect*. 2014;122:1299-1305. doi:10.1289/ehp.1307943
62. Seo S-H, Son M-H, Choi S-D, Lee D-H, Chang Y-S. Influence of exposure to perfluoroalkyl substances (PFASs) on the Korean general population: 10-year trend and health effects. *Environ Int*. 2018;113:149-161. doi:10.1016/j.envint.2018.01.025
63. Hyötyläinen T, Bodin J, Duberg D, Dirven H, Nygaard UC, Orešič M. lipidomic analyses reveal modulation of lipid metabolism by the PFAS perfluoroundecanoic acid (PFUnDA) in non-obese diabetic mice. *Front Genet*. 2021;12:721507. doi:10.3389/fgene.2021.721507
64. Vitali F, Torrandell-Haro G, Branigan G, et al. Asymptomatic carotid artery stenosis is associated with increased Alzheimer's disease and non-Alzheimer's disease dementia risk. *Stroke Vasc Neurol*. 2024:svn-2024-003164. doi:10.1136/svn-2024-003164
65. Lind PM, Salihovic S, Stubleski J, Kärrman A, Lind L. Changes in plasma levels of perfluoroalkyl substances (PFASs) are related to increase in carotid intima-media thickness over 10 years – a longitudinal study. *Environ Health*. 2018;17:59. doi:10.1186/s12940-018-0403-0
66. Lind PM, Salihovic S, van Bavel B, Lind L. Circulating levels of perfluoroalkyl substances (PFASs) and carotid artery atherosclerosis. *Environ Res*. 2017;152:157-164. doi:10.1016/j.envres.2016.10.002
67. Lin C-Y, Lin L-Y, Wen T-W, et al. Association between levels of serum perfluorooctane sulfate and carotid artery intima–media thickness in adolescents and young adults. *Int J Cardiol*. 2013;168:3309-3316. doi:10.1016/j.ijcard.2013.04.042
68. Song P, Fang Z, Wang H, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health*. 2020;8:e721-e729. doi:10.1016/s2214-109x(20)30117-0
69. Yang J, Zhang K, Shen C, et al. The association of hypertension with perfluoroalkyl and polyfluoroalkyl substances. *Int Heart J*. 2023;64:1079-1087. doi:10.1536/ihj.23-036
70. Gui S-Y, Qiao J-C, Xu K-X, et al. Association between per- and polyfluoroalkyl substances exposure and risk of diabetes: a systematic review and meta-analysis. *J Exposure Sci Environ Epidemiol*. 2022;33:40-55. doi:10.1038/s41370-022-00464-3
71. Pitter G, Zare Jeddi M, Barbieri G, et al. Perfluoroalkyl substances are associated with elevated blood pressure and hypertension in highly exposed young adults. *Environ Health*. 2020;19:102. doi:10.1186/s12940-020-00656-0
72. Li J, Ye S, Zhao Z, et al. Association of PFDeA exposure with hypertension (NHANES, 2013-2018). *Sci Rep*. 2024;14:918. doi:10.1038/s41598-024-51187-4
73. Elumalai S, Karunakaran U, Won KC, Chung SM, Moon JS. Perfluorooctane sulfonate-induced oxidative stress contributes to pancreatic $\beta$-cell apoptosis by inhibiting cyclic adenosine monophosphate pathway: prevention by pentoxifylline. *Environ Pollut*. 2023;320:120959-9. doi:10.1016/j.envpol.2022.120959
74. Park SK, Wang X, Ding N, et al. Per- and polyfluoroalkyl substances and incident diabetes in midlife women: the Study of Women's Health across the Nation (SWAN). *Diabetologia*. 2022;65:1157-1168. doi:10.1007/s00125-022-05695-5
75. Roth K, Petriello MC. Exposure to per- and polyfluoroalkyl substances (PFAS) and type 2 diabetes risk. *Front Endocrinol*. 2022;13:965384. doi:10.3389/fendo.2022.965384
76. Qin W-P, Cao L-Y, Li C-H, Guo L-H, Colbourne JK, Ren X-M. Perfluoroalkyl substances stimulate insulin secretion by Islet $\beta$ cells via G protein-coupled receptor 40. *Environ Sci Technol*. 2020;54:3428-3436. doi:10.1021/acs.est.9b07295

77. Grandjean P, Meddis A, Nielsen F, et al. Weight loss relapse associated with exposure to perfluorinated alkylate substances. *Obesity*. 2023;31:1686-1696. doi:10.1002/oby.23755
78. Ding N, Karvonen-Gutierrez CA, Herman WH, Calafat AM, Mukherjee B, Park SK. Perfluoroalkyl and polyfluoroalkyl substances and body size and composition trajectories in midlife women: the Study of Women's Health across the Nation 1999-2018. *Int J Obes*. 2021;45:1937-1948. doi:10.1038/s41366-021-00848-9
79. Alzheimer's disease facts and figures. *Alzheimers Dementia*. 2021;17:327-406. doi:10.1002/alz.12328
80. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: mild cognitive impairment. *Neurology*. 2018;90:126-135. doi:10.1212/wnl.0000000000004826
81. Khalil YA, Rabès J-P, Boileau C, Varret M. APOE gene variants in primary dyslipidemia. *Atherosclerosis*. 2021;328:11-22. doi:10.1016/j.atherosclerosis.2021.05.007
82. Gardener H, Caunca MR, Dong C, et al. Ultrasound markers of carotid atherosclerosis and cognition. *Stroke*. 2017;48:1855-1861. doi:10.1161/strokeaha.117.016921
83. Rundek T, Gardener H, Dias Saporta AS, et al. Global vascular risk score and CAIDE dementia risk score predict cognitive function in the Northern Manhattan Study. *Alzheimers Disease*. 2020;73:1221-1231. doi:10.3233/jad-190925
84. Tiozzo E, Gardener H, Hudson BI, et al. Subfractions of high-density lipoprotein-cholesterol and carotid intima-media thickness. *Stroke*. 2016;47:1508-1513. doi:10.1161/strokeaha.115.012009
85. Gardener H, Morte DD, Elkind MS, Sacco RL, Rundek T. Lipids and carotid plaque in the Northern Manhattan Study (NOMAS). *BMC Cardiovasc Disord*. 2009;9:55. doi:10.1186/1471-2261-9-55
86. Tiozzo E, Gardener H, Hudson BI, et al. High-density lipoprotein subfractions and carotid plaque: the Northern Manhattan Study. *Atherosclerosis*. 2014;237:163-168. doi:10.1016/j.atherosclerosis.2014.09.002
87. Liu SH, Kuiper JR, Chen Y, Feuerstahler L, Teresi J, Buckley JP. Developing an exposure burden score for chemical mixtures using item response theory, with applications to PFAS mixtures. *Environ Health Perspect*. 2022;130:117001. doi:10.1289/ehp10125
88. Wright CB, DeRosa JT, Moon MP, et al. Race/ethnic disparities in mild cognitive impairment and dementia: the Northern Manhattan Study. *Alzheimers Disease*. 2021;80:1129-1138. doi:10.3233/JAD-201370
89. Yaffe K, Petersen RC, Lindquist K, Kramer J, Miller B. Subtype of mild cognitive impairment and progression to dementia and death. *Dement Geriatr Cogn Disord*. 2006;22:312-319. doi:10.1159/000095427
90. White H, Boden-Albala B, Wang C, et al. Ischemic stroke subtype incidence among Whites, Blacks, and Hispanics. *Circulation*. 2005;111:1327-1331. doi:10.1161/01.cir.0000157736.19739.d0
91. Sacco RL, Anand K, Lee H-S, et al. Homocysteine and the risk of ischemic stroke in a triethnic cohort. *Stroke*. 2004;35:2263-2269. doi:10.1161/01.str.0000142374.33919.92
92. Gardener H, Wright CB, Dong C, et al. Ideal cardiovascular health and cognitive aging in the Northern Manhattan Study. *J Am Heart Assoc*. 2016;5. doi:10.1161/jaha.115.002731
93. Sacco RL, Khatri M, Rundek T, et al. Improving global vascular risk prediction with behavioral and anthropometric factors. *J Am Coll Cardiol*. 2009;54:2303-2311. doi:10.1016/j.jacc.2009.07.047
94. Elkind MSV, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Moderate alcohol consumption reduces risk of ischemic stroke. *Stroke*. 2006;37:13-19. doi:10.1161/01.str.0000195048.86810.5b
95. Gardener H, Wright CB, Gu Y, et al. Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study. *Am J Clin Nutr*. 2011;94:1458-1464. doi:10.3945/ajcn.111.012799
96. Gardener H, Levin B, DeRosa J, et al. Social connectivity is related to mild cognitive impairment and dementia. *Alzheimers Disease*. 2021;84:1811-1820. doi:10.3233/JAD-210519
97. DeLuca NM, Thomas K, Luben TJ, Melnyk LJ. Associations between self-reported consumption of foods and serum PFAS concentrations in a sample of pregnant women in the United States. *Environ Res*. 2025;276:121461. doi:10.1016/j.envres.2025.121461
98. Booth S, Talegawkar S, Fung T, et al. Dietary patterns and risk of cognitive decline, dementia, Alzheimer's disease, and mild cognitive impairment: a systematic review. *USDA Nutrition Evidence Systematic Review*. 2024. doi:10.52570/NESR.DGAC2025.SR20
99. Lin P-ID, Cardenas A, Hauser R, et al. Per- and polyfluoroalkyl substances and kidney function: follow-up results from the diabetes prevention program trial. *Environ Int*. 2021;148:106375. doi:10.1016/j.envint.2020.106375
100. Pei X, Bakerally NB, Wang Z, et al. Kidney function and cognitive impairment: a systematic review and meta-analysis. *Ren Fail*. 2025;47:2463565. doi:10.1080/0886022x.2025.2463565
101. United States Environmental Protection Agency. Per- and Polyfluoroalkyl Substances (PFAS) Final PFAS National Primary Drinking Water Regulation. Accessed March 21, 2025. https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas
102. Lefèvre-Arbogast S, Chaker J, Mercier F, et al. Assessing the contribution of the chemical exposome to neurodegenerative disease. *Nat Neurosci*. 2024;27:812-821. doi:10.1038/s41593-024-01627-1

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Gardener H, Levin B, Kannan K, Rundek T. The role of per- and polyfluoroalkyl substances in cognitive impairment and dementia. *Alzheimer's Dement*. 2025;21:e70226. https://doi.org/10.1002/alz.70226