Date: 2/2/2025

To: World Trade Center Health Program
WTC@cdc.gov

John Howard, MD
Administrator, World Trade Center (WTC) Health Program
and Director of the National Institute of Safety and Health (NIOSH)

Re: Petition to add dementia and its prodrome, mild cognitive impairment, to the list of WTC-covered conditions under the Zadroga Act – including reference list with abstracts

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Dear Dr. Howard,

We are writing to recommend that dementia before age 65 years old (early onset dementia; **ICD-10 codes**: G30.0, G31.0, G31.9, F00.0, and F03 if symptom onset occurred before age ≤65 years) and MCI that occurred before age that continues to progress to dementia be added to the list of WTC-covered certifiable conditions under the Zadroga Act.

Our petition is based on evidence from multiple high-quality epidemiologic studies, supplemented with multiple high-quality biomarker studies, that demonstrate a consistently strong statistically significant association between WTC exposure and new-onset mild cognitive impairment and dementia in General Responders, Firefighters, and Survivors. Our proposal is consistent with the Administrator's recently published policy for adding non-cancers as WTC-covered conditions. Below, we summarize why this evidence meets WTC Health Program criteria for a "Category I (substantial likelihood for causal association)" designation and therefore qualifies for further review and a favorable decision.

To date, symptoms of cognitive impairment have only been covered if associated with a WTC-certified condition such as brain cancer or metastatic cancer and not due to other causes including neurodegenerative conditions. Our request would not include dementia due to cerebrovascular diseases including stroke, traumatic brain injury unrelated to the WTC response efforts, brain tumor, aneurysms or medically induced delirium. However, it would include dementias identified alongside behavioral problems because behavioral disturbances are common comorbidities and can result from neurodegenerative conditions.

Executive Summary

Alzheimer's disease or related dementia (ADRD) affects hundreds of thousands of Americans annually (2). The strongest risk factor for dementia is older age (3); **ADRD before the age of 65 years is very rare** (4). When present in individuals under the age of 65, ADRD tends to have similar symptoms and etiology, but more severe outcomes (5). **There is a scientific consensus that air pollution exposure causes ADRD in the general population (6). There is also consensus among a scientific panel convened by NIOSH that there isevidence supporting the critical importance of the types of exposures reported among WTC affected populations causing cognitive impairment and dementia** (7). These consensuses are built upon a wide array of studies across disciplines reporting, for example, severe exposures can cause neuropathology consistent in mice exposed to traffic exhaust (8) or dust settled following the World Trade Center (WTC) disaster (9, 10), children and teens exposed to heavy industrial air pollutants who died of accidents or suicides (11), children (12) and older adults (13) exposed to polychlorinated biphenyls, children and adults exposed to polycyclic aromatic hydrocarbons (14), as well as the neurotoxicity of fine particulate exposures containing heavy metals (15).

A recent study of WTC responders reported that the incidence of dementia before age 65 in WTC responders was 14.3/1,000 person-years (1), approximately 12 times higher than expected in people under age 65 years (16). **Results from the General Responder Cohort are generalizable to other WTC-affected populations**. For example, while much of the work thus far has focused on General Responders including NYPD and construction workers, studies of Survivors show that the prevalence of cognitive impairment was high (59% screened positive for any cognitive impairment) and appeared concentrated among survivors reporting any dust exposures (17). Similarly, studies of Firefighter responders have reported levels of MCI and dementia that were consistent with or higher than those generally reported in the General Responder Cohort (18). Building on the accumulation of strong and varying evidence, this application justifies the proposal for the WTC Health Program should cover ADRD before age 65 years in WTC-affected populations. In addition, patients that exhibit MCI prior to age 65 which continues to progress to dementia should be covered.

1. Background

ADRD affects hundreds of thousands of Americans annually (19). ADRD is most often recognized by its symptoms, which include progressive loss in memory, executive function, visuospatial functioning, and numeracy but can also include changes to physical functioning, mood, psychosis, or personality (20). Because of this complicated symptom structure, approximately 38% of cases of all-cause dementia remain undiagnosed in the general population (21).

ADRD is a catchall diagnosis for dementias resulting from a variety of neuropathological processes that specifically exclude cognitive impairment rising from other conditions including cerebrovascular diseases, drug-induced impairment, psychotic disease, and delirium. However, individuals with MCI and ADRD are at increased risk of poorer overall outcomes including increased vulnerability to financial problems (22, 23), difficulty managing care (24), functional limitations (25), and mortality (26). ADRD is defined, clinically, as evidence of functional limitations that result from neuropathological processes causing accelerated cognitive declines in domains of fluid cognition (27). However, researchers often report earliest changes include neuroinflammation (28), amyloidosis (29, 30), as well as mild to severe cognitive impairment (31).

ADRD is usually observed when there are at least two different types of neuropathology present in the cerebrum. The most common diagnosis is Alzheimer's disease (AD) as defined by the confluence of amyloidosis alongside tauopathy and neurodegeneration (32). AD-related dementias, like dementia with Lewy bodies or frontotemporal dementia, are often characterized by the presence of low-grade amyloidosis alongside a secondary neuropathology including cerebral tauopathy, alpha-synuclein, or TDP-43 (32). These neuropathological changes are progressive and can be synergistic (33). Ultimately, these changes result in cerebral atrophy evident across the hippocampi, cortex, cerebellum, and white matter (34, 35).

The latency period for ADRD is usually estimated to be 15-25 years long, based on the rate of cognitive decline exhibited by those who develop dementia (36). While the etiology of the array of different causes of ADRD is not well understood, agreed-upon risk factors include cardiovascular disease, repeated head trauma, low education (37), long-term exposure to air pollution (38), and a sedentary lifestyle (39).

1.1. ADRD Subtypes and Prodromes

ADRD before the age of 65 years is rare (4). For example, one study estimated the global incidence rate of ADRD before age 65 years to be 1.19/1,000 person-years (16). The largest known risk factor for dementia is old age, with one study of >400,000 participants reporting that the incidence rate of dementia was 31 times higher among participants aged ≥65 years than among individuals aged 40-50 years (3). Individuals with ADRD before age 65 often have similar etiology but more severe symptoms (5). Treatments are now available for some diseases causing dementia (40).

ADRD is characterized by the presence of 1) severe cognitive impairment that is 2) a result of accelerated cognitive decline and 3) is characterized by changes consistent with neurodegeneration or neuroinflammation that 4) is not due to low lifetime cognition or to 5) rapid cognitive decline over the course of a day or week consistent with a new-onset (non-WTC-related) traumatic brain injury or due to delirium (20). Since 2018, subtypes of ADRD can be described specifically using

biomarker support with focus placed on the presence of amyloidosis, tauopathy, with or without obvious neurodegeneration (33).

Mild cognitive impairment (MCI) was developed to be a precursor for ADRD at all ages (41). MCI indicates the presence of milder symptoms that are not impairing everyday functioning but may be indicative of the risk of more severe disease in the future and, as such, MCI is a risk factor for dementia before age 65 years. MCI can afflict only one type of cognitive function and may be labelled by that domain – the most common single-domain MCI is amnestic, but executive MCI and visuospatial MCI also exist. Multi-domain MCI is generally thought to be more severe than single-domain MCI.

While ADRD is a commonly used term, other terms like "cognitive impairment" and "severe cognitive impairment" are sometimes used to indicate similar overall constructs when the etiology of the disease or the timing of symptom onset is unclear.

1.2. Biological Plausibility of Air Pollution Exposures

The **Environmental Protection Agency (EPA)** has determined that fine particulate air pollution PM2.5 mm in diameter is a major environmental threat to global public health (42-44). Over the past few decades, the EPA has published air pollution research demonstrating a link between some of the pollutants found at the WTC-sites including PM2.5, polycyclic aromatic hydrocarbons, dioxins, heavy metals including lead, and increased risk of dementia. Based on a review of that literature, the EPA judged long-term exposure to PM2.5 as being likely to cause nervous system effects, including ADRD (45). Each one-unit increase in PM2.5 mass was associated with an increase of 6-7% in the incidence of dementia (46). As such, the British Alzheimer's Society (www.alzheimers.org.uk) and the Alzheimer's Society of Canada (www.Alzheimer.ca) both have stated that they consider PM2.5 to be a risk factor for dementia. The U.S. Alzheimer's Association (www.alz.org) has clarified in their annual "Facts and Figures" report that air pollution was a modifiable risk factor for ADRD.

There is consensus that air pollution causes likely account for 3% of avoidable all-cause ADRD (6, 47) despite the fact that there is no consensus yet about which specific types of air pollutants may be necessary or sufficient to cause ADRD (48, 49). Numerous mechanisms have been shown to contribute to the adverse outcomes including cerebrovascular dysfunction, cerebral amyloidosis (50), cortical atrophy (51), and neuroinflammation (52). As a result, air pollution exposures are the subject of ongoing epidemiological and environmental health studies (53, 54). Mounting evidence suggests that exposure to air pollutants, including the particulate matter that is <2.5μm in aerodynamic diameter ($PM_{2.5}$), polycyclic aromatic hydrocarbons, and dioxins likely each contribute to increasing the risk of ADRD (55). Epidemiologic work has found that cognitive impairment in children, adults, and the elderly was associated with exposure to various airborne contaminants (56, 57).

Persistent organic pollutants like dioxins and heavy metal exposures have been associated with cognitive decline and impairment in older adults. For example, studies have linked dioxins with cognitive impairment in older residents of Canada (58) and the U.S. (59), while studies have also linked dioxins to the rates of cognitive decline in older studies of the general population (60), and in a study of older adults reporting Hispanic race/ethnicity (61). Heavy metals have been identified within the brains of children and adults exposed to ambient air pollution when living near industrial processing plants (11, 55, 62).

Air pollution exposure has at least three potential pathways thought to impact the brain including: 1) "direct translocation" through the olfactory bulb causing localized damage (63, 64); 2) "barrier invasion" when toxic substances invade the brain by sporadically crossing the blood-lung, gut-blood, and blood-brain barriers after ingestion as they circulate in the body (65); and 3) as a secondary symptom of "systemic inflammation" when the lungs and gut cause low-grade but persistent inflammation that degrades brain health (38, 66-68). Crucially, these processes may not be separate since one hypothesized mechanism suggests that PM2.5 invasion in the brain causes an immunogenic amyloidosis as part of the neuroimmune efforts potentially tying the neuroinflammatory and macrophagic reactions directly to amyloidosis (50, 69).

While there are three putative pathways, there is strong support for the view that air pollutants enter the brain directly through the olfactory and peripheral pathways. For example, imaging studies using structural MRI have identified associations between lifetime exposure and both brain atrophy and disruption in white matter connectivity (70, 71), while animal modeling has found that β-Amyloid increases after long-term exposure to air pollution (72) and to dust (10). Upon infiltration into the brain, $PM_{2.5}$ may cause physical damage as evidenced by **tau burden** (38, 73, 74). Mechanisms linking these pathways to brain health have been proposed, notably $PM_{2.5}$ being recognized as an antigen that is thought to cause an **Aβ-related**, immunogenic amyloid response (75, 76). The confluence of these events may mean that certain communities face pollution disparities that increase their risk of ADRD but are trapped in the cerebrospinal fluid, cerebrum, or cerebellar parenchyma.

2. **Results in WTC responders**

There are several neurotoxic exposures reported at the WTC sites. For example, the ambient air, dust, sludge, and runoff were replete with neurotoxic heavy metals, PM2.5, polycyclic aromatic hydrocarbons (PAHs), and dioxins. Dioxins were abundant in all measured materials near the WTC sites including runoff and dust (77), and were also found in the ambient air at levels that increased as one approached the WTC sites (78). Fine particulate matter (PM2.5) was found in 0.9–1.3% of all settled dust materials near the WTC sites (79), and 9.8% of the metals found in the dust included established neurotoxic metals (e.g., lead, thallium, cadmium, arsenic, chromium, and copper).

Studies have clarified that symptoms of mild to severe cognitive impairment are evident across several WTC-affected populations. In the first study of its kind, a recent study of GRC responders at SBU reported that WTC exposure severity was associated with a 9-fold increase in the incidence of dementia before the age of 65 among individuals without dementia at their initial cognitive assessment (1). Additional prior work from SBU has reported that MCI in WTC responders can be characterized using common, validated, metrics including the MoCA, and that prevalent MCI was associated with age (80). Prospective studies of General Responders also report that exposures were associated with a high prevalence of MCI and ADRD in General Responders (1, 81). These results have been replicated and expanded upon in WTC survivors (17), and FDNY responders (18).

2.1. Estimated Prevalence

Based on published peer-reviewed papers and annual reports, the WTC Health Program monitors 132,539 individuals. From prevalence results shown in Table 1, it is estimated that **6,242 WTC-affected individuals may have already developed ADRD**. This is a relatively large patient population that is currently not served by the WTC Health Program.

Table 1. Estimated Prevalence of Alzheimer's disease or a related dementia in World Trade Center Affected Populations

	FDNY[a]	General Responders[b]	Survivors[c]
Dementia, Cases/N (%)	17/343 (5.0%)	228/5,010* (4.6%)	52/480 (10.8%)

a = New onset 2022 through 2024 (confirmed)
b = New onset of dementia before age 65 years from 2014 through 2022 (confirmed)
c = Expected onset 2001 - 2020 (SCI is MoCA Score < 20), which we estimated using details shown in the publication.
**Prevalence estimates references only the prevalence of early-onset dementia, or dementia occurring prior to age 65 years.*

Symptoms of MCI in WTC responders are somewhat unusual because they tend to be consistent with multidomain MCI rather than amnestic MCI. This result is consistent with a more widespread and potentially severe condition. To address this problem, we developed a WTC-tailored cognitive risk score that was matched directly to evidence of WTC-related cortical atrophy on neuroimaging, which we called the cognitive atrophy risk score (82). In that paper, we found that this atrophy risk score was also associated with increased incidence of both MCI and dementia. Still, while not published in our original paper on dementia before age 65, validation efforts revealed that the incidence of early-onset dementia was higher among individuals who had MCI at baseline (HR = 8.77 [5.97 – 12.89] p<0.001).

Biomarkers support associations between WTC exposures and neuropathology. Positron emission tomography shows that duration of exposure to WTC ambient air was associated with increased olfactory amyloidosis (83), and we also identified increases in the presence of glial or macrophagic activation (84) that were replicated in serology in WTC responders with MCI (85). Analyses of serology show that increased exposure duration and exposure activities were associated with increased serological phosphorylated tau-181 (86).

2.2. Biomarker Case Validation Studies

Consistent with ADRD research, **WTC responders have evidence of neurodegeneration on neuroimaging.** For example, individuals diagnosed with dementia at midlife have evidence of hippocampal (87), cerebellar (88), and cortical atrophy (89) consistent with a neurodegenerative disease. A WTC-specific cortical signature using a neural network protocol with cortical atrophy information showed that a single signature was >90% effective at identifying cases of CI in the testing cohort and in a second validation study (90). The signature had a very high accuracy but also unexpectedly showed the presence of atrophy across several regions of the brain that may be consistent with a WTC-specific disorder (90). Finally, a positron emission tomography study identified that the presence of cerebral amyloidosis near the olfactory regions among WTC responders was associated with exposure among individuals not wearing personalized protective equipment (83).

The presence of dementia even when validated using neuroimaging could reflect the presence of sporadic age-related diseases. To examine this question, we first generated a WTC-specific mapping of cerebral atrophy and found that it was able to detect the presence of MCI with 90% accuracy (90). Next, we linked a cognitive functioning symptomatology to that map, again with high levels of accuracy (AUC = 0.91). This study then reported that **the incidence of these cognitive symptoms associated with WTC cerebral atrophy was associated with being on-site**

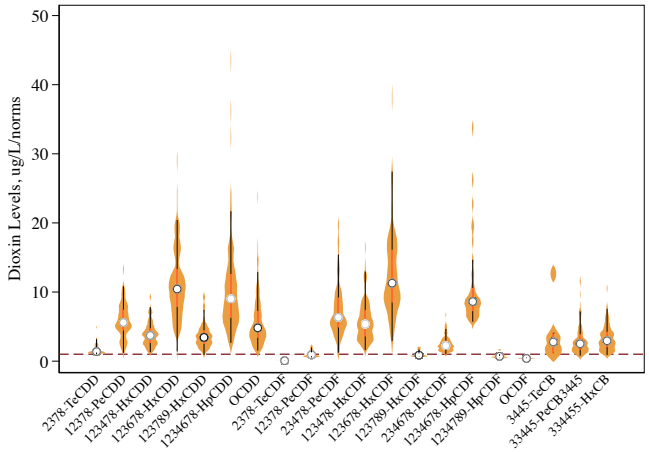
for >5 weeks (aHR = 2.82, P<0.001) (82). Together, this work shows that these signatures were likely to arise from the specific WTC exposures.

2.3. Seeking Exposure Validation

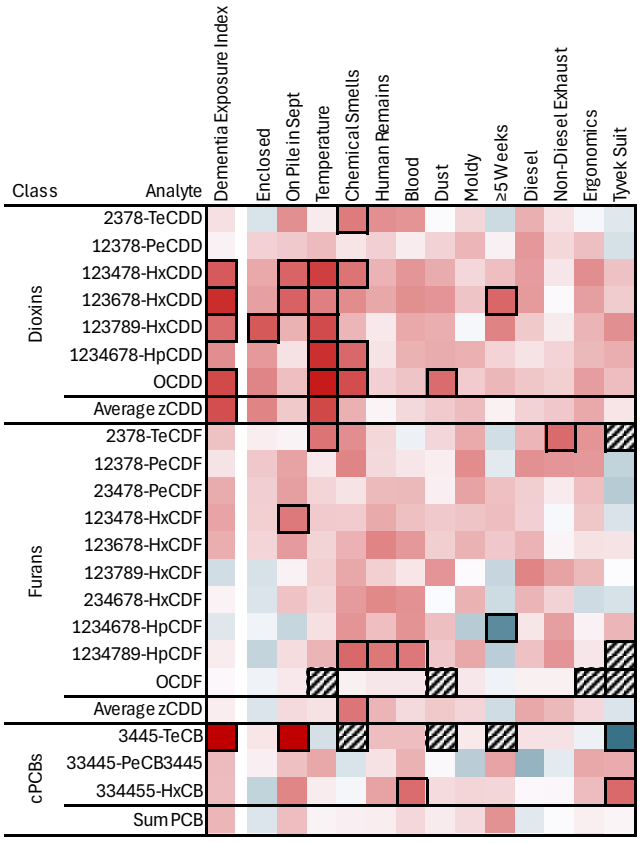
We are concerned about the lack of objective biomarkers of exposure that could help to explain these results. **Yet unpublished data (n=150 General Responders, Figure 2), however, show that WTC responders who were severely exposed to WTC dust have high levels of dioxins measured in their blood 23 years after the exposure on 9/11 (Figure 2A). Additionally, we found that persistent organic pollutant measures are statistically significantly associated with WTC exposures (Figure 2B).** In this figure, each cell represents a single statistical model, and all models adjust for demographics. For ease, direction for each finding is reported using colors (blue indicates less exposure associated with a specific activity, red indicates more dioxin exposure) and cells that have been encapsulated with borders are statistically significant ($p<0.05$). Our results show high levels of **persistent organic pollutants, and especially dioxins,** were associated with several responder-reported exposure activities (Figure 2B). These results show that **the dementia exposure index, as well as reporting having been on the pile in September, working in very hot places with chemical smells, and working for longer than 5 weeks on-site were also associated with high levels of toxicants.** However, since this is a relatively small study it is also worth noting that most of the **persistent organic pollutant** measures were trending in the expected directions so that levels were higher for most relevant exposures and lower only for the presence of common

Figure 2. Unpublished results from an analysis of persistent organic pollutants measurements from serology in SBU General Responders. Panel A shows the distribution of different dioxin analytes in comparison to established norms provided by the NHANES data. Panel B shows correlations between the published dementia exposure index, as well as related on-site exposure activities as compared to specific and average persistent organic pollutants.

A)



B)



forms of PPE including Tyvek suits. Not reflected in Figure 1, unpublished analyses show that serological levels of the PeCDF12378 were associated with the presence of dementia on a trend test (P=0.029).

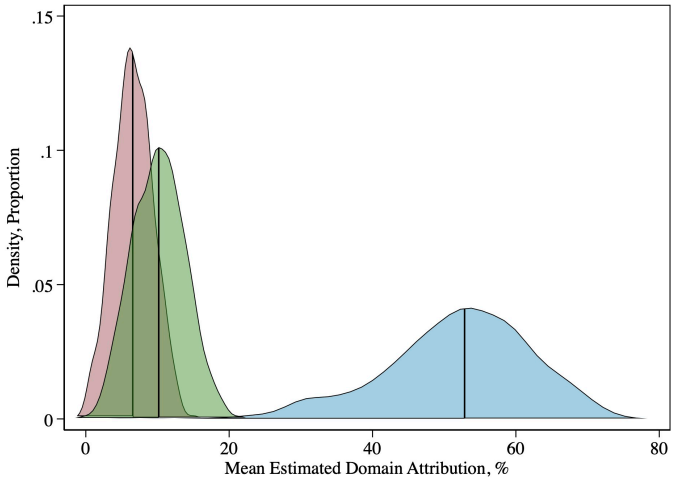
2.4. Contributions of Post-Traumatic Stress Disorder

There is an experiential pathway relying on terrifying sights and sounds that may exacerbate the severity of dementia through the presence of re-experiencing symptoms consistent with post-traumatic stress disorder (PTSD) (91). PTSD symptoms have long been independently associated with cognitive function (92) and the incidence of MCI (81). However, since then we have also found that PTSD is more strongly associated with changes in associated movements (93, 94) and behavioral impairments (95) that often reduce quality of life and survival in individuals with dementia. However, in our population, most patients with CI do not have PTSD. Indeed, in unpublished data we found that the GRC only 10.1% of cases of EOD in the GRC cohort published by Clouston et al. (96) have a certified diagnosis of PTSD. Similarly, in data that is under review in the FDNY study only 8.2% of cases of SCI had concomitant PTSD.

For PTSD to be a potential mediator for exposures at the WTC, PTSD would need to be associated with these exposures. However, in unpublished data analyzed for this application we found that WTC exposure duration was not associated with the presence of re-experiencing symptoms (rho = 0.006, p=0.887), the primary PTSD symptom cluster associated with MCI, or with the overall PTSD checklist score (rho = 0.0004, p=0.988) in the General Responder Cohort. While the impact of traumatic exposures is mediated by the presence of PTSD symptoms, biomarker analyses in PTSD and MCI/ADRD have clarified that neuropathological underpinnings of PTSD-related CI appear to differ somewhat from exposure-related ADRD in WTC responders. For example, while exposures are associated with changes in phosphorylated tau and concurrent neurofilament light (86), PTSD was not. In contrast, while PTSD is associated with a range of changes in systemic inflammatory markers (97) alongside changes in glial activation (84, 98, 99), this was not evident in responders with ADRD who lacked PTSD.

One recent study showed that PTSD-related CI was associated with polygenic risk for PTSD while exposure-related CI was associated with polygenic risk for ADRD even when adjusting for PTSD (100). These results imply that PTSD is an important secondary cause of worsened brain health that might exacerbate ADRD but does not entirely explain the presence of dementia in this cohort. In our recent attempts to determine the extent to which PTSD accounts for MCI and dementia in WTC responders we have found that though associations are always consistent, that they are never

Figure 3. Unpublished results showing simulations of the percentage of cases that are attributable to different risk factors when relying on data published by Clouston et al. 2024. The blue curve shows the cases attributable to exposure, red shows proportion of cases attributable to PTSD, and green shows the residual proportion of cases that attributed to all other causes including normal aging.



large. For example, when we have attempted to calculate the fraction of cases of MCI or dementia that are attributable to PTSD, we find that these estimates are relatively low. For example, in an unpublished but forthcoming paper, in the FDNY cohort we have estimated that PTSD accounts for 8.4% of all cases of MCI in FDNY responders. In similar, also unpublished, simulation work in the General Responder cohort (shown in **Figure 3**) we find that PTSD only accounts for roughly 6.6% (1.1-12.0) of cases of dementia before age 65.

PTSD does not explain exposure-related risk of cognitive outcomes.

Finally, while PTSD is a significant risk factor for MCI and dementia, PTSD is relatively uncommon in cases of dementia. For example, while PTSD is common in around 20% of SBU General Responder Cohort with dementia, the remaining 80% of cases never had PTSD. Similarly, of the 17 FDNY responders with severe cognitive impairment consistent with dementia, only 5 had PTSD and the remaining 12 (71% of cases) did not have PTSD. Overall, our assessment is that although PTSD and its comorbidity with depression are significantly associated with MCI among WTC-exposed FDNY responders, population attributable fraction estimates suggest that most MCI cases (>90%) cannot be attributed to these psychiatric disorders, even if a causal relationship is assumed.

2.5. Self-Reported Cognitive Complaints

Screening for cognitive impairment using a self-reported questionnaire based on memory and/or functional complaints has limited utility. There are several measures that have been developed to do this task. **However, as several reviews have pointed out, subjective memory complaints are not strongly associated with MCI but are heavily biased by the presence of depression** (101, 102) as well as a host of other psychiatric and behavioral comorbidities including ongoing stress exposures or nearly anything that impairs sleep (103). Similar results show that PTSD is a strong predictor of cognitive complaints, and is a better predictor of cognitive impairment than subjective complaints (104). PTSD is predictive of cognitive complaints even when cognitive performance is maintained (105). Similar results suggest that there is a strong association between PTSD and depression and cognitive complaints in WTC responders (106, 107), but as is shown in the FDNY study there is minimal association between cognitive complaints and evidence of MCI (108).

2.6. Timeliness

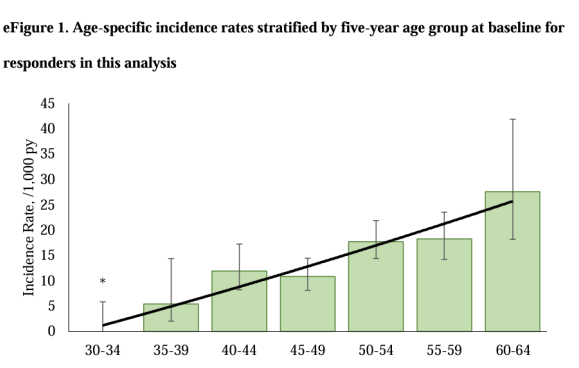
It is critical to consider MCI and ADRD now because WTC-affected populations are aging and, as a result, differentiating WTC cases from sporadic ADRD will become harder with time. At the commencement of our studies in 2014 the average age of the WTC responder population (who were 38 on average on 9/11) was 51. Now, the average age is 58 and this number is increasing progressively alongside the overall burden of patients with MCI or dementia. As a result, we now provide a risk of incident dementia for WTC responders by age before age 65 (Figure 4). These estimates simply show that as responders are aging, they are at increasing risk of experiencing dementia. Overall, these results suggest that the incidence of MCI and dementia appears to be relatively common and increasing rapidly with time as WTC responders age.

2.7. Alternative Explanations

Confounding was addressed in all analyses either using statistical adjustment or relying on matching by design. These studies have accounted for various common confounders including those in the neurological literature like demographics including sex, education, and race/ethnicity,

and medical risk factors including stroke, hypertension, diabetes, and cancer, while also accounting for head injuries both by excluding individuals who were hit in the head during the WTC response efforts, and by accounting for histories of head injuries. Finally, in all cases, we have considered other WTC-related conditions and have found that other than psychiatric diseases including PTSD and depression, other diseases diagnosed by the WTC clinic staff including pulmonary disease, sleep apnea, and gastroesophageal reflux disease are often comorbid with other conditions, including CI, in this population but do not appear to be more common in those with CI as compared to those without.

Figure 4. The proportion of the World Trade Center responder population who have Dementia (Black Solid Line) by age in years, with overlaid trendlines. Source: Clouston et al. 2024 Supplemental Materials (1)



Measurement bias was considered in several studies, noting that cognitively impairing diseases are often made more difficult because the symptoms are often distributed across several different types of functions and can masquerade as other diseases making diagnosis somewhat difficult. To determine whether measurements might be biased by past experiences and/or by population characteristics, we first examined whether different measures showed similar results, whether changes in cognition were evident in longitudinal data, whether cognitive impairment was associated with symptoms such as depressive symptoms or physical functional changes common in people with dementia, results from blood biomarkers thought to indicate the presence of a neurodegenerative condition (86, 109). Finally, we examined results from neuroimaging studies to determine whether indications of atrophy consistent with early onset ADRD (88, 89, 110).

Measurement sensitivity was addressed in several ways in the research. For example, results from the original study showed changes in depressive symptomatology consistent with a neurodegenerative condition (80), potentially indicating that changes in depressive behaviors may sometimes have a similar etiology. One complaint may be that brief screening tests may be insensitive to cognitive impairment in WTC responders, though if so, this is a particularly concerning possibility. Notably, there may be concern that we may identify something other than a progressive neurodegenerative condition. To examine this possibility, we examined physical functional changes and found not only that the same overall patterns were evident when examining predictors of non-cognitive symptoms of dementia (93, 111), but also that these symptoms were often comorbid with the presence of cognitive impairment (95). Additional results showed that cognitively impaired individuals also experienced increasing levels of depressive symptoms over time and that individuals with genetic risk for Alzheimer's disease were more likely to have reduced cognitive scores (100). Further follow-up that developed a novel scoring technique to determine the risk of cortical atrophy on imaging reported that lengthy exposures to the WTC and PTSD were both risk factors for a high risk score for cortical atrophy and also reported that individuals at high atrophy risk had a higher risk of developing dementia and of dying since cognitive assessments were completed (82).

3. Conclusion

The Zadroga Act states that the program should conduct (section 3311 and 3321) "medical monitoring and clinical examinations to examine the long-term health consequences of enrolled WTC-affected individuals who were likely to have been exposed to airborne toxins, and further notes (sections 3312, 3322, and 3323) that the program should provide for follow-up monitoring and treatment and payment … for all medically necessary health and mental health care expenses of an individual concerning a WTC-related health condition." In our ongoing work, we have shown that long periods experienced on-site and the presence of flashbacks and nightmares consistent with PTSD are both associated with the presence of a neurodegenerative disease that is causing some responders to experience mild to severe cognitive impairment and dementia. In the presence of amyloid, as identified on neuroimaging, MCI is increasingly being treated by monoclonal antibody treatments. Furthermore, overall well-being and helping patients to manage complex healthcare regimens is equally important. MCI can increase morbidity as it progresses and ultimately reduce quality of life and shorten lifespan for the individual who is affected. If it does progress to dementia, MCI often requires intensive management from family members and healthcare providers and can result in a need for long-term specialized care, which causes substantial caregiver burden and increases economic costs. In recognition of the need for care management, patient protection, and further outreach as they age, we therefore request that NIOSH consider adding MCI to the list of covered conditions.

3.1. Potential Consideration of Dementia as a Category II Condition

Under the unlikely possibility that the Administrator may consider the evidence to be more consistent with a Category II designation (high rather than substantial likelihood for causal association), we still believe our petition should move forward. According to the WTC Health Program's policy for adding non-cancer health conditions to the list of WTC-related health conditions, petitions based on Category II evidence allow the Administrator to consider additional data from the following sources:

1. Sources of highly relevant scientific information regarding non-9/11 exposures published or funded by the US government, including the Environmental Protection Agency (EPA)
2. Evaluation of additional highly relevant scientific information regarding non-9/11 exposures – bio-plausibility based on physical and mental health exposures.
3. Findings and recommendations solicited from the WTC Clinical Centers of Excellence and Data Centers, and the WTC Health Registry at the New York City Department of Health and Mental Hygiene
4. Findings and recommendations from other sources of information relevant to 9/11 exposures, including expert judgment from the NIOSH WTC Science Team and the NIOSH WTC Scientific Advisory Committee (STAC)
5. Information from the public solicited through a request for information published in the *Federal Register*

We are confident that public comment will be favorable. The science, the impact these conditions have on quality of life, and the availability of FDA-approved treatments that unquestionably improve quality of life and prognosis, should provide the basis for such support.

In summary, the researchers at Stony Brook University respectfully request that the WTC Administer allow the NIOSH WTC Health Program Science Team and the STAC to consider whether WTC Health Program coverage can be extended to include mild cognitive impairment and dementia from all causes, excluding TBI and stroke. To maintain the program's credibility and fiduciary responsibility, we recommend that this coverage require the same exposure requirements as is required for other WTC-related conditions – an incidence occurring post-9/11 and only in those with significant WTC exposure.

Signatures:

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