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Racial/Ethnic Disparities in Alzheimer's Disease Risk: Role of Exposure to Ambient Fine Particles

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Abstract:

Background: Whether racial/ethnic disparities in Alzheimer's disease (AD) risk may be explained by ambient fine particles ($PM_{2.5}$) has not been studied.

Methods: We conducted a prospective, population-based study on a cohort of Black (n=481) and White (n=6004) older women (aged 65-79) without dementia at enrollment (1995-98). Cox models accounting for competing risk were used to estimate the hazard ratio (HR) for racial/ethnic disparities in AD (1996-2010) defined by DSM-IV and the association with time-varying annual average $PM_{2.5}$ (1999-2010) estimated by spatiotemporal model.

Results: Over an average follow-up of 8.3 (±3.5) years with 158 incident cases (21 in Black women), the racial disparities in AD risk (range of adjusted $HR_{Black\ women}$ = 1.85-2.41) observed in various models could not be explained by geographic region, age, socioeconomic characteristics, lifestyle factors, cardiovascular risk factors, and hormone therapy assignment. Estimated $PM_{2.5}$ exposure was higher in Black (14.38±2.21 $\mu g/m^3$) than in White (12.55±2.76 $\mu g/m^3$) women, and further adjustment for the association between $PM_{2.5}$ and AD (adjusted $HR_{PM2.5}$ = 1.18-1.28) slightly reduced the racial disparities by 2-6% ($HR_{Black\ women}$ = 1.81-2.26). The observed association between $PM_{2.5}$ and AD risk was ~2 times greater in Black ($HR_{PM2.5}$ = 2.10-2.60) than in White ($HR_{PM2.5}$ = 1.07-1.15) women (range of interaction *P*s: <.01 to .01). We found similar results after further adjusting for social engagement (social strain; social support; social activity; living alone), stressful life events, WHI clinic sites, and neighborhood socioeconomic characteristics.

Conclusions: $PM_{2.5}$ may contribute to racial/ethnic disparities in AD risk and its associated increase in AD risk was stronger amongst Black women.

KEYWORDS: Air pollution; Dementia; Incidence; Epidemiology

Introduction

Significant differences in Alzheimer's disease (AD) incidence across racial/ethnic groups exist, with Black individuals approximately 2-3 times more likely to develop AD compared to White.[1] In the U.S., Black women had the highest prevalence (15.1%) of AD and related dementias (ADRD) among nearly 5 million people (aged ≥65 years) diagnosed in 2014.[2] Several well-established AD risk factors (e.g., genetics; socio-demographics; vascular conditions) could not fully explain these racial disparities.[1] In the study on "*Critical Perspectives on Racial and Ethnic Differences in Health in Later Life*," the National Research Council noted that "little work has been published addressing ethnic differences in the environmental risk factors that…explain ethnic group differences in frequency of AD".[3]

Fine particulate matter (PM with aerodynamic diameter <2.5 μm; $PM_{2.5}$) may be one such environmental risk factor potentially contributing to the racial disparities in AD risk. Neurotoxicological data in animal models have demonstrated associations between inhaled exposures to particles and increased early markers of neurodegenerative disease (accumulation of amyloid-β; phosphorylation of tau), as well as structural and functional changes in the brain.[4-12] Neuroimaging studies in humans have provided evidence for associations between $PM_{2.5}$ and increased amyloid-β plaques[13] and smaller gray matter volumes in brain areas vulnerable to AD neuropathologies.[14, 15] Converging with these data, several cohort studies have reported associations between $PM_{2.5}$ and increased risk of ADRD.[16] Although Black individuals in the U.S. are more likely to reside near PM-emitting facilities and have significantly greater exposures,[17] whether $PM_{2.5}$ may contribute to the racial/ethnic disparities in AD risk has been overlooked. Extant epidemiologic evidence suggests minority populations may be more susceptible to the adverse health effects of $PM_{2.5}$.[18] One recent study found that the attributable

burden of dementia death associated with $PM_{2.5}$ was greater amongst Black individuals.[19] However, no studies have explored whether the adverse effects of $PM_{2.5}$ on ADRD incidence differentially affect Black populations.

We conducted a longitudinal study to address these knowledge gaps. First, we investigated whether the putative increase in AD risk among Black compared to White women may be explained by between-individual differences in estimated exposure to ambient $PM_{2.5}$. Second, we examined whether race/ethnicity imparts differential susceptibility to the putative $PM_{2.5}$ neurotoxicity by testing the hypothesis that the association between $PM_{2.5}$ and AD risk is stronger in Black than in White women.

Method

Study design and population

Participants were drawn from the Women's Health Initiative (WHI) Memory Study (WHIMS)[20] – an ancillary study to the WHI hormone therapy (WHI-HT) trials designed to test the efficacy of hormone therapy on dementia. Community-dwelling postmenopausal women (N=7,479) without dementia during 1995-1998 were recruited (65-80 years old at enrollment) from more than 40 study sites across 24 U.S. states and Washington, DC. During baseline screenings, all participants chose the racial or ethnic group they identified with most. As part of the annual contact in 2003-4, personal information was updated with race/ethnicity questions used in the 2000 U.S. census. For this study, we included women who self-identified as African-American or Black (Black) or Non-Hispanic White (White). Written informed consent was obtained from all participants as part of WHI-HT and WHIMS studies.

Incident AD ascertainment

Our primary outcome was clinically-defined AD, as determined using WHIMS protocols.[20] Centrally-trained, masked, and certified technicians administered the *Modified Mini-Mental State* (3MS)[21] examination to screen for cognitive impairment at baseline and annually. Women scoring below an education-adjusted cut point underwent further extensive neuropsychological testing (including a modified Consortium to Establish a Registry for Alzheimer's Disease battery[22]) and were evaluated by a board-certified physician-specialist with experience in diagnosing dementia. Suspected dementia cases underwent further clinical work-up, including a cranial computerized axial tomography scan and laboratory blood tests to rule out possible reversible causes of cognitive decline and dementia. Starting in 2008, screening of global cognitive impairment was based on the *Telephone Interview for Cognitive Status-modified*,[23] which is highly correlated with 3MS (0.89) and has excellent sensitivity (0.87)/specificity (0.89) to differentiate dementia cases from normal controls. Data were then transmitted to a central adjudication committee for final confirmation of dementia. The experts reviewed all the data and classified the WHIMS participant as having no dementia, mild cognitive impairment, or probable dementia. For those incident cases of probable dementia, their clinical phenotypes were then further classified (e.g., vascular; AD; mixed type; unknown; other dementia-related classifications) based on *DSM-IV*, which has substantial inter-rater reliability and good validity for AD diagnosis (compared with post-mortem confirmation).[24] Our study focused on cases with primary AD diagnosis defined as cases of incident probable dementia that were further classified as AD only. In order to reduce the bias in ascertaining dementia cases among minority groups, including Black individuals who tended to have lower neuropsychological testing scores, normative data by race wherever available were provided to

the adjudicators who were blinded to residential locations and estimated air pollution exposure levels.

Air pollution exposure assessment

Detailed procedures for air pollution estimation have been reported elsewhere[25] and summarized in the eMethods. Briefly, residential addresses prospectively collected at each clinic visit and updated at least biannually were geocoded to obtain the latitude and longitude of each location using standardized protocols.[26] We generated individual-level $PM_{2.5}$ estimates by constructing spatiotemporal models that are a space-time function using the Bayesian Maximum Entropy (BME) method. The BME data fusion method integrates daily observed $PM_{2.5}$ obtained from the U.S. Environmental Protection Agency (EPA) Air Quality System nationwide monitoring data, yielding daily $PM_{2.5}$ observations at a total of 2001 monitoring station locations across 48 states along with the District of Columbia. These monitoring data were combined with the output of chemical transport models (CTM), which characterize the local emission sources, meteorology, chemical transformations, and transport of pollutants.[25] In the first step of the BME data fusion, a Regionalized Air quality Model Performance (RAMP) analysis[25] was conducted to perform a localized bias correction of CTM outputs. The CTM outputs were obtained at an hourly time scale and at the finest spatial grid resolution available, which varied from 36 km for the nationwide domain down to 4 km in some highly populated areas.[25, 27] These resolutions provided a fine scale description of $PM_{2.5}$ across the nationwide domain. Next, we performed a BME data integration to obtain geostatistical estimates of $PM_{2.5}$, using EPA observations as hard data and the RAMP corrected CTM output as soft data. This BME estimation resulted in maps of $PM_{2.5}$ that combined the precision of observations and the fine scale resolution of CTM outputs. The statistically-validated BME model (average Pearson's R^2=0.70) was then applied to each

geocoded residential location to estimate daily ambient $PM_{2.5}$ concentrations in 1999-2010. The daily estimates were aggregated to the 1-year moving average exposure, accounting for residential mobility and length of stay at each residence. We focused on annual average, as did previous studies showing an association with increased dementia mortality,[19] hospitalization,[28, 29] and incidence,[30] considering their underlying pathogenic processes may be accelerated by late-life exposures to $PM_{2.5}$.[31]

Statistical analysis

Cause-specific proportional hazard models accounting for death as the competing event were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for racial disparities (Black vs. White women) in AD risk, comparing models with and without adjustment for time-varying $PM_{2.5}$ exposure. Follow-up time was calculated as days from WHI-HT inception[32] to the date of the cognitive assessment that triggered the referral for additional testing subsequently leading to classification of primary AD, death, or the date of last cognitive assessment (through December 31, 2010), whichever came first. In Cox models, cases of incident probable dementia that were not classified as exclusively AD-related (e.g., vascular; mixed type; unknown; other dementia-related classifications) were excluded, while women with mild cognitive impairment remained as they were still considered at risk for developing AD during the follow-up. The proportional hazard assumption was supported by the proportionality test. Covariates considered in our analyses (details in the eMethods) included age, socioeconomic characteristics (education; family income; employment status), lifestyle factors (smoking status; alcohol use; physical activity), clinical characteristics (cardiovascular diseases [CVD]; hypertension; history of depression; body mass index [BMI]; diabetes mellitus; postmenopausal hormone treatment), and WHI-HT intervention assignment. To evaluate the possibility of differential susceptibility to

$PM_{2.5}$, a product term of race/ethnicity and $PM_{2.5}$ was included in models to examine whether the putative association between $PM_{2.5}$ and AD risk differed by race/ethnicity (Black vs. White women).

The robustness of our findings were tested with several sensitivity analyses: further adjusting for census track-level socioeconomic characteristics of residential neighborhood (details in the eMethods); adjusting for WHI clinic sites to account for possible spatial confounding by other unmeasured covariates; further adjusting for measures of social engagement (social strain; social support; social activity; living alone) (details in the eMethods); further adjusting for a measure of stressful life events (details in the eMethods); and defining the outcome as cases of incident probable dementia that were further classified as either AD or mixed type (i.e., etiologies of both AD and vascular dementia).

All reported *P* values are 2-sided and values <.05 indicated statistical significance. Analyses were performed using SAS software version 9.4 (SAS Institute).

Results

Compared to women missing data (n=687), those with complete data were younger, more likely to be White, residing in the Northeast, and physically active, had higher household incomes and educational attainment, had lower annual average $PM_{2.5}$ exposure, and were less likely to have depression or diabetes (eTable 1). During follow-up (mean 8.3 years), 158 (137 White; 21 Black) incident AD cases were identified, with incidence rates much higher in Black than White women (4.88 vs. 2.41 cases per 1,000 person-years). Annual average $PM_{2.5}$ exposure was higher in Black (mean, 14.38; median, 14.38; range, 7.32-21.19 $\mu g/m^3$) compared to White (mean, 12.55; median, 12.13; range, 3.86-25.54 $\mu g/m^3$) women. Compared to White women, Black women were slightly younger and more likely to reside in the South and currently smoke,

had lower household incomes and educational attainment, but were less likely to be drinking alcohol or physically active. Black women were more likely to have a higher BMI and history of diabetes and hypertension. They were also more likely to live alone, experience more social strain and activity, report greater stressful life events, but had less social support (Table 1). Compared to their counterparts, women exposed to higher levels of $PM_{2.5}$ were older, were more likely to reside in the South and Midwest, had lower household incomes, were less likely to drink, were less physically active, were more likely to have a history of hypercholesterolemia and hypertension, and were more socially active (Table 1).

In Table 2, we present the results of cause-specific Cox models examining racial/ethnic disparities in AD risk (Black vs. White women, $HR_{Black\ women}$) before and after adjusting for $PM_{2.5}$ exposure. In crude analyses, AD risk was greater in Black compared to White women ($HR_{Black\ women}$, 2.10 [95% CI, 1.33 to 3.34]; without $PM_{2.5}$-adjustment). Adjustment for age, region, socioeconomic factors, and lifestyle factors modestly reduced the racial disparities in AD ($HR_{Black\ women}$, 1.85 [95% CI, 1.14 to 3.01]), with income making a major contribution to this observed difference. Additional adjustment for history of depression, hormone therapy use, WHI-HT assignment, and cardiovascular risk profiles (Models 4-5; without $PM_{2.5}$-adjustment) did not further reduce the racial disparities. Adjustment for $PM_{2.5}$ exposure slightly reduced the racial disparities in AD risk by 3-6% (Models 1-5; with $PM_{2.5}$-adjustment). In the model accounting for the full list of covariates (Model 5; with $PM_{2.5}$-adjustment), each interquartile range increment (IQR, 3.73 $\mu g/m^3$) in $PM_{2.5}$ was associated with a 28% increase in AD risk ($HR_{PM2.5}$, 1.28 [95% CI, 1.02, 1.61]). These findings were robust in our sensitivity analyses (eTables 2 and 3) further adjusting for residential neighborhood socioeconomic characteristics, WHI clinic site, measures of social engagement, or stressful life events. Additionally, these racial

disparities were sustained when defining the outcome variable as AD or mixed type dementia, though the elevated AD risk associated with $PM_{2.5}$ exposure did not reach statistical significance (eTable 4).

In Figure 1, we present the association between $PM_{2.5}$ and AD risk, stratified by race/ethnicity. The association of increased AD risk with $PM_{2.5}$ exposure was 2 times stronger (range of interaction *P*s, .002 to .01) in Black women (range of $HR_{PM2.5}$, 2.10-2.60; *P*s<.01) than in White women ($HR_{PM2.5}$, 1.07-1.15; *P*s=.19-.58). These racial disparities in the $PM_{2.5}$-AD association were sustained in our sensitivity analyses where we defined the outcome variable as AD or mixed type dementia (eTable 5). An *ad hoc* analysis was conducted to examine whether cardiovascular risk factors or stressful life events more commonly found in Black populations could explain this observed racial difference in the $PM_{2.5}$ effect. After further adjusting for the interactions with these cardiovascular risk factors (eTable 6) and stressful life events (eTable 7), the positive $PM_{2.5}$-AD association was still 2-2.5 times stronger in Black than in White women (eTables 8 and 9).

Discussion

In this geographically-diverse prospective cohort of community-dwelling older women, increased exposure to ambient $PM_{2.5}$ partially contributed to Black-White disparities in the risk for clinically-defined AD. We also found Black women were ~2 times more likely to suffer from the adverse $PM_{2.5}$ effect on increased AD risk. These associations could not be explained by sociodemographics, lifestyle factors, measures of social engagement, stressful life events, and CVD and related comorbidities, and were robust after accounting for spatial confounding by neighborhood socioeconomic characteristics and WHI clinic site. These novel results provide the first direct evidence linking environmental pollutants with racial/ethnic disparities in AD risk.

These findings may offer new impetus for studying environmental neurotoxins that disproportionately affect Black and other minority groups to help "decrease disparities in Alzheimer's for ethnic and racial minority populations," as mandated by the National Alzheimer's Project Act.[33]

Our data contribute to the current literature investigating why Black individuals had elevated incidence of AD. Although it has been suggested that genetics, lifestyle factors, and CVD and related comorbidities may explain the greater AD risk amongst Black individuals,[1] several population-based U.S. cohort studies[34-43] still showed a 27-140% higher AD risk in Black than in White individuals after adjusting for these conventional risk factors (eTable 10). A meta-analysis yielded a combined rate ratio of 1.64 (95% CI, 1.35 to 2.00), suggesting Black individuals are 64% more likely to develop AD than White.[44] *Compared to these earlier studies which mostly used localized populations, our observation of racial disparities in AD incidence in this nationwide, geographically diverse sample has greater generalizability. Previous* reports of *racial disparities in AD based on geographically-diverse cohorts*[36, 40, 42] *did not control for regional difference or spatial confounding. In our study, the increased AD risk in Black women was adjusted for geographic region (adjusted models, Table 2) and was not sensitive to further adjustment for other spatial variations (eTable 2; Model 7), further supporting the internal validity of our findings. Additionally, previous studies did not explore the role of social factors, although their possible contribution to racial disparities in AD risk has been suggested.*[45] We found that *the AD risk was 152% higher in Black older women after adjusting for the full set of conventional risk factors* (Table 2) *and persisted in sensitivity analyses further adjusting for measures of social engagement and stressful life events (eTable 3). The pervasive evidence of racial disparities in ADRD not explained by behavioral and biological factors points to the need*

to investigate the role of racism as a structural cause of accelerated brain aging.[46] *Environmental neurotoxins, including $PM_{2.5}$, are an example of environmental racism contributing to racial disparities in brain aging.* We call for new research that moves us closer to a better understanding of the importance of environmental racism and its impact on the pathogenetic processes of ADRD.

Our study illustrates the importance for environmental-neuroepidemiologic studies of ADRD to include high-risk minority populations. After we adjusted for $PM_{2.5}$, the increased AD risk among Black women (*85-141% higher than White women) was reduced to 81-126%* (Table 2). *This finding suggests* that the environmental risk imparted by $PM_{2.5}$ may partially contribute to the racial disparities in AD risk. Several studies on Western countries have reported an association between long-term exposure to late-life $PM_{2.5}$ and ADRD[16] in White populations, while the present study is the first to depict this relationship in a biracial population. The REasons for Geographic and Racial Differences in Stroke cohort was the only other geographically-diverse, biracial U.S. population used to study $PM_{2.5}$ neurotoxicity, but investigators did not find a significant association between $PM_{2.5}$ and incident cognitive impairment.[47] The advances of environmental neurosciences of air pollution and brain aging need to be built on studying racially diverse populations, as the clinical manifestation of AD may differ across racial groups.[1]

Our study findings also raised several questions concerning the environmental health disparities in AD as related to air pollution neurotoxicity on brain aging. The increased risk of AD associated with $PM_{2.5}$ was ~2 times greater in Black ($HR_{PM2.5}$, 2.10-2.60) than in White ($HR_{PM2.5}$, 1.07-1.15) women (Figure 1). Studies have demonstrated that Black individuals may be more susceptible to the adverse effect of $PM_{2.5}$ on several health outcomes,[48-50] but our study

was the first to examine the race-related environmental health disparities in brain aging. Although the reasons for this increased susceptibility amongst Black populations are unclear, our *ad hoc* analyses suggest that cardiovascular risk factors and stressful life events typically found to be more prevalent in Black individuals could not explain this finding (eTables 8 and 9). Understanding the reasons for these greater health burdens from air pollution amongst Black populations is important, as the EPA's Office of Environmental Justice mandates that no race should experience disproportionate negative consequences from environmental stressors.[51] Black populations are likely much more vulnerable to the adverse health effects of ambient air pollution due to the lifetime adversities and injustices they have experienced as a result of structural racism. For example, the race-based residential segregation that has persisted in the U.S. for decades has shaped the racial inequities in exposure to air pollution,[52] quality of education,[53] socioeconomic opportunities,[54] psychosocial stress,[55] and access to high quality food,[56] all contributing to brain aging.[31] These lifetime experiences shape cognitive reserve, which has important implications for cognitive aging and AD-related brain pathologies.[57] Residing in highly segregated neighborhoods in young adulthood has even been directly linked to worse cognitive performance in mid-life amongst Black individuals.[58] Health disparities related to aging emerge over the life course as a product of several factors that likely interact across many levels, such as environmental (e.g., toxins; exposures) and sociocultural (e.g., institutional racism), to compromise health.[59] Therefore, future studies should investigate whether the neurotoxic effects of $PM_{2.5}$ may interact with these contextual factors resulting from *structural racism to impact brain aging. Additionally, the collective evidence demonstrating the increased* susceptibility to the health effects of $PM_{2.5}$ *amongst* Black populations highlights the

need for stronger enforcement of the Clean Air Act's mandate to provide safe margins of air quality for susceptible populations.[60]

We recognize several limitations of our study. First, limited access to quality education and test anxiety from perceived discrimination[61] may lower cognitive test performance in Black individuals, leading to an overdiagnosis of AD in Black populations and an overestimation of the racial/ethnic differences.[3] However, the longitudinal nature of WHIMS protocols alleviates concerns of over-diagnosis[1] and if present, such bias would likely be non-differential with respect to $PM_{2.5}$ exposure. Second, although $PM_{2.5}$ was estimated with a statistically cross-validated (average Pearson's R^2=0.70) model, the possible non-differential measurement errors would attenuate the observed associations. Third, we did not investigate other environmental exposures that may be more prevalent amongst Black individuals (e.g., occupational dust) or other exposure sources of $PM_{2.5}$ (e.g., traffic emissions). Fourth, our covariates measured at baseline do not capture the entirety of an individual's lifetime experience (e.g., adverse life experiences including racial discrimination in early life), which may contribute to the racial differences in AD risk.[45] Fifth, the number of Black participants is relatively small compared to the number of White participants; however, the relative proportion of Black and White women in WHIMS was comparable to U.S. women ≥65 years old in the 1990s.[62] Sixth, our findings may not be generalizable to men or younger women.

This study also had several strengths. Our study utilized a large, biracial sample of Black and White individuals prospectively followed annually up to 15 years. The population was a nationwide, geographically-diverse cohort, capturing individuals with varying backgrounds and allowing sufficient $PM_{2.5}$ gradients. Our $PM_{2.5}$ estimates allowed us to explore environmental risk factors potentially contributing to the racial disparities in AD risk. We accounted for

competing risk of death, reducing the risk of biased effect estimates.[63] Lastly, the rich data allowed us to adjust for potential confounding and reduce other sources of biases.

In summary, this study on a geographically-diverse, biracial cohort showed that Black older women had a greater risk for clinical AD than White women. Such racial/ethnic differences persisted after accounting for conventional risk factors, with the remaining disparities partly explained by late-life exposure to $PM_{2.5}$. Additionally, the association between $PM_{2.5}$ and increased AD risk was much stronger in Black, compared to White, older women. These results provide new evidence for the potential role of environmental neurotoxins in the racial/ethnic disparities in AD risk and may help inform strategies aimed towards AD prevention in at-risk minority populations.

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Author Contributions

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Conflicts of Interest

The authors report no conflicts of interest.

References

1. Barnes LL, Bennett DA. Alzheimer's Disease In African Americans: Risk Factors And Challenges For The Future. *Health affairs (Project Hope)*. 2014;33(4):580-586. doi:10.1377/hlthaff.2013.1353
2. Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015-2060) in adults aged ≥65 years. *Alzheimers Dement*. 01 2019;15(1):17-24. doi:10.1016/j.jalz.2018.06.3063
3. Manly JJ, Mayeux R. *Chapter 4: Ethnic Differences in Dementia and Alzheimer's Disease*. Critical Perspectives on Racial and Ethnic Differences in Health in Late Life. National Academies Press; 2004.
4. 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*. Oct 2011;16(10):987-95, 973. doi:mp201176 [pii]

10.1038/mp.2011.76

5. Bhatt DP, Puig KL, Gorr MW, Wold LE, Combs CK. A pilot study to assess effects of long-term inhalation of airborne particulate matter on early Alzheimer-like changes in the mouse brain. *PLoS One*. 2015;10(5):e0127102. doi:10.1371/journal.pone.0127102
6. Cheng L, Lau WKW, Fung TKH, et al. PM2.5 Exposure Suppresses Dendritic Maturation in Subgranular Zone in Aged Rats. *Neurotox Res*. Jul 2017;32(1):50-57. doi:10.1007/s12640-017-9710-4
7. Ku T, Li B, Gao R, et al. NF-κB-regulated microRNA-574-5p underlies synaptic and cognitive impairment in response to atmospheric $PM_{2.5}$ Aspiration. *Part Fibre Toxicol*. 08 2017;14(1):34. doi:10.1186/s12989-017-0215-3

8. Cacciottolo M, Wang X, Driscoll I, et al. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Transl Psychiatry*. 01 2017;7(1):e1022. doi:10.1038/tp.2016.280
9. Zhang Q, Li Q, Ma J, Zhao Y. PM2.5 impairs neurobehavior by oxidative stress and myelin sheaths injury of brain in the rat. *Environ Pollut*. Nov 2018;242(Pt A):994-1001. doi:10.1016/j.envpol.2018.07.031
10. Wei W, Chen M, Li G, Sang N. Atmospheric PM 2.5 aspiration causes tauopathy by disturbing the insulin signaling pathway. *Ecotoxicol Environ Saf*. Mar 2019;169:301-305. doi:10.1016/j.ecoenv.2018.11.001
11. Cacciottolo M, Morgan TE, Saffari AA, et al. Traffic-related air pollutants (TRAP-PM) promote neuronal amyloidogenesis through oxidative damage to lipid rafts. *Free Radic Biol Med*. Feb 2020;147:242-251. doi:10.1016/j.freeradbiomed.2019.12.023
12. Sahu B, Mackos AR, Floden AM, Wold LE, Combs CK. Particulate Matter Exposure Exacerbates Amyloid-β Plaque Deposition and Gliosis in APP/PS1 Mice. *J Alzheimers Dis*. Feb 2021;doi:10.3233/JAD-200919
13. Iaccarino L, La Joie R, Lesman-Segev OH, et al. Association Between Ambient Air Pollution and Amyloid Positron Emission Tomography Positivity in Older Adults With Cognitive Impairment. *JAMA Neurol*. Nov 30 2020;doi:10.1001/jamaneurol.2020.3962
14. Crous-Bou M, Gascon M, Gispert JD, et al. Impact of urban environmental exposures on cognitive performance and brain structure of healthy individuals at risk for Alzheimer's dementia. *Environ Int*. Feb 2020:105546. doi:10.1016/j.envint.2020.105546

15. Younan D, Wang X, Casanova R, et al. $PM_{2.5}$ associated with gray matter atrophy reflecting increased Alzheimers risk in older women. *Neurology*. 11 2020;doi:10.1212/WNL.0000000000011149
16. Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air Pollution and Dementia: A Systematic Review. *J Alzheimers Dis*. Feb 2019;doi:10.3233/JAD-180631
17. Bell ML, Ebisu K. Environmental inequality in exposures to airborne particulate matter components in the United States. *Environ Health Perspect*. Dec 2012;120(12):1699-704. doi:10.1289/ehp.1205201
18. Gwynn RC, Thurston GD. The burden of air pollution: impacts among racial minorities. *Environmental health perspectives*. 2001;109(suppl 4):501-506.
19. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of Cause-Specific Mortality Associated With PM2.5 Air Pollution in the United States. *JAMA Netw Open*. 11 2019;2(11):e1915834. doi:10.1001/jamanetworkopen.2019.15834
20. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control Clin Trials*. Dec 1998;19(6):604-21.
21. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *The Journal of clinical psychiatry*. 1987;
22. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assesment of Alzheimer's disease. *Neurology*. 1989;39(9):1159-1159.
23. Brandt J, Spencer M, Folstein M. The Telephone Interview for Cognitive Status. *Neuropsychiatr Neuropsychol Behav Neurol*. 1988;1(2):111-117.

24. Hogervorst E, Bandelow S, Combrinck M, Irani SR, Smith AD. The validity and reliability of 6 sets of clinical criteria to classify Alzheimer's disease and vascular dementia in cases confirmed post-mortem: added value of a decision tree approach. *Dement Geriatr Cogn Disord*. 2003;16(3):170-80. doi:71006

71006 [pii]

25. Reyes JM, Xu Y, Vizuete W, Serre ML. Regionalized PM2.5 Community Multiscale Air Quality model performance evaluation across a continuous spatiotemporal domain. *Atmos Environ (1994)*. Jan 2017;148:258-265. doi:10.1016/j.atmosenv.2016.10.048

26. Whitsel EA, Rose KM, Wood JL, Henley AC, Liao D, Heiss G. Accuracy and repeatability of commercial geocoding. *Am J Epidemiol*. Nov 2004;160(10):1023-9. doi:10.1093/aje/kwh310

27. Xu Y, Serre ML, Reyes J, Vizuete W. Bayesian Maximum Entropy Integration of Ozone Observations and Model Predictions: A National Application. *Environ Sci Technol*. Apr 2016;50(8):4393-400. doi:10.1021/acs.est.6b00096

28. Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, et al. Long-term PM2.5 Exposure and Neurological Hospital Admissions in the Northeastern United States. *Environ Health Perspect*. 01 2016;124(1):23-9. doi:10.1289/ehp.1408973

29. Lee M, Schwartz J, Wang Y, Dominici F, Zanobetti A. Long-term effect of fine particulate matter on hospitalization with dementia. *Environ Pollut*. Jul 2019;254(Pt A):112926. doi:10.1016/j.envpol.2019.07.094

30. Smargiassi A, Laouan Sidi EA, Robert L-E, et al. Exposure to ambient air pollutants and the onset of dementia in Québec, Canada. *Environmental Research*. 2020/07/23/ 2020:109870. doi:https://doi.org/10.1016/j.envres.2020.109870

31. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. Jul 2020;doi:10.1016/S0140-6736(20)30367-6

32. Griffin BA, Anderson GL, Shih RA, Whitsel EA. Use of alternative time scales in Cox proportional hazard models: implications for time-varying environmental exposures. *Stat Med*. Nov 2012;31(27):3320-7. doi:10.1002/sim.5347

33. Services UDoHaH. National plan to address Alzheimer's disease: 2018 Update. Accessed September 18, 2019, https://aspe.hhs.gov/system/files/pdf/259581/NatPlan2018.pdf

34. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*. Jan 2001;56(1):49-56. doi:10.1212/wnl.56.1.49

35. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol*. Nov 2002;59(11):1737-46.

36. Fitzpatrick AL, Kuller LH, Ives DG, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. *J Am Geriatr Soc*. Feb 2004;52(2):195-204.

37. Hebert LE, Bienias JL, Aggarwal NT, et al. Change in risk of Alzheimer disease over time. *Neurology*. Aug 2010;75(9):786-91. doi:10.1212/WNL.0b013e3181f0754f

38. Weuve J, Barnes LL, Mendes de Leon CF, et al. Cognitive Aging in Black and White Americans: Cognition, Cognitive Decline, and Incidence of Alzheimer Disease Dementia. *Epidemiology*. 01 2018;29(1):151-159. doi:10.1097/EDE.0000000000000747

39. Rajan KB, Weuve J, Barnes LL, Wilson RS, Evans DA. Prevalence and incidence of clinically diagnosed Alzheimer's disease dementia from 1994 to 2012 in a population study. *Alzheimers Dement*. 01 2019;15(1):1-7. doi:10.1016/j.jalz.2018.07.216

40. Plassman BL, Langa KM, McCammon RJ, et al. Incidence of dementia and cognitive impairment, not dementia in the United States. *Ann Neurol*. Sep 2011;70(3):418-26. doi:10.1002/ana.22362

41. Katz MJ, Lipton RB, Hall CB, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. *Alzheimer Dis Assoc Disord*. 2012 Oct-Dec 2012;26(4):335-43. doi:10.1097/WAD.0b013e31823dbcfc

42. Arvanitakis Z, Leurgans SE, Fleischman DA, et al. Memory complaints, dementia, and neuropathology in older blacks and whites. *Ann Neurol*. 04 2018;83(4):718-729. doi:10.1002/ana.25189

43. Evans DA, Bennett DA, Wilson RS, et al. Incidence of Alzheimer disease in a biracial urban community: relation to apolipoprotein E allele status. *Arch Neurol*. Feb 2003;60(2):185-9. doi:10.1001/archneur.60.2.185

44. Steenland K, Goldstein FC, Levey A, Wharton W. A Meta-Analysis of Alzheimer's Disease Incidence and Prevalence Comparing African-Americans and Caucasians. *J Alzheimers Dis*. 2016;50(1):71-6. doi:10.3233/JAD-150778

45. Glymour MM, Manly JJ. Lifecourse social conditions and racial and ethnic patterns of cognitive aging. *Neuropsychol Rev*. Sep 2008;18(3):223-54. doi:10.1007/s11065-008-9064-z

46. Bailey ZD, Krieger N, Agénor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. *Lancet*. 04 2017;389(10077):1453-1463. doi:10.1016/S0140-6736(17)30569-X

47. Loop MS, Kent ST, Al-Hamdan MZ, et al. Fine particulate matter and incident cognitive impairment in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. *PLoS One*. 2013;8(9):e75001. doi:10.1371/journal.pone.0075001

48. Bell ML, Ebisu K, Belanger K. Ambient air pollution and low birth weight in Connecticut and Massachusetts. *Environ Health Perspect*. Jul 2007;115(7):1118-24. doi:10.1289/ehp.9759

49. Nachman KE, Parker JD. Exposures to fine particulate air pollution and respiratory outcomes in adults using two national datasets: a cross-sectional study. *Environ Health*. Apr 2012;11:25. doi:10.1186/1476-069X-11-25

50. Hicken MT, Adar SD, Hajat A, et al. Air Pollution, Cardiovascular Outcomes, and Social Disadvantage: The Multi-ethnic Study of Atherosclerosis. *Epidemiology*. Jan 2016;27(1):42-50. doi:10.1097/EDE.0000000000000367

51. Agency USEP. Learn About Environmental Justice. Accessed August 7, 2020, https://www.epa.gov/environmentaljustice/learn-about-environmental-justice

52. Woo B, Kravitz-Wirtz N, Sass V, Crowder K, Teixeira S, Takeuchi DT. Residential Segregation and Racial/Ethnic Disparities in Ambient Air Pollution. *Race Soc Probl*. Mar 2019;11(1):60-67. doi:10.1007/s12552-018-9254-0

53. Logan JR, Stowell J, Oakley D. Choosing Segregation: Racial Imbalance in American Public Schools, 1990-2000. 2002;

54. Massey DS, Denton NA. The Dimensions of Residential Segregation. *Social Forces*. 1988;67(2):281-315. doi:10.2307/2579183

55. Gee GC, Payne-Sturges DC. Environmental health disparities: a framework integrating psychosocial and environmental concepts. *Environ Health Perspect*. Dec 2004;112(17):1645-53. doi:10.1289/ehp.7074

56. Zenk SN, Schulz AJ, Israel BA, James SA, Bao S, Wilson ML. Neighborhood racial composition, neighborhood poverty, and the spatial accessibility of supermarkets in metropolitan Detroit. *Am J Public Health*. Apr 2005;95(4):660-7. doi:10.2105/AJPH.2004.042150

57. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement*. Sep 2018;doi:10.1016/j.jalz.2018.07.219

58. Caunca MR, Odden MC, Glymour MM, et al. Association of Racial Residential Segregation Throughout Young Adulthood and Cognitive Performance in Middle-aged Participants in the CARDIA Study. *JAMA Neurol*. May 2020;doi:10.1001/jamaneurol.2020.0860

59. Hill CV, Pérez-Stable EJ, Anderson NA, Bernard MA. The National Institute on Aging Health Disparities Research Framework. *Ethn Dis*. Aug 2015;25(3):245-54. doi:10.18865/ed.25.3.245

60. Frey HC, Adams PJ, Adgate JL, et al. The Need for a Tighter Particulate-Matter Air-Quality Standard. *N Engl J Med*. 08 2020;383(7):680-683. doi:10.1056/NEJMsb2011009

61. Thames AD, Hinkin CH, Byrd DA, et al. Effects of stereotype threat, perceived discrimination, and examiner race on neuropsychological performance: simple as black and white? *J Int Neuropsychol Soc*. May 2013;19(5):583-93. doi:10.1017/S1355617713000076

62. Census U. Table 2-2 Population 65 Years and Over by Age, Sex, Race, and Hispanic Origin: July 1, 1994; http://www.census.gov/prod/1/pop/p23-190/p23-190.pdf.

63. Weuve J, Proust-Lima C, Power MC, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimers Dement*. Sep 2015;11(9):1098-109. doi:10.1016/j.jalz.2015.06.1885

Table 1. Population characteristics at baseline by annual average $PM_{2.5}$ and stratified by race/ethnicity in the biracial WHIMS cohort, 1996-2010 **(N = 6485)**

		Annual Average $PM_{2.5}$[a]		Racial/Ethnic Group[b]		
Characteristic	**N**	**(N = 6485)**	***P* value[c]**	**Blacks (n = 481)**	**Whites (n = 6004)**	***P* value[d]**
U.S. geographic region			<.001			<.001
Northeast	1795	12.1 (1.7)		102 (21.2)	1693 (28.2)	
South	1363	13.5 (2.1)		212 (44.1)	1151 (19.2)	
Midwest	1642	13.0 (2.3)		110 (22.9)	1532 (25.5)	
West	1685	12.3 (4.1)		57 (11.9)	1628 (27.1)	
Age			<.001			.003
65-69	3026	12.6 (2.8)		260 (54.1)	2766 (46.1)	
70-74	2334	12.6 (2.9)		149 (31.0)	2185 (36.4)	
≥75	1125	13.0 (2.7)		72 (15.0)	1053 (17.5)	
Income			<.001			<.001
<$10,000	323	12.9 (2.8)		73 (15.2)	250 (4.2)	
$10,000 to $34,999	3142	12.6 (2.8)		230 (47.8)	2912 (48.5)	
$35,000 to $74,999	2149	12.8 (2.7)		128 (26.6)	2021 (33.7)	
≥$75,000	640	13.0 (2.7)		42 (8.7)	598 (10.0)	
Missing	231	12.4 (2.5)		8 (1.7)	223 (3.7)	
Education			.08			<.001

< High school	424	12.9 (2.7)		72 (15.1)	352 (5.9)	
High school/GED	1419	12.6 (2.7)		73 (15.3)	1346 (22.5)	
> High school	4624	12.7 (2.8)		332 (69.6)	4292 (71.7)	
Employment Status			.06			.36
Currently employed	1170	12.8 (2.7)		79 (16.5)	1091 (18.2)	
Not working	669	12.9 (2.8)		44 (9.2)	625 (10.4)	
Retired	4626	12.6 (2.8)		357 (74.4)	4269 (71.3)	
Alcohol intake			<.001			<.001
Non-drinker	776	13.2 (2.8)		92 (19.4)	684 (11.5)	
Past drinker	1234	12.8 (2.8)		155 (32.7)	1079 (18.1)	
< 1 drink per day	3617	12.6 (2.7)		215 (45.4)	3402 (57.1)	
> 1 drink per day	803	12.5 (2.7)		12 (2.5)	791 (13.3)	
Smoking status			.28			.004
Never smoked	3389	12.7 (2.8)		228 (48.6)	3161 (53.3)	
Past smoker	2579	12.6 (2.8)		193 (41.2)	2386 (40.2)	
Current smoker	429	12.8 (2.6)		48 (10.2)	381 (6.4)	
Moderate or strenuous activities ≥ 20 minutes			<.001			<.001
No activity	3748	12.8 (2.8)		343 (71.6)	3405 (56.8)	
Some activity	309	12.9 (2.7)		20 (4.2)	289 (4.8)	
2-4 episodes/week	1281	12.5 (2.8)		67 (14.0)	1214 (20.3)	
>4 episodes/week	1131	12.4 (2.8)		49 (10.2)	1082 (18.1)	
Body mass index, kg/m^2			.73			<.001

< 25	1862	12.7 (2.7)		78 (16.4)	1784 (29.9)	
25-29	2333	12.7 (2.8)		152 (31.9)	2181 (36.5)	
≥30	2254	12.7 (2.8)		247 (51.8)	2007 (33.6)	
Cardiovascular disease			.11			.13
No	5281	12.7 (2.8)		377 (80.0)	4904 (82.8)	
Yes	1111	12.8 (2.8)		94 (20.0)	1017 (17.2)	
History of Depression			.27			.27
No	5845	12.7 (2.7)		422 (90.8)	5423 (92.2)	
Yes	502	12.8 (2.9)		43 (9.2)	459 (7.8)	
Diabetes treated ever (pills or shots)			.72			<.001
No	6095	12.7 (2.8)		413 (86.2)	5682 (94.8)	
Yes	380	12.7 (2.7)		66 (13.8)	314 (5.2)	
Hypercholesterolemia requiring pills ever			.02			.08
No	5245	12.6 (2.8)		371 (78.9)	4874 (82.2)	
Yes	1155	12.8 (2.8)		99 (21.1)	1056 (17.8)	
Hormone therapy use ever			.18			.24
No	3541	12.7 (2.6)		275 (57.2)	3266 (54.4)	
Yes	2942	12.6 (3.0)		206 (42.8)	2736 (45.6)	
Hypertension ever			.01			<.001

No	3915	12.6 (2.7)		194 (41.5)	3721 (62.6)	
Yes	2497	12.8 (2.8)		273 (58.5)	2224 (37.4)	
WHI-HT intervention assignment			.79			.61
Control	3309	12.7 (2.8)		240 (49.9)	3069 (51.1)	
Intervention	3176	12.7 (2.7)		241 (50.1)	2935 (48.9)	
Social Strain[e]			.23			<.001
Low	4162	12.6 (2.8)		216 (48.5)	3946 (67.4)	
High	2136	12.7 (2.7)		229 (51.5)	1907 (32.6)	
Social Support[f]			.52			.002
Low	3296	12.7 (2.8)		264 (59.3)	3032 (51.9)	
High	2993	12.7 (2.8)		181 (40.7)	2812 (48.1)	
Social Activity[g]			<.001			<.001
Low	3262	12.5 (2.8)		174 (36.6)	3088 (51.6)	
High	3202	12.8 (2.7)		301 (63.4)	2901 (48.4)	
Living alone[h]			.10			.003
No	4319	12.6 (2.7)		284 (61.1)	4035 (67.7)	
Yes	2105	12.8 (2.8)		181 (38.9)	1924 (32.3)	
Stressful life events[i]			.13			<.001
Low	3542	12.6 (2.8)		183 (40.3)	3359 (57.3)	
High	2774	12.7 (2.7)		271 (59.7)	2503 (42.7)	

[a]Data are expressed as mean (SD) of participants

[b]Data are expressed as number (percentage) of participants

[c]*P* value testing statistical difference across subcategories using ANOVA tests

[d]*P* value testing the distribution of racial/ethnic groups across subcategories using chi-square tests

[e]How many of an individual's social ties are characterized by strain

[f]Availability of support, affection, and positive social interactions

[g]Frequency of engagement in social clubs/organizations and religious services/church activities

[h]Whether the participant lives alone

[i]Stressful life events over the previous year

Table 2. Hazard ratios of Alzheimer's disease incidence in Black vs. White women before and after adjusting for annual average $PM_{2.5}$ exposure

		Without $PM_{2.5}$-adjustment			With $PM_{2.5}$-adjustment					
	N (cases)	$HR_{Black\ women}$	95% CI	*P* Value	$HR_{Black\ women}$	95% CI	*P* value	$HR_{PM2.5}$	95% CI	*P* Value
Crude	6485 (158)	2.10	1.33, 3.34	.002	1.97	1.21, 3.22	.006	1.24	1.02, 1.51	.03
Adjusted										
Model 1[a]	6485 (158)	2.03	1.28, 3.21	.003	1.97	1.21, 3.21	.007	1.20	0.97, 1.50	.10
Model 2[b]	6450 (156)	1.89	1.18, 3.02	.008	1.83	1.09, 3.06	.02	1.20	0.96, 1.50	.11
Model 3[c]	6319 (150)	1.85	1.14, 3.01	.01	1.81	1.06, 3.07	.03	1.18	0.93, 1.48	.17
Model 4[d]	5995 (136)	2.32	1.43, 3.76	<.001	2.22	1.30, 3.81	.004	1.24	0.98, 1.58	.07
Model	5798 (130)	2.41	1.44, 4.04	<.001	2.26	1.29, 3.96	.005	1.28	1.02, 1.61	.04

5[e]

Abbreviations: $HR_{Black\ women}$, risk of incident Alzheimer's disease of Black compared to White women; $HR_{PM2.5}$, risk of incident Alzheimer's disease associated with each interquartile range increment (3.73 µg/m^3) of annual average $PM_{2.5}$ exposure; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 µm

[a]Adjusting for age and region

[b]Model 1 + socioeconomic factors (income, education, and employment status)

[c]Model 2 + lifestyle factors (alcohol use, smoking, and physical activity)

[d]Model 3 + history of depression, hormone therapy use before baseline, and WHI hormone therapy intervention assignment

[e]Model 4 + cardiovascular risk profiles (body mass index, hypercholesterolemia, diabetes, hypertension, and cardiovascular disease)

Figure 1. Hazard ratios of Alzheimer's disease incidence associated with annual average $PM_{2.5}$ exposure, stratified by race/ethnicity

Abbreviations: $HR_{PM2.5}$, risk of incident Alzheimer's disease associated with each interquartile range increment (3.73 μg/m^3) of annual average $PM_{2.5}$ exposure; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm

Note: Hazard ratios presented in the figure for all participants are the main effects reported in Table 2.

[a]*P* = .009 for interaction

[b]Adjusting for age and region; *P* = .004 for interaction

[c]Model 1 + socioeconomic factors (income, education, and employment status); *P* = .01 for interaction

[d]Model 2 + lifestyle factors (alcohol use, smoking, and physical activity); *P* = .010 for interaction

[e]Model 3 + history of depression, hormone therapy use before baseline, and WHI hormone therapy intervention assignment; *P* = .008 for interaction

[f]Model 4 + cardiovascular risk profiles (body mass index, hypercholesterolemia, diabetes, hypertension, and cardiovascular disease); *P* = .002 for interaction

Figure 1

	N (cases)	$HR_{PM2.5}$ (95% CI)
Crude[a]		
All participants	6485 (158)	1.24 (1.02, 1.51)
Black participants	481 (21)	2.14 (1.38, 3.31)
White participants	6004 (137)	1.15 (0.93, 1.42)
Model 1[b]		
All participants	6485 (158)	1.20 (0.97, 1.50)
Black participants	481 (21)	2.34 (1.44, 3.80)
White participants	6004 (137)	1.10 (0.87, 1.39)
Model 2[c]		
All participants	6450 (156)	1.20 (0.96, 1.50)
Black participants	477 (21)	2.10 (1.30, 3.41)
White participants	5973 (135)	1.10 (0.87, 1.40)
Model 3[d]		
All participants	6319 (150)	1.18 (0.93, 1.48)
Black participants	460 (21)	2.11 (1.30, 3.44)
White participants	5859 (129)	1.07 (0.84, 1.38)
Model 4[e]		
All participants	5995 (136)	1.24 (0.98, 1.58)
Black participants	424 (21)	2.33 (1.38, 3.91)
White participants	5571 (115)	1.12 (0.87, 1.45)
Model 5[f]		
All participants	5798 (130)	1.28 (1.02, 1.61)
Black participants	398 (19)	2.60 (1.57, 4.30)
White participants	5400 (111)	1.14 (0.89, 1.46)