

Increased A β 40 in plasma is associated with severity of exposure to airborne pollutants at the World Trade Center: a cross-sectional study of neurological biomarkers

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Abstract

World Trade Center (WTC) responders who were more severely exposed to the airborne pollution while working in rescue and recovery work would have heightened circulating levels of β -Amyloid (A β) levels in plasma. Plasma for 905 WTC responders was retrieved in 2019 and flash frozen and assayed using single molecule analysis to measure circulating levels of two subtypes of A β (A β 40, A β 42), alongside phosphorylated tau-181, glial fibrillary acidic protein (GFAP), and neurofilament-light. Plasma data were linked to demographics, blood volume, apolipoprotein- ϵ 4 status, and medical outcomes as well as, in a subsample, with neuroimaging-based measures of cortical thickness. Amyloidogenesis was measured using the ratio of observed/expected levels of A β 40 and labeled Normalized A β 40. Spearman's rho was used to examine correlations; generalized linear modeling was used to examine multivariable-adjusted associations. The average age of WTC responders was 55.98 years, and 73.9% had completed at least some college. Observed A β 40 levels were 24.61% higher than expected values, and lower in minimally exposed WTC responders as compared to severely exposed WTC responders (17.26 vs 44.48%, $P = .005$). Results remained statistically significant upon adjusting for covariates (adjusted blood volume ratio = 1.11 [1.02–1.22] $P = .019$). Normalized A β 40 levels were associated with higher measures of phosphorylated tau-181, A β 42, GFAP, and neurofilament-light in serology as well as, in a subsample ($n = 70$), with reduced cortical thickness ($\rho = -0.29$, $P = .020$). Increased amyloidogenesis may be a neuropathological response in people who are severely or chronically exposed to airborne neurotoxic pollutants.

Keywords: age-related pathology; biology of aging; environmental health; epidemiology; neuromarkers

Background

Alzheimer's disease (AD) and related dementias (ADRD) refer to a host of age-related progressive neurodegenerative conditions resulting in cognitive impairment.¹ Risk factors for ADRD include low education, age, and exposures to Airborne Pollutants (APx).² AD is characterized by the development of β -Amyloid (A β) plaques,³ which often initially develop as diffuse plaques containing predominantly one specific subtype of A β (A β 42) and can affect substantial portions of the brain before symptoms present.⁴ A β 40, however, is also used neuropathologically when forming dense-core plaques that are more severe and usually not present until late-stage AD.⁵

To understand the development and spread of cerebral amyloidosis, many researchers use a ratio of A β 42 to a reference A β subtype called A β 40 based on the hypothesis that A β 42 declines in blood when it begins to bind to the cerebral cortex while A β 40 acts as the referent for normal levels of A β 42 expression. However, amyloidogenesis—the process of β -Amyloid production—may also serve an adaptive purpose when isolating viral particles. Prior research has reported that A β 40 is upregulated following infection and could help the brain to isolate and interrupt replication of viral particles.⁶ Increases in A β 40 levels, are associated with increased phosphorylated tau burden in the cerebrospinal fluid,^{7–9} neuroinflammation,¹⁰ and

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activated astrocytes.¹¹ Thus, it is important that we better understand the determinants of A β 40 expression in humans.

Emerging research suggests that APx exposures could trigger amyloidogenesis and may have neuropathological implications. Indeed, APx contains a mix of contaminants and chemicals (eg, fine particulate matter, dioxins, heavy metals, and polycyclic aromatic hydrocarbons) that are small enough to cross the blood-brain barrier and could induce a neuroimmune response increase the risk of cognitive dysfunction and dementia.^{12,13} APx exposure has long been associated with changes in cognition in mice¹⁴ but studies of human aging have also reported a dose-response relationship between APx exposure and lower levels of verbal recall¹⁵ and executive functioning.¹⁶ In conditions of APx exposure, researchers have reported sustained increases in circulating levels of both A β 40 and A β 42 when examining rodents¹⁷ and among people with lengthy exposures to traffic exhaust.¹⁸ Seeking to better understand the interpretation of APx exposures and amyloidogenesis, several autopsy studies have reported that APx exposures are associated with evidence of metal in the brain coincident with the development of other inflammatory signatures including gliosis¹⁴ as well as hyperphosphorylated tau.¹⁹

Following the collapse of the World Trade Center (WTC) on September 11, 2001, survivors and first responders were severely and repeatedly exposed to fine particulate matter and known neurotoxic materials,²⁰ including heavy metals, polycyclic aromatic hydrocarbons, and persistent organic pollutants including dioxins.^{21,22} Building on these exposures, studies of WTC survivors and responders have reported that cognitive performance was reduced among those reporting WTC exposure duration²³ and dust exposure among WTC survivors.²⁴ Interrogating temporal change in cognition, a recent study clarified that WTC exposure severity was also associated with an increased incidence of dementia in WTC responders who were under 65 years old.²⁵ Neuroimaging studies have supported these results, showing that WTC exposure duration was associated with hippocampal atrophy²⁶ and neuroinflammation.^{27,28} Interrogating biomarkers, studies have reported that dust exposures is associated with cerebral amyloidosis in mice,²⁹ and phosphorylated tau-181 (pTAU181) without changes in the A β -40/42 ratio among WTC responders.³⁰

In this study, we hypothesized that responders who were most severely exposed at the WTC while working in rescue and recovery work might express heightened levels A β 40. Furthermore, we felt that if A β 40 is responding to a potential exposure to neurotoxins, then increased levels of A β 40 might also be associated with other neuropathological outcomes including increased levels of phosphorylated tau and neurofilament-light alongside cortical degeneration.

Methods

Ethics

This study was approved by the Stony Brook University Institutional Review Board. All participants provided written informed consent.

Setting

Since 2016, studies of first responders who were severely exposed to APx during response efforts at the WTC have reported that more severe exposures are associated with

cognitive dysfunction³¹ and recently reported that exposures were associated with increased levels of circulating phosphorylated tau absent increased amyloid burden as measured using the Alzheimer's disease A β -40/42 ratio.³⁰

Inclusion/exclusion criteria include consenting to research and willingness to provide plasma, successful processing and storage of bloodwork prior to assessment. We also excluded observations where glial fibrillary acidic protein (GFAP) values were indicative of evidence of stroke (history of stroke or GFAP $\geq$ 200)³² and excluded individuals with outlying values on other measures including for neurofilament light (NfL $\geq$ 50), 0.45 > pTAU181 $\geq$ 20, or 1 > A β 42 $\geq$ 20 because these values were rare and potentially influential.

Plasma collection

Non-fasting plasma samples were collected from consented patients during routine monitoring visits in 2019. These whole blood samples were collected via venipuncture in BD Vacutainers containing K2 EDTA. Samples were centrifuged at 4°C at 2000 g for 15 minutes. The supernatant (plasma) was transferred into cryogenic vials and stored in -80°C freezers until analysis. We used the Simoa Human Neurology four-plex assay to measure A β 40 (lower limit of quantification [LLOQ]=1.02 picograms per milliliter [pg/mL]), A β 42 (LLOQ=0.38 pg/mL), GFAP (LLOQ=0.686 pg/mL) and NfL (LLOQ=0.40 pg/mL) along with a pTAU181 single-assay kit (LLOQ=0.09 pg/mL). Assays passed quality control procedures, and mean coefficients of variation were within acceptable ranges (<5%). Several samples (five pTAU181, one NfL, and one A β 42) had analytes below the LLOQ. Due to instrumentation error, we removed five participants were missing information on A β 42, A β 40, and NfL, and 12 were missing information on pTAU181. Those with missing plasma samples did not differ when compared to those whose data were successfully assayed. Our outcome of interest in this study was amyloidogenesis, which we proxied as the total circulating levels of A β 40. To facilitate comparisons between individuals of different ages and genders, we normalized A β 40 levels using a calculation based on data for the least exposed WTC responders with minimal exposures and without cardiovascular disease (CVD) or Post-Traumatic Stress Disorder (PTSD): Normalized A β 40=observed A β 40/expected A β 40, where expected A β 40=0.272*(Age-50)-0.050*(Age-50)²+0.263*BVOL-12.73 8*Black+0.695 *Hispanic-1.316*Other+68.911.

Measures

World Trade Center Exposure Severity was measured using a validated expert-assessed Neurotoxic Exposure Severity Index.²⁵ This measure is a combined measure using self-reported information about exposures, response activities, and timing measures that has five categories ranging from minimal exposure, a category reserved for people who never reported dust exposures or who consistently wore full personalized protective equipment during their response period, to severe exposure, a category reserved for individuals who were regularly and extensively exposed to dust and other debris while conducting dangerous work without personalized protective equipment.

Post-Traumatic Stress Disorder is a common psychological response after traumatic exposures³³ that is associated with symptoms of neurodegeneration³⁴ and evidence of neuroinflammation in WTC responders.³⁵ We incorporated measures of probable PTSD assessed using the 17-item PTSD Checklist

(PCL) designed for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.³⁶ PCL items were modified to specifically focus on WTC trauma, and the PCL score was created by summing symptoms (Cronbach's $\alpha=0.95$).

Demographic and Medical Factors were retrieved from questionnaires and medical records. Demographics included age, sex, race/ethnicity, educational attainment, and whether a person was trained as a first responder. Medical conditions including a history of severe or chronic head injuries including during military service, as well as several diseases like obstructive airway disease, cancer, and gastroesophageal disease that are common in this population. Since cardiovascular disease (CVD) burden is known to affect the risk of cerebral amyloid angiopathy (CAA), a condition that is known to involve A β 40 deposition in the occipital lobe, we measured CVD using a summation of the number of diagnosed cardiovascular diseases including hypertension, heart disease, diabetes, and stroke.

Neuroimaging sub-study

In a subgroup of individuals, we examined correlations between normalized A β 40 levels and cortical thickness measures derived from our nested neuroimaging study.³⁷ Briefly, neuroimaging was completed on 70 participants for whom blood was also available, and a T1-weighted magnetization prepared rapid gradient echo sequence was completed. Cortical thickness was measured across 68 unilateral regions using Computational Anatomical Tomography (CAT12) following an established and validated protocol.³⁸ To simplify data analysis, we used a previously validated cortical thickness meta-region of interest that was derived to facilitate detection of WTC-related early-onset dementia and represents evidence of bilateral reductions in cortical thickness in the frontal pole, lateral and medial orbitofrontal, supramarginal, isthmus cingulate, middle, superior, and transverse temporal, pericalcarine, precentral, and rostral anterior and posterior cingulate alongside the pars opercularis, triangularis, and orbitalis.³⁹

Genotyping

A sub-study of participants also completed an apolipoprotein- ϵ 4 (APOE4) genotyping study ($n=690$), however since APOE4 was not associated with A β 40 distribution (Figure S1) before or after covariable adjustment, and further since examinations of whether APOE4 status might moderate associations between A β 40 and serological measures of neurodegeneration, we chose not to show genotyping results in the current study.

Statistical analyses

We began by describing the sample overall and, for descriptive purposes alone, we stratified the sample into high versus low exposure. Next, we examined correlations between age, CVD burden, and WTC exposure severity with Normalized A β 40 levels. We provided scatter plots with linear best-fitting lines to show overall direction of association. A β 40 levels were not expected to follow a Gaussian distribution, so we also provided violin plots showing expectations for normalized A β 40 levels to show differences by exposure status. Non-Gaussian distribution led us to use Spearman's rho to examine unadjusted associations with putative biomarkers. For multivariable-adjusted models, we implemented a log-Gamma model with a robust variance estimator. Log-gamma models were used because they accurately address distributional skew in outcomes as a result of being measured as distributional weight

or volume in standardized serological samples.⁴⁰ Log-Gamma coefficients were transformed to report blood volume ratios (VR) and multivariable-adjusted volume ratios (aVR) alongside 95% confidence intervals [95% C.I.] and associated *P*-values. Analyses were completed using Stata 17/MP [StataCorp].

Results

Our study included 970 individuals with exposure information for whom plasma data were successfully measured. Of these, 46 responders were excluded due to high GFAP levels or a history of stroke. Exclusions for outlying values resulted in loss of seven A β 42, two NfL, and four pTAU181 observations. As shown in Table 1, the analytic sample of responders ($N=905$) was predominantly male, and most had at least some college education. The average responder was aged 55.98 when plasma biomarkers were retrieved.

WTC exposure, CVD burden, and amyloidogenesis

To examine factors that might be associated with raw A β 40 levels (Table 2). Overall, these results showed that A β 40 levels were 104.79 in severely exposed WTC responders as compared to 99.09 in minimally exposed WTC responders. Interestingly, we also found that both in raw and normalized measures, age, CVD burden, and any WTC exposure were associated with statistically significant increases in A β 40 levels before and after normalization, though results were somewhat stronger when using normalized data as compared to raw data.

Correlations among putative neurodegenerative biomarkers

Next, we examined correlations between increased Normalized A β 40 levels and other markers of Alzheimer's-related

Table 1. Characteristics describing the whole sample, and stratified by minimal to mild versus moderate to severe exposures for descriptive purposes alone.

Characteristics	Sample ($n=905$)	Minimal to mild exposure severity ($n=533$)	Moderate to severe exposure ($n=372$)
Age, years	58.05 (7.64)	57.16 (6.92)	59.33 (8.42)
Estimated blood volume, mL	59.6 (4.82)	59.6 (4.63)	59.6 (5.09)
Cardiovascular disease burden	1.61 (0.75)	1.55 (0.73)	1.7 (0.77)
	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)
Female	65 (6.7%)	42 (7.6%)	18 (4.7%)
Education			
High school diploma	224 (24.8%)	100 (18.8%)	124 (33.3%)
Some college	466 (51.5%)	288 (54%)	178 (47.8%)
University degree	215 (23.8%)	145 (27.2%)	70 (18.8%)
Untrained responder	242 (26.7%)	49 (9.2%)	193 (51.9%)
Supervisor	134 (14.8%)	108 (20.3%)	26 (7%)
Post-traumatic stress disorder, Sx	1.62 (0.75)	1.5 (0.65)	1.8 (0.84)
Obstructive airway disease	134 (14.8%)	108 (20.3%)	26 (7%)
All-cause cancer	40 (4.4%)	23 (4.3%)	17 (4.6%)

We report frequency (%) or means (standard deviations). Abbreviations: mL; milliliters; Sx, symptom severity.

Table 2. Plasma blood volume ratios (VR) and 95% confidence intervals derived from log-gamma generalized linear models showing associations with normalized A β 40 levels.

Characteristics	Unadjusted model			Multivariable-adjusted model		
	VR	95% CI	P	aVR	95% CI	P
Age, years	1.014	1.012-1.016	<.001	1.014	1.012-1.016	<.001
Cardiovascular disease burden	1.058	1.038-1.078	<.001	1.059	1.039-1.079	<.001
WTC neurotoxic exposure severity						
Minimal	1.000			1.000		
Mild	1.078	1.018-1.141	.010	1.080	1.020-1.142	.008
Moderate	1.083	1.021-1.147	.008	1.091	1.029-1.156	.003
High	1.105	1.026-1.191	.008	1.119	1.038-1.205	.003
Severe	1.095	1.004-1.194	.040	1.112	1.018-1.215	.019

Multivariable-adjusted models account for age, sex/gender, race/ethnicity, education, occupation, supervisor status, PTSD symptom severity, obstructive airway disease, all-cause cancer, blood volume, and cardiovascular disease burden.

Abbreviations: aVR, multivariable-adjusted distribution volume ratios estimated from a log-Gamma model; PTSD, post-traumatic stress disorder; VR, distribution volume ratios estimated from a log-Gamma model; WTC, World Trade Center; 95% CI, 95% confidence interval.

Table 3. Spearman's correlations between normalized β -amyloid levels in plasma, and biomarkers of cerebral damage.

Plasma levels	Non-parametric unadjusted correlation		Multivariable-adjusted log-gamma coefficient		
	Rho	P	B	SE	P
Phosphorylated Tau 181	0.16	<.001	0.384	0.083	<.001
β -Amyloid42	0.54	<.001	0.635	0.033	<.001
Neurofilament light	0.16	<.001	0.436	0.065	<.001
Glial fibrillary acidic protein	0.14	<.001	0.431	0.054	<.001
Ratios					
Amyloid ratio, A β 40/42	0.31	<.001	0.245	0.033	<.001
Amyloid-linked tauopathy, pTAU181/A β 42	-0.28	<.001	-0.480	0.091	<.001
Neurodegenerative tau, pTAU181 & NfL	0.18	<.001	0.539	0.078	<.001
Neuroinflammation, GFAP/NfL	-0.02	.593	0.007	0.070	.923

Multivariable-adjusted models account for age, sex/gender, race/ethnicity, education, occupation, supervisor status, PTSD symptom severity, obstructive airway disease, all-cause cancer, blood volume, and cardiovascular disease burden.

Abbreviations: A β , β -amyloid; GFAP, glial fibrillary acidic protein; NfL, neurofilament-light; pg/mL, picograms per milliliter; PTSD, post-traumatic stress disorder; SE, standard error.

eurodegeneration (Table 3). Bivariate correlational analyses (first column) showed consistent, positive associations between higher levels of Normalized A β 40 and higher levels of pTAU181, NfL, and GFAP as well as variation in the cerebral tauopathy, and neurodegenerative tauopathy ratios. As would be expected, Normalized A β 40 was associated with higher amyloid ratios consistent with reduced cerebral amyloidosis. After adjusting for confounders (second column), log-Gamma models revealed statistically significant associations between Normalized A β 40 and higher levels of pTAU181, NfL, and GFAP. Similar associations were evidence in ratio measures of neuropathology.

Neuroimaging results

To address the concern that elevated cerebral immune response in plasma could cause biased results when examining other biomarkers in blood, we next validated these results using

results from the structural neuroimaging study (Figure 1). These analyses revealed that increased A β 40 was moderately associated with evidence of cortical atrophy across WTC-related regions of interest ($\rho = -0.29$, $P = .02$) and appeared somewhat stronger among cognitively impaired responders ($\rho = -0.41$, $P = .02$).

Discussion

Amyloid burden is a topic of interest across studies of blood-based biomarkers in Alzheimer's disease. Many researchers use a ratio of A β 40 and A β 42 based on the hypothesis that A β 42 declines when it begins to bind to the cerebral cortex, while A β 40 is used as a generic reference. In this study of WTC responders, we examined A β 40 levels with and without normalization and found that higher A β 40 levels in the blood increased with age and were associated with both CVD burden and WTC exposure severity. These findings suggest that using A β 40 to normalize A β 42 levels are likely to be biased by the degree of CVD burden and by potential neurotoxic exposures. Nevertheless, we have also shown that increased levels of A β 40 are associated with increases in other blood-based biomarkers and, also, with reduced cortical thickness.

Severe or prolonged exposures to air pollution (APx) produce long-term effects on a person's physical health. These particulates are small enough to affect not just the respiratory system but also the cortices of the brain, resulting in decreased cognitive function.⁴¹ Symptoms appear to include cognitive impairment, often at midlife,⁴² accompanied by relatively unique signs of neurodegeneration in the cerebral³⁷ and cerebellar cortices⁴³ and in the hippocampus.²⁶ In this study, we examined whether increased amyloidogenesis as measured in plasma was associated with other biomarkers of neurodegenerative diseases. The findings in this study supported a model where exposure severity correlated to an increase in amyloidogenesis, and corresponding evidence of phosphorylated tau-181, neurofilament-light, and cortical atrophy.

This study follows on a mouse modeling study that showed that inhaled exposure to WTC dust resulted in an amyloidogenic response, causing both an increase in A β 40 and A β 42 levels in the rodent hippocampus, results that were accompanied by increases in glial activation in a second rodent model.⁴⁴ Here, we similarly reported increases in circulating A β 40 levels were coincident with increases in circulating A β 42 and with

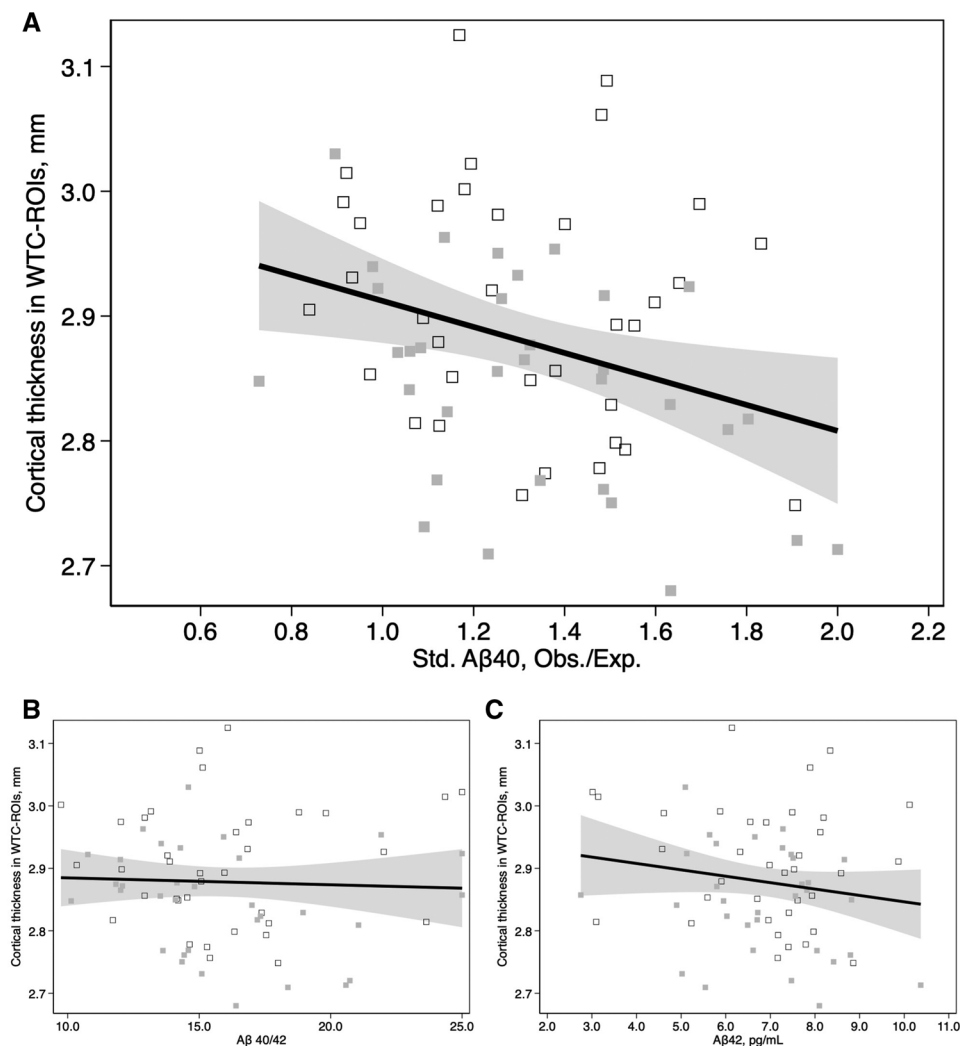


Figure 1. Scatter plot showing the correlation between lower cortical thickness and higher plasma distribution of (A) normalized A β 40 ($\rho = -0.29$, $P = .02$), (B) A β 42 (not significant), and the (C) A β -40/42 ratio (not significant) in a nested study of responders who completed neuroimaging ($n = 70$). For descriptive purposes, gray squares indicate responders with mild to severe cognitive impairment while hollow squares show individuals who are cognitively unimpaired. Exp., expected; Obs., observed; Std., standardized; WTC-ROI, a World Trade Center (WTC) signature meta-region of interest (ROI) established on cortical thickness analysis.

increases in glial activation as measured using GFAP, as well as with axonal injury as measured using both cortical thickness and Neurofilament-light. These results match well with studies showing changes in cerebral amyloid in mice exposed to inhaled WTC dust.²⁹ Together with prior results showing that increases in WTC exposure duration were associated with increased glial activation as measured using translocator protein²⁷ coupled with evidence of neuroinflammation in the hippocampi,⁴⁵ our results suggest that amyloidogenesis might be a central part to the brain's response to neurotoxic infiltrate.

Interestingly, we found that A β 40 was associated with exposures but not with APOE4 allele possession. Studies suggest that the impact of APOE4 on the risk of AD is predominantly characterized by variability in levels of circulating A β 42 rather than levels of A β 40,⁴⁶ resulting in the use of the A β 40/42 ratio in studies of AD. Here, we propose that A β 40 levels, which are used as a putative reference category, may be biased in part by neurotoxic exposures that is not associated with genotype. However, genotype does predict risk of cognitive decline in this population³⁴ and prior research has also found that APOE4 allele possession increases the association between WTC

exposure duration and incidence of MCI.⁴² Explanations for variation in findings may include that genotype affects the onset of symptoms following neuropathology. APOE4 could also reduce cognitive reserve in APx exposure, though such results have not been generally found in previous studies of AD.⁴⁷ Further work is needed to determine the effect of genotype in the context of APx exposure.

To date, relatively little is known about the distal consequences and mechanisms linking WTC exposures to neurodegeneration and the role that A β 40 might play. One theory is that there is a direct association between exposure and tauopathy, as shown in a study of mice introduced to ambient outdoor fine particulate air pollution for a period of three months that produced increased level of phosphorylated tau in the olfactory bulb and hippocampus.⁴⁸ In each case, studies have shown that phosphorylated tau presents a significant intercorrelation with memory across several studies including in the present cohort.⁴⁹ However, researchers have noted that the presence of amyloidogenesis in humans may be an indicator of the presence of CAA among individuals with comorbid Alzheimer's disease,⁵⁰ a condition that can increase the disease

severity. This presents further opportunities for longitudinal studies to examine how changes in amyloidogenesis might be correlated with cognitive performance and decline.

Strengths and limitations

This study is subject to several important limitations. First, while the distribution of A β 40 and A β 42 was measured, there are other amyloid proteins that were not measured, and little is known about their role in this process. However, unlike in imaging studies, we could analyze the presence of these two factors and could therefore, for the first time, also show that while the ratio of A β 40 might increase consistent with a cerebral amyloidosis, this increase was associated with an increase in A β 40 rather than a decrease in A β 42 as is generally hypothesized.

Second, while APx exposures at the WTC sites are not unique, the severity and complexity of the exposure is unique. Several chemicals that were common in the WTC dust include extremely toxic substances including dioxins and furans that are more heavily regulated now than they were in the 1970s when the WTC was built. Similarly, the airplanes and jet engines were a sizable part of the detritus on the ground that burned throughout the response periods, and these are made up of high-temperature alloys that are uncommon in the general population. Thus, the generalizability of this exposure to other APx exposures remains unclear.

Third, while studies have shown that plasma produces equal or better predictors of cognitive decline in several biomarkers when compared to measures of cerebral spinal fluid,⁵¹ this is not generally true of serological measures of amyloid since, in part, amyloid is not expressed in the brain and can be recruited to respond to pathology in other organs.⁵²

Fourth, as the population is predominately White males, the sample population lacks power when it comes to these findings being definitively significant for both women and those of minority background. This study also does not have an external control group comprised of non-responders who were not exposed to the aftermath of the WTC attacks for comparison.

Finally, since there were 18 years between the 9/11 disaster and blood draw, there may be additional factors including chronic exposure to residential or occupational air pollutants, or other unobserved factors that could modify the distribution of A β 40 in this sample.

Conclusion

Amyloidogenesis may be dysregulated by exposures to APx, and by older age and the presence of CVD. This may imply that Amyloidogenesis may bias levels of A β 40 in serology and may therefore become a poor reference score for identifying ADRD in some populations. In addition, our finding that the increased distribution of Amyloidogenesis was associated with decreased cortical thickness in the brains of neuroimaged responders with/without cognitive impairment who lacked evidence of stroke implies, further, that not only are A β 40 levels changed by these factors but that such changes may be pathogenic. These findings, coupled with others,²⁰ may suggest that exposures to dust and fumes from an uncontrolled building collapse has the potential to cause a toxic encephalopathy with a lengthy latency period potentially consistent with a latent form of Type II toxic encephalopathy.²⁰ Future work is warranted examining the potential role of A β 40 in this condition and, also, its correlation with cerebral amyloidosis or tauopathy in studies of cerebral etiology.

Author contributions

Alissa Barber, Ryan Chacon, Sean A.P. Clouston, and Benjamin J. Luft contributed to the conception or design of the work; Alissa Barber, Ryan Chacon, Melissa A. Carr, Sean A.P. Clouston, Frank D. Mann, Benjamin J. Luft, Pei-Fen Kuan, and Xiaohua Yang contributed to the acquisition, analysis, or interpretation of data for the work; Alissa Barber and Ryan Chacon drafted the work or revising it critically for important intellectual content; all authors oversaw the final approval of the version to be published. Sean A.P. Clouston agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Supplementary material

Supplementary material is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflicts of interest

None declared.

Institution and ethics approval and informed consent

Ethical approval to conduct data analyses were obtained at Stony Brook University. All participants provided informed written consent.

Data availability statement

Data can be provided to bona fide investigators following receipt of a written statement of interest to the corresponding author.

References

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2023;19:1598-1695. <https://doi.org/10.1002/alz.13016>
2. 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. [https://doi.org/10.1016/S0140-6736\(24\)01296-0](https://doi.org/10.1016/S0140-6736(24)01296-0)
3. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* 2010;9:119-128. [https://doi.org/10.1016/S1474-4422\(09\)70299-6](https://doi.org/10.1016/S1474-4422(09)70299-6)
4. Dickson T, Vickers J. The morphological phenotype of β -amyloid plaques and associated neuritic changes in Alzheimer's disease. *Neuroscience.* 2001;105:99-107.
5. Kumar-Singh S, Pirici D, McGowan E, et al. Dense-core plaques in Tg2576 and PSAPP mouse models of Alzheimer's disease are centered

- on vessel walls. *Am J Pathol.* 2005;167:527-543. [https://doi.org/10.1016/S0002-9440\(10\)62995-1](https://doi.org/10.1016/S0002-9440(10)62995-1)
6. Wainberg M, Luquez T, Koelle DM, et al. The viral hypothesis: how herpesviruses may contribute to Alzheimer's disease. *Mol Psychiatry.* 2021;26:5476-5480. <https://doi.org/10.1038/s41380-021-01138-6>
 7. Lehmann S, Dumurgier J, Aygnac X, et al. Cerebrospinal fluid A beta 1-40 peptides increase in Alzheimer's disease and are highly correlated with phospho-tau in control individuals. *Alzheimers Res Ther.* 2020;12:123. <https://doi.org/10.1186/s13195-020-00696-1>
 8. Leal SL, Lockhart SN, Maass A, Bell RK, Jagust WJ. Subthreshold amyloid predicts tau deposition in aging. *Journal of Neuroscience.* 2018;38:4482-4489.
 9. Stein TD, Montenegro PH, Alvarez VE, et al. Beta-amyloid deposition in chronic traumatic encephalopathy. *Acta Neuropathologica.* 2015;130:21-34.
 10. Kulesh AA, Drobakha VE, Kuklina EM, Shestakov VV. Amyloid-beta 40 as a biomarker of cognitive impairment in acute ischemic stroke. *Bull Sib Med.* 2017;16:79-86.
 11. Serrano-Pozo A, Mielke ML, Muzitansky A, et al. Stable size distribution of amyloid plaques over the course of Alzheimer disease. *J Neuropathol Exp Neurol.* 2012;71:694-701.
 12. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet commission. *Lancet.* 2020;396:413-446. [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6)
 13. Calderon-Garciduenas L, Villarreal-Rios R. Living close to heavy traffic roads, air pollution, and dementia. *Lancet.* 2017;389:675-677. [https://doi.org/10.1016/S0140-6736\(16\)32596-X](https://doi.org/10.1016/S0140-6736(16)32596-X)
 14. Fonken LK, Xu X, Weil ZM, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. *Mol Psychiatry.* 2011;16:987-995. <https://doi.org/10.1038/mp.2011.76>
 15. Salinas-Rodriguez A, Fernandez-Nino JA, Manrique-Espinoza B, et al. Exposure to ambient PM(2.5) concentrations and cognitive function among older Mexican adults. *Environ Int.* 2018;117:1-9. <https://doi.org/10.1016/j.envint.2018.04.033>
 16. Ailshire JA, Clarke P. Fine particulate matter air pollution and cognitive function among US older adults. *J Gerontol B Psychol Sci Soc Sci.* 2015;70:322-328.
 17. Kim SH, Knight EM, Saunders EL, et al. Rapid doubling of Alzheimer's amyloid-beta40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution. *F1000Res.* 2012;1:70. <https://doi.org/10.12688/f1000research.1-70.v1>
 18. Hajat A, Park C, Adam C, et al. Air pollution and plasma amyloid beta in a cohort of older adults: evidence from the Ginkgo Evaluation of Memory study. *Environ Int.* 2023;172:107800. <https://doi.org/10.1016/j.envint.2023.107800>
 19. Calderon-Garciduenas L, Stommel EW, Torres-Jardon R, et al. Alzheimer and Parkinson diseases, frontotemporal lobar degeneration and amyotrophic lateral sclerosis overlapping neuropathology start in the first two decades of life in pollution exposed urbanites and brain ultrafine particulate matter and industrial nanoparticles, including Fe, Ti, Al, V, Ni, Hg, Co, Cu, Zn, Ag, Pt, Ce, La, Pr and W are key players. Metropolitan Mexico City health crisis is in progress. *Front Hum Neurosci.* 2023;17:1297467. <https://doi.org/10.3389/fnhum.2023.1297467>
 20. Clouston SAP, Hall CB, Kritikos M, et al. Cognitive impairment and World Trade Centre-related exposures. *Nat Rev Neurol.* 2022;18:103-116. <https://doi.org/10.1038/s41582-021-00576-8>
 21. Lioy PJ, Georgopoulos P. The anatomy of the exposures that occurred around the World Trade Center site: 9/11 and beyond. *Ann N Y Acad Sci.* 2006;1076:54-79. <https://doi.org/10.1196/annals.1371.002>
 22. Landrigan PJ, Lioy PJ, Thurston G, et al. Health and environmental consequences of the world trade center disaster. *Environ Health Perspect.* 2004;112:731-739. <https://doi.org/10.1289/ehp.6702>
 23. Chen APE, Clouston SAP, Kritikos M, et al. A deep learning approach for monitoring parietal-dominant Alzheimer's disease in World Trade Center responders at midlife. *Brain Commun.* 2021;3:fcab145. <https://doi.org/10.1093/braincomms/fcab145>
 24. Rosen R, Shao Y, Zhang Q, et al. Cognitive function among World Trade Center-exposed community members with mental health symptoms. *Int J Environ Res Public Health.* 2022;19:3440. <https://doi.org/10.3390/ijerph19063440>
 25. Clouston SAP, Mann FD, Meliker J, et al. Incidence of Dementia Before Age 65 Years Among World Trade Center Attack Responders. *JAMA network open.* 2024;7:e2416504. <https://doi.org/10.1001/jamanetworkopen.2024.16504>
 26. Deri Y, Clouston SAP, DeLorenzo C, et al. Selective hippocampal subfield volume reductions in World Trade Center responders with cognitive impairment. *Alzheimers Dement (Amst).* 2021;13:e12165. <https://doi.org/10.1002/dad2.12165>
 27. Deri Y, Clouston SAP, DeLorenzo C, et al. Neuroinflammation in World Trade Center responders at midlife: A pilot study using [(18)F]-FEPPA PET imaging. *Brain Behav Immun Health.* 2021;16:100287. <https://doi.org/10.1016/j.bbih.2021.100287>
 28. Kritikos M, Huang C, Clouston SAP, et al. DTI connectometry analysis reveals white matter changes in cognitively impaired World Trade Center responders at midlife. *J Alzheimers Dis.* 2022;89:1075-1089. <https://doi.org/10.3233/JAD-220255>
 29. Iban-Arias R, Trageser KJ, Yang EJ, et al. Exposure to World Trade Center dust exacerbates cognitive impairment and evokes a central and peripheral pro-inflammatory transcriptional profile in an animal model of Alzheimer's disease. *J Alzheimers Dis.* 2023;91:779-794. <https://doi.org/10.3233/JAD-221046>
 30. Kritikos M, Diminich ED, Meliker J, et al. Plasma amyloid beta 40/42, phosphorylated tau 181, and neurofilament light are associated with cognitive impairment and neuropathological changes among World Trade Center responders: a prospective cohort study of exposures and cognitive aging at midlife. *Alzheimers Dement (Amst).* 2023;15:e12409. <https://doi.org/10.1002/dad2.12409>
 31. Clouston S, Pietrzak RH, Kotov R, et al. Traumatic exposures, post-traumatic stress disorder, and cognitive functioning in World Trade Center responders. *Alzheimers Dement (N Y).* 2017;3:593-602. <https://doi.org/10.1016/j.trci.2017.09.001>
 32. Mayer CA, Brunkhorst R, Niessner M, Pfeilschifter W, Steinmetz H, Foerch C. Blood levels of glial fibrillary acidic protein (GFAP) in patients with neurological diseases. *PLoS One.* 2013;8:e62101. <https://doi.org/10.1371/journal.pone.0062101>
 33. Bromet EJ, Hobbs MJ, Clouston SA, Gonzalez A, Kotov R, Luft BJ. DSM-IV post-traumatic stress disorder among World Trade Center responders 11-13 years after the disaster of 11 September 2001 (9/11). *Psychol Med.* 2016;46:771-783. <https://doi.org/10.1017/S0033291715002184>
 34. Mann FD, Clouston SAP, Cuevas A, et al. Genetic liability, exposure severity, and post-traumatic stress disorder predict cognitive impairment in World Trade Center responders. *J Alzheimers Dis.* 2023;92:701-712. <https://doi.org/10.3233/JAD-220892>
 35. Natale G, Kritikos M, Kuan PF, et al. Glial suppression and post-traumatic stress disorder: a cross-sectional study of 1,520 world trade center responders. *Brain Behav Immun Health.* 2023;30:100631. <https://doi.org/10.1016/j.bbih.2023.100631>
 36. Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist (PCL): reliability, validity, and diagnostic utility. Annual meeting of the international society for traumatic stress studies, San Antonio, TX; 1993.
 37. Clouston SAP, Deri Y, Horton M, et al. Reduced cortical thickness in World Trade Center responders with cognitive impairment. *Alzheimers Dement (Amst).* 2020;12:e12059. <https://doi.org/10.1002/dad2.12059>
 38. Seiger R, Ganger S, Kranz GS, Hahn A, Lanzenberger R. Cortical thickness estimations of FreeSurfer and the CAT12 Toolbox in patients with Alzheimer's disease and healthy controls. *J Neuroimaging.* 2018;28:515-523. <https://doi.org/10.1111/jon.12521>
 39. Clouston SAP, Kritikos M, Deri Y, et al. A cortical thinning signature to identify World Trade Center responders with possible dementia. *Intell Based Med.* 2021;5:100032. <https://doi.org/10.1016/j.ibmed.2021.100032>

40. Merrill SJ. The stochastic dance of early HIV infection. *J Comput Appl Math*. 2005;184:242-257.
41. Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro , AIII, Schwartz J. Traffic-related air pollution and cognitive function in a cohort of older men. *Environ Health Perspect*. 2011;119:682-687. <https://doi.org/10.1289/ehp.1002767>
42. Clouston SAP, Diminich ED, Kotov R, et al. Incidence of mild cognitive impairment in World Trade Center responders: long-term consequences of re-experiencing the events on 9/11/2001. *Alzheimers Dement (Amst)*. 2019;11:628-636. <https://doi.org/10.1016/j.dadm.2019.07.006>
43. Clouston SAP, Kritikos M, Huang C, et al. Reduced cerebellar cortical thickness in World Trade Center responders with cognitive impairment. *Transl Psychiatry*. 2022;12:107. <https://doi.org/10.1038/s41398-022-01873-6>
44. Hernandez M, Vaughan J, Gordon T, Lippmann M, Gandy S, Chen LC. World Trade Center dust induces nasal and neurological tissue injury while propagating reduced olfaction capabilities and increased anxiety behaviors. *Inhal Toxicol*. 2022;34:175-188. <https://doi.org/10.1080/08958378.2022.2072027>
45. Huang C, Kritikos M, Sosa MS, et al. World Trade Center site exposure duration is associated with hippocampal and cerebral white matter neuroinflammation. *Mol Neurobiol*. 2023;60:160-170. <https://doi.org/10.1007/s12035-022-03059-z>
46. Fryer JD, Simmons K, Parsadanian M, et al. Human apolipoprotein E4 alters the amyloid- β 40:42 ratio and promotes the formation of cerebral amyloid angiopathy in an amyloid precursor protein transgenic model. *J Neurosci*. 2005;25:2803-2810. <https://doi.org/10.1523/jneurosci.5170-04.2005>
47. Almeida RP, Schultz SA, Austin BP, et al. Effect of cognitive reserve on age-related changes in cerebrospinal fluid biomarkers of Alzheimer disease. *JAMA Neurol*. 2015;72:699-706. <https://doi.org/10.1001/jamaneurol.2015.0098>
48. Lee SH, Chen YH, Chien CC, et al. Three month inhalation exposure to low-level PM2.5 induced brain toxicity in an Alzheimer's disease mouse model. *PLoS One*. 2021;16:e0254587. <https://doi.org/10.1371/journal.pone.0254587>
49. Berron D, Vogel JW, Insel PS, et al. Early stages of tau pathology and its associations with functional connectivity, atrophy and memory. *Brain*. 2021;144:2771-2783. <https://doi.org/10.1093/brain/awab114>
50. Leitner D, Kavanagh T, Kanshin E, et al. Differences in the cerebral amyloid angiopathy proteome in Alzheimer's disease and mild cognitive impairment. *Acta Neuropathol*. 2024;148:9. <https://doi.org/10.1007/s00401-024-02767-1>
51. Pereira JB, Janelidze S, Stomrud E, et al. Plasma markers predict changes in amyloid, tau, atrophy and cognition in non-demented subjects. *Brain*. 2021;144:2826-2836. <https://doi.org/10.1093/brain/awab163>
52. Janelidze S, Stomrud E, Palmqvist S, et al. Plasma beta-amyloid in Alzheimer's disease and vascular disease. *Sci Rep*. 2016;6:26801. <https://doi.org/10.1038/srep26801>