

Plasma Biomarkers of Neuropathology Among World Trade Center Affected Community Members

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INTRODUCTION

More than 20 years after the destruction of the World Trade Center, exposed community members continue to experience long-term health consequences related to this environmental health disaster. Prior studies in the WTC Environmental Health Center (WTC-EHC) have documented persistent physical and mental health effects among community members, including chronic inflammation, posttraumatic stress pathology, and persistent PTSD symptoms, underscoring the lasting biological and psychological impact of 9/11 exposure. As this population ages, there is also evidence indicating that cognitive decline associated with WTC dust cloud exposure.¹⁻³ Evidence from a prospective study of WTC responders further suggests that several Alzheimer's disease (AD) plasma biomarkers are associated with cognitive impairment and neuropathological changes in WTC-exposed populations.⁴ In addition, blood-based biomarkers have shown promise in differentiating cognitively normal individuals, those with subjective cognitive decline (SCD), and those with mild cognitive impairment (MCI), supporting their potential utility in identifying early neurodegenerative processes.⁵ However, these biomarkers have not previously been evaluated in WTC-exposed community members. This study examined plasma biomarkers of neuropathology in WTC-EHC enrollees and compared them with participants from the NYU Alzheimer's Disease Research Center (NYU-ADRC), including cognitively unimpaired controls.

PURPOSE

To determine whether World Trade Center dust cloud exposure is associated with plasma biomarkers of neuropathology among WTC Environmental Health Center enrollees, and to compare these biomarker profiles with cognitively unimpaired and mild cognitive impairment participants from the NYU Alzheimer's Disease Research Center, in order to assess whether WTC exposure may be linked to biological changes associated with increased risk of cognitive decline.

METHODS

Plasma Aβ42, Aβ40, NfL, and GFAP were first assessed in 101 enrollees from the WTC-EHC to examine associations with WTC dust cloud exposure on 9/11. Within the WTC-EHC cohort, linear regression models were used to evaluate the association of dust cloud exposure (yes/no) with each biomarker, adjusting for age. A separate analysis was then conducted among participants aged 60 to 80 years to improve age comparability between WTC-EHC and NYU-ADRC cohorts (Table 1). This subset included WTC-EHC participants without WTC dust cloud exposure (n = 28), WTC-EHC participants with dust cloud exposure (n = 37), and NYU-ADRC participants categorized as cognitively unimpaired (CU, n = 104), subjective cognitive decline (SCD, n = 120), or mild cognitive impairment (MCI, n = 41). In the age-restricted analysis, Aβ42 was evaluated as the primary follow-up biomarker based on the initial WTC-EHC findings. Linear regression models compared biomarker levels across groups using CU as the reference group and adjusted for age, sex, and race/ethnicity (non-Hispanic White vs. all others). Biomarker distributions were evaluated, log transformation was applied where appropriate to reduce skewness, and a sensitivity analysis for Aβ42 was performed using Winsorization with values capped at the 99.5 percentile. Analyses of Aβ40, NfL, and GFAP in the age-restricted subset were considered secondary and exploratory and were interpreted accordingly.

The cloud in Lower Manhattan, south of Chambers Street



TABLES

Table 1. Cohort Group Demographics

	Exposure		Diagnostic group		
	no dust cloud	dust cloud	CU	SCD	MCI
Cohort	WTC-EHC	WTC-EHC	NYU-ADRC	NYU-ADRC	NYU-ADRC
n	28	37	104	120	41
Age					
mean (SD)	69.1 (6.23)	67.8 (5.04)	71.5 (4.98)	72.0 (5.05)	71.3 (5.37)
range	[60.5-79.5]	[60.9-78.4]	[60.9-79.7]	[60.3-79.7]	[61.2-80.0]
Female, n(%)	20 (71%)	23 (62%)	61 (59%)	95 (79%)	28 (68%)
Non-Hispanic White, n (%)	16 (57%)	12 (32%)	37 (36%)	48 (40%)	12 (29%)

Table 2. Linear Regression of Plasma Aβ42

	β	95% CI	p
Intercept	-1.36	[-2.79, 0.07]	0.06
no dust cloud vs. CU	0.06	[-0.33, 0.45]	0.77
dust cloud vs. CU	-0.41	[-0.76, -0.06]	0.02
SCD vs. CU	-0.09	[-0.33, 0.16]	0.49
MCI vs. CU	-0.29	[-0.62, 0.04]	0.09
Age	0.02	[0, 0.04]	0.05
Sex	-0.06	[-0.28, 0.16]	0.58
NHW	0.06	[-0.15, 0.27]	0.57

RESULTS

WTC-EHC cohort:

- WTC dust cloud exposure on 9/11 was associated with lower plasma Aβ42 levels (β = -1.06, 95% CI [-2.11, -0.01], p = 0.05)
- WTC dust cloud exposure did not reach significance for Aβ40, NfL, and GFAP

WTC-EHC vs. NYU-ADRC CU control

- Sample:** participants aged 60 to 80 years to improve age comparability between cohorts (Table 1)
- Reference group:** NYU-ADRC cognitively unimpaired (CU) participants
- Plasma Aβ42:**
 - WTC dust cloud exposure group had significantly lower plasma Aβ42 levels than CU (β = -0.142, p = 0.021) (Table 2)
 - WTC no dust cloud exposure group did not differ from CU (β = 0.020, p = 0.770)
 - Sensitivity analysis:* The association for the WTC dust group remained significant after Winsorization (Figure 1)
- Additional biomarkers:**
 - WTC dust was not significantly associated with Aβ40 relative to CU
 - WTC dust was not significantly associated with NfL relative to CU
 - Both WTC groups had lower GFAP than CU

FIGURE 1

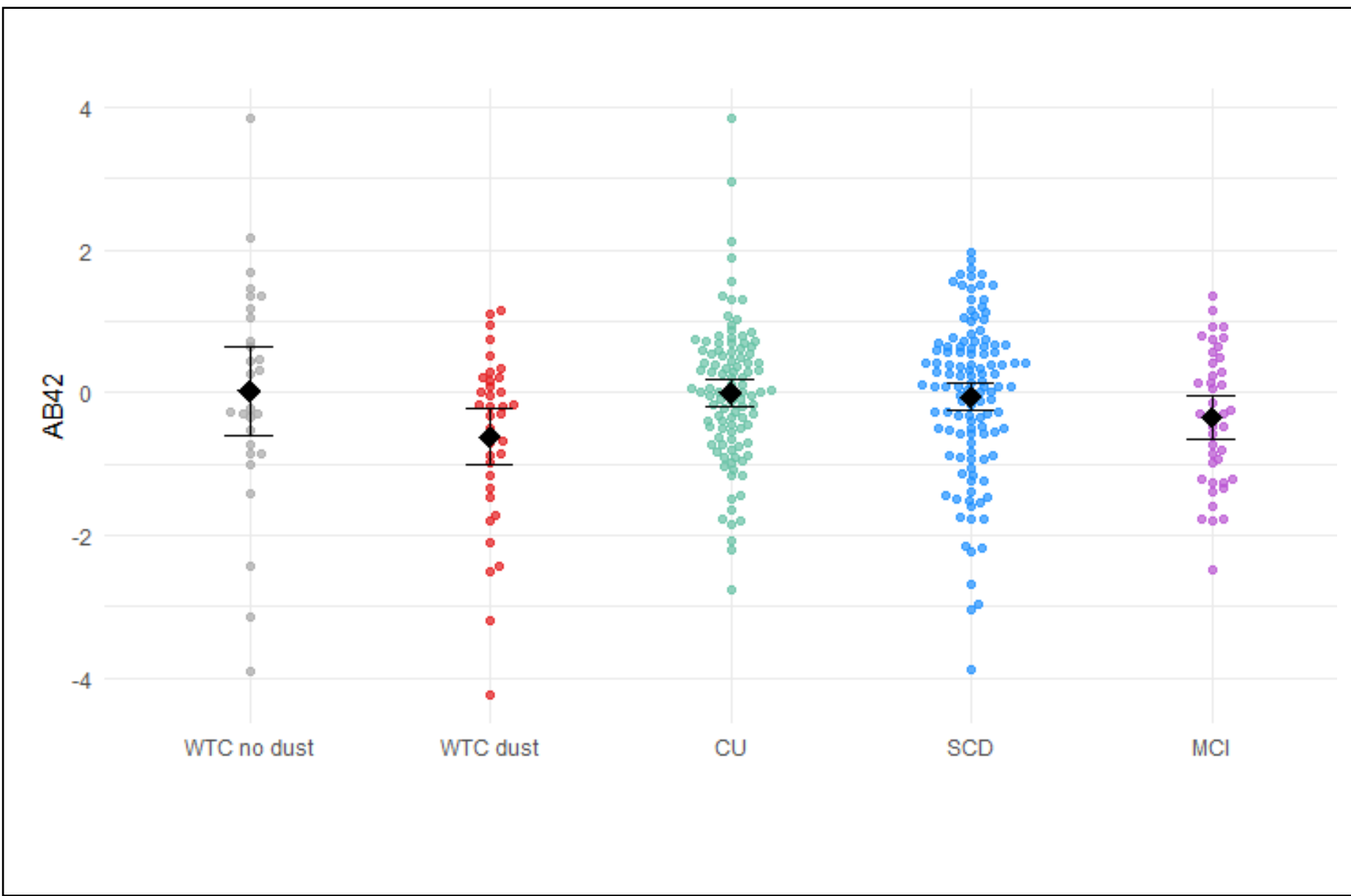


Figure 2

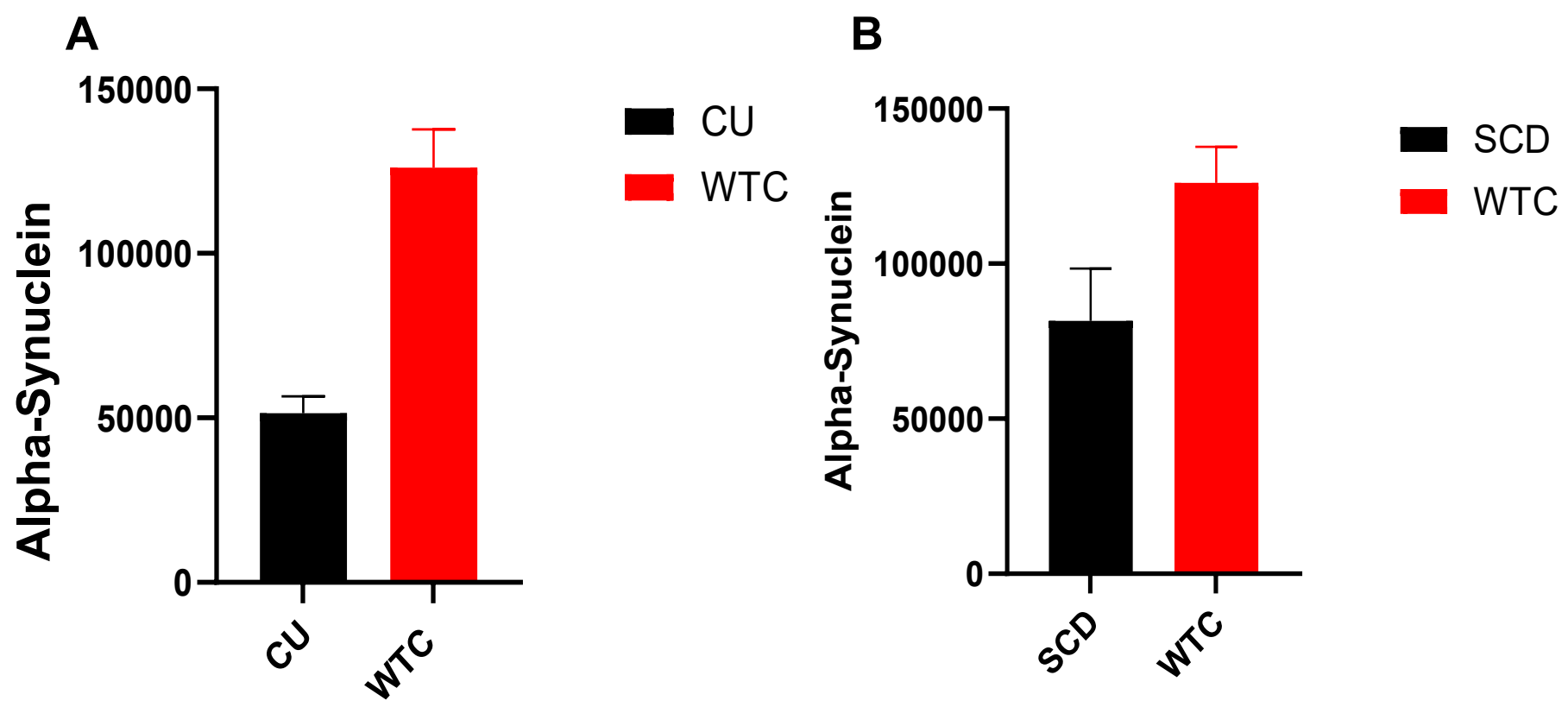


Figure 2: A) When we compared cognitively unpaired (CU) participants with negative WTC exposure to the WTC exposure cohort, the latter showed significantly higher levels of alpha-synuclein in their plasma samples (one-tailed t-test, p<0.0001). B) Patient participants With Subjective Cognitive Decline (SCD) were also compared to WTC exposure cohort, with the latter showing a significantly higher level of Alpha – Synuclein in plasma samples (One-tailed T-test, p=0.048)

CONCLUSION

More than 20 years after 9/11, those WTC-exposed community members with WTC dust cloud exposure showed lower plasma Aβ42 levels within the WTC-EHC cohort, and the dust-exposed group also had lower Aβ42 than NYU-ADRC cognitively unimpaired controls in the age-restricted cross-cohort analysis. These findings suggest that WTC dust cloud exposure may be associated with amyloid-related biological changes relevant to cognitive aging. Together, these results extend prior work demonstrating persistent physical and mental health effects in WTC-exposed populations, including chronic inflammation and posttraumatic stress burden, as well as lower MoCA scores being significantly associated with WTC dust cloud exposure¹⁻³ and align with emerging evidence that blood-based biomarkers may help identify neuropathological changes and cognitive risk in both WTC-exposed and aging populations.^{4,5} Further longitudinal studies are needed to determine whether reduced plasma Aβ42 predicts accelerated cognitive decline or neurodegenerative disease risk among WTC-exposed community members. Increased Alpha- Synuclein levels in the WTC cohort suggest an increased propensity for Lewy Body Dementia and Parkinson's Disease.

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