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Traffic-related air pollution and *APOE4* can synergistically affect hippocampal volume in older women: new findings from UK Biobank

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A growing research body supports the connection between neurodegenerative disorders, including Alzheimer's disease (AD), and traffic-related air pollution (TRAP). However, the underlying mechanisms are not well understood. A deeper investigation of TRAP effects on hippocampal volume (HV), a major biomarker of neurodegeneration, may help clarify these mechanisms. Here, we explored TRAP associations with the HV in older participants of the UK Biobank (UKB), taking into account the presence of *APOE* e4 allele (*APOE4*), the strongest genetic risk factor for AD. Exposure to TRAP was approximated by the distance of the participant's main residence to the nearest major road (DNMR). The left/right HV was measured by magnetic resonance imaging (MRI) in cubic millimeters (mm^3). Analysis of variance (ANOVA), Welch test, and regression were used to examine statistical significance. We found significant interactions between DNMR and *APOE4* that influenced HV. Specifically, DNMR <50m (equivalent of a chronically high exposure to TRAP), and carrying *APOE4* were synergistically associated with a significant ($P = 0.01$) reduction in the right HV by about 2.5% in women aged 60–75 years (results for men didn't reach a statistical significance). Results of our study suggest that TRAP and *APOE4* jointly promote neurodegeneration in women. Living farther from major roads may help reduce the risks of neurodegenerative disorders, including AD, in female *APOE4* carriers.

KEYWORDS

hippocampal volume, neurodegeneration, air pollution, TRAP, major road, *APOE*, aging, Alzheimer's disease

1 Introduction

A growing body of research points to a connection between exposure to air pollution and neurodegenerative disorders, including Alzheimer's disease (AD), though mechanisms are not fully understood (Tham and Schikowski, 2021; Parra et al., 2022; Finch, 2023; Franz et al., 2023; Yuan et al., 2023). Various pollutants are present in the air, and some may pose risks to human health. For example, inhalable particulate matter (PM) and nitrogen dioxide (NO_2) have been intensively studied in this regard (Akimoto, 2003; Craig et al., 2008; Dominski et al., 2021). A recent study of UKB (UK Biobank, 2023) data found that higher exposure to $PM_{2.5}$ (median particle with diameter $\leq$ 2.5 μm) and NO_2 was associated with multimorbidity in a dose-dependent manner

(Ronaldson et al., 2022). The PM, NO_2, and volatile organic compounds (VOCs) are common components of the traffic-related air pollution (TRAP). These and other types of air pollution (such as ozone, sulfur oxides, carbon monoxide, and lead), might be harmful to the central nervous system (CNS) and promote neuroinflammation and neurodegeneration (Hogan et al., 2015; Calderón-Garcidueñas et al., 2016a; Cheng et al., 2016; Spangenberg and Green, 2017; Costa et al., 2020). A review of epidemiological and experimental studies of the role of PM in neurodegeneration emphasized a link between chronic exposure to PM and onsets of cognitive deficits, dementia, and AD (You et al., 2022). A meta-analysis of 14 studies concluded that $PM_{2.5}$ is a risk factor for dementia, with more limited support for nitrogen oxides, though the authors stressed that these results should be interpreted with caution (Wilker et al., 2023). Higher exposure to NO_2 itself was associated with lower cortical thickness of brain regions relevant to AD (Crous-Bou et al., 2020). Another study that used the UKB data (Li et al., 2023) reported an association between residential distance to major roads and dementia that was mediated by TRAP, mainly NO_2.

Exposure to environmental pollutants, including TRAP, could be especially detrimental for hippocampus, a key brain structure for learning and memory, and a primary brain region affected by AD (van der Flier and Scheltens, 2009; Rao et al., 2022). Hippocampal atrophy, manifested in reduced hippocampal volume (HV), is considered one of the major biomarkers of neurodegeneration and preclinical AD pathology (Jack et al., 2018; Grober et al., 2021). It has been associated with a decline in cognitive function and progression of mild cognitive impairment (MCI) to AD (Jack et al., 2000; Henneman et al., 2009; Qu et al., 2023). It was shown that exposure to PM can create profound metabolic disturbances in hippocampus, and adversely affect HV (Park et al., 2020; Balboni et al., 2022). A study that used brain imaging and air pollution data from the UKB found an association between higher $PM_{2.5}$ concentration and smaller left HV in adult UKB participants (Hedges et al., 2019).

Genetic factors may also influence HV. For example, carrying the *APOE* e4 allele (*APOE4*), the strongest genetic risk factor for AD, may accelerate hippocampal atrophy, along with cognitive decline (Abushakra et al., 2020). Several studies (Tohgi et al., 1997; Reiman et al., 1998; O'Dwyer et al., 2012; Saeed et al., 2021) reported that individuals with *APOE4* have markedly smaller HV, along with increased risks of AD and other dementias, compared to those without *APOE4*. The *APOE4* may also interact with exposure to air pollution, including TRAP, potentially modifying its effects on AD-related traits (Schikowski et al., 2015; Ma et al., 2023).

In this study, we used the UKB data to further explore the interactions between *APOE4* and TRAP, to better understand how the exposure to TRAP may influence HV in older adults, who carry the strongest genetic risk factor for AD.

2 Materials and methods

2.1 Data and phenotypes

This study was performed using the UKB (UK Biobank, 2023), a population-based study with extensive genetic and phenotypic data for approximately 500,000 individuals from across the UK. Data for the study were obtained (November, 2019) from the UKB database. Written informed consent was obtained by the UKB from the participants in accordance with the UK national legislation and the UKB requirements. The latest (at the time of calculations) available information on participants' withdrawal in UKB was taken into account.

TABLE 1 UKB sample used for analysis.

Group/subjects	Female, age 60–75	Male, age 60–75
DNMR	661	584
noDNMR	9,968	9,102
APOE4	2,969	2,627
noAPOE4	7,660	7,059
DNMR APOE4	199	167
DNMR noAPOE4	462	417
noDNMR APOE4	2,770	2,460
noDNMR noAPOE4	7,198	6,642
All	10,629	9,686

In our analysis, TRAP was approximated by the participant's residence distance (in meters) to the nearest major road (DNMR). The DNMR was defined based on the local road network taken from the Ordnance Survey Meridian 2 road network 2009 with scale 1:50,000 and one meter accuracy (McGarva, 2017; Environmental Exposures Metadata and Resource 2010 UK, 2023). The median value of the DNMR was 377.4 (interquartile range: [165.9, 751.9]).

Among those subjects who had both DNMR and *APOE4* carrier status information, participants aged between 60 and 75 years, who attended the assessment center during the first imaging visit (starting January 1, 2014), were chosen. The *APOE4* carrier status was approximated by carrying C allele of the SNP rs429358. The left and right HV were measured in cubic millimeters (mm^3), and respective information was obtained from the UKB data-fields 25019 and 25020. To normalize for head size, these measurements were multiplied by the head size scaling factor obtained from the UKB data-field 25,000 (Smith et al., 2022; Supplementary material, MRI measurements).

The analytic sample (Table 1) was divided into one factor and two factor groups, as follows:

G1. One factor groups

DNMR group consists of subjects with residential proximity to the nearest major road <50m, noDNMR group consists of subjects with residential proximity to the nearest major road more than 50m, APOE4 group consists of *APOE4* carriers, noAPOE4 group consists of *APOE4* non-carriers.

G2. Two factor groups

DNMR_APOE4 group contains subjects from both DNMR and APOE4 groups, DNMR_noAPOE4 group contains subjects from both DNMR and noAPOE4 groups, noDNMR_APOE4 group contains subjects from both noDNMR and APOE4 groups,

noDNMR_noAPOE4 group contains subjects from both noDNMR and noAPOE4 groups.

The study sample contained participants having DNMR and *APOE4* carrier status data, who attended the assessment center during the first imaging visit (between January 1, 2014 and October 31, 2019) at age 60–75 years. It, thus, only included individuals, who were at risk for the late-onset but not the early onset AD.

2.2 Analytic approach

Analysis of variance (ANOVA), the Tukey's test, and the Welch test (Welch, 1947; Chambers et al., 1992; Yandell, 1997) were utilized. We considered three sets of regression models Set1 = HV~*Age*,*dnmr* (8 models), Set2 = HV~*Age*,*snp* (8 models), and Set3 = HV~*Age*,*snp*,*dnmr* (64 models) (Supplementary material, Analytic approach) having HV as a response variable HV = HV (mm^3) left/right and independent variables: $dnmr = 1$ (DNMR < 50), $dnmr = 0$ (DNMR ≥ 50), $snp = 1$ (*APOE4* carrier), $snp = 0$ (*APOE4* non-carrier), and age at the time attending assessment center during the first imaging visit as the *Age* variable.

The regression models were evaluated using the Akaike information criterion (AIC) (Akaike, 1973). The optimal, with respect to the minimal AIC criteria, significant results for regression model were found for the regression sets described above. Here, significant regression model means that all regression coefficients were significant ($P < 0.05$) in a specific model, non-significance means the opposite. R standard software packages (version 3.6.3), along with *glmulti* package (Calcagno, 2022), were utilized.

3 Results

We found significant difference in the right HV between groups DNMR and noDNMR, between groups APOE4 and noAPOE4, and between groups DNMR_APOE4 and noDNMR_noAPOE4 for females aged 60–75 years (Table 2, Figure 1). One can see that there was a 0.5% decrease in the right HV for *APOE4* carriers, a 1.0% decrease in the right HV for those with DNMR < 50, and a 2.5% decrease in right HV for *APOE4* carriers with DNMR < 50. Note that joint impact of DNMR and *APOE4* is larger than separate contributions of *APOE4* and DNMR (2.5% $>$ 0.5%, 2.5% $>$ 1.0%), or their sum (2.5% $>$ 0.5% + 1.0%).

There was a 0.6% decrease in the left HV for *APOE4* carriers in women aged 60–75 years; differences between other groups were not statistically significant (Supplementary Table 1, Supplementary Figure 1). Normal aging is associated with gradual reducing of HV even without any possible adverse factors (Harman, 2001; Fotuhi et al., 2012; López-Otín et al., 2013). In our analysis, we performed the Welch test to check a possible difference in age between groups (Supplementary Tables 2, 3). We found that on average the subjects in the group DNMR were older than the subjects in the group noDNMR, which might contribute to the reduced HV in the group DNMR compared to the group noDNMR. The subjects in the group APOE4, on average, were younger than the subjects in the group noAPOE4. Note that such age difference between APOE4 and noAPOE4 groups strengthened our results because younger subjects generally tend to have bigger HV than the older ones. The subjects in the group DNMR_APOE4, on average, were the same age as the subjects in the group noDNMR_noAPOE4.

Difference in the right HV between two groups DNMR and noDNMR in the Figure 1A could be attributed to the age only, with participants in the DNMR group older than participants in the noDNMR group (Supplementary Table 3). Based on Table 3, the decrease in the right HV became more pronounced with age in women aged 60–75 years: from 0.8% at age 60 to 0.9% at age 75 for the right HV. Difference in HV between two groups APOE4 and noAPOE4 in the Figure 1B could be attributed to the age and *APOE4* carrier status, with participants being younger in the APOE4 compared those in noAPOE4 (Supplementary Table 3). Based on Table 3, the decrease in the right HV became more pronounced with age in women aged 60–75 years: from 0.6% at age 60 to 0.8% at age 75 for the right HV. When taking into account three factors (age, proximity to the nearest major road, and *APOE4* carrier status), based on Table 3, difference in the right HV gradually increased from 2.4% at age 60 to 2.8% at age 75, for *APOE4* carriers with proximity to the nearest major road <50m. The right HV decreased with age in women aged 60–75 years, losing about 27 mm^3/year.

For males aged 60–75 years differences in the left/right HV between studied groups (Supplementary Tables 4, 5) were not statistically significant. For males aged 60–75 years, regression analysis found that for all regression sets Set1 = HV~*Age*,*dnmr* (8 models), Set2 = HV~*Age*,*snp* (8 models), Set3 = HV~*Age*,*snp*,*dnmr* (64 models) the best (with respect to the minimal AIC criterion) models depend only on *Age* variable (Supplementary Tables 6–8).

Comparison of the regression model with interactive term with the reference model, i.e., the regression with main additive effects (Table 3, model 13 in Set3: HV~*Age*,*snp*,*dnmr*) allows estimating deviation from the reference model, which was: deviation = 106.2 + 0.4**Age*-(43.3 + 32.7) = 54.2, for *Age* = 60 and deviation = 60.2, for *Age* = 75, that is, deviation gradually increases with age. This observation reasonably supported synergy (Roell et al., 2017) in the interaction between DNMR and APOE e4 status with respect to HV decrease.

4 Discussion

Our study, using the UKB data, found that female *APOE4* carriers aged 60–75 years, who live <50 meters from a major road, had the right HV that was significantly smaller (by about 2.5%) than the HV of the same age women without these conditions. We also showed for the first time that exposure to TRAP (approximated by closeness of participant's main residence to major roads), and carrying the *APOE4*, synergistically affected HV in women. These findings imply that living farther from major roads may be especially beneficial to older female *APOE4* carriers and could help reduce their risks of neurodegenerative disorders, including AD. In our study, the right HV also decreased with age in women aged 60–75 years, losing, on average, about 27 mm^3/year. This is in agreement with an earlier report of the HV change with age by the UKB (Nobis et al., 2019).

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TABLE 2 Comparison of the right HV between groups of females aged 60–75.

Test	*P*-value	95% confidence intervals	HV estimate (mm^3)
Females, age 60–75, HV (mm^3) right			
ANOVA	2.30e-02		
DNMR		[5,038, 5,128]	5,082
noDNMR		[5,123, 5,146]	5,135
DNMR – noDNMR		[−98, −7]	−53
Females, age 60–75, HV (mm^3) right			
ANOVA	3.42e-02		
APOE4		[5,091, 5,134]	5,112
noAPOE4		[5,126, 5,151]	5,139
APOE4 – noAPOE4		[−51, −2]	−26
Females, age [60–75], HV (mm^3) right			
Tukey	1.70e-01		
DNMR_APOE4		[4,934, 5098]	5,012
DNMR_noAPOE4		[5,059, 5,161]	5,112
DNMR_APOE4 – DNMR_noAPOE4		[−226, 25]	−100
Females, age [60–75], HV (mm^3) right			
Tukey	5.37e-02		
DNMR_APOE4		[4,934, 5,098]	5,012
noDNMR_APOE4		[5,098, 5 140]	5,120
DNMR_APOE4 – noDNMR_APOE4		[−216, 1]	−108
Females, age [60–75], HV (mm^3) right			
Tukey	1.04e-02		
DNMR_APOE4		[4,934, 5,098]	5,012
noDNMR_noAPOE4		[5,127, 5,154]	5,140
DNMR_APOE4 – noDNMR_noAPOE4		[−235, −22]	−128
Females, age [60–75], HV (mm^3) right			
Tukey	9.94e-01		
DNMR_noAPOE4		[5,059, 5,161]	5,112
noDNMR_APOE4		[5,098, 5,140]	5,120
DNMR_noAPOE4 – noDNMR_APOE4		[−82, 67]	−7
Females, age [60–75], HV (mm^3) right			
Tukey	7.36e-01		
DNMR_noAPOE4		[5,059, 5,161]	5,112
noDNMR_noAPOE4		[5,127, 5,154]	5,140
DNMR_noAPOE4 – noDNMR_noAPOE4		[−99, 43]	−28
Females, age [60–75], HV (mm^3) right			
Tukey	3.66e-01		
noDNMR_APOE4		[5,098, 5,140]	5,120
noDNMR_noAPOE4		[5,127, 5,154]	5,140
noDNMR_APOE4 – noDNMR_noAPOE4		[−54, 12]	−21

In this table, differences between the following groups are considered: DNMR and noDNMR, APOE4 and noAPOE4, DNMR_APOE4 and DNMR_noAPOE4, DNMR_APOE4 and noDNMR_APOE4, DNMR_APOE4 and noDNMR_noAPOE4, DNMR_noAPOE4 and noDNMR_APOE4, DNMR_noAPOE4 and noDNMR_noAPOE4, noDNMR_APOE4 and noDNMR_noAPOE4. The sign minus between two groups denotes the difference between the means in two groups (effect size). For instance, DNMR_APOE4 - DNMR_noAPOE4 equals to the difference between the right HV mean value in the group DNMR_APOE4 and group DNMR_noAPOE4. Scientific notation "e" means that the base number is multiplied by 10 raised to the given power.

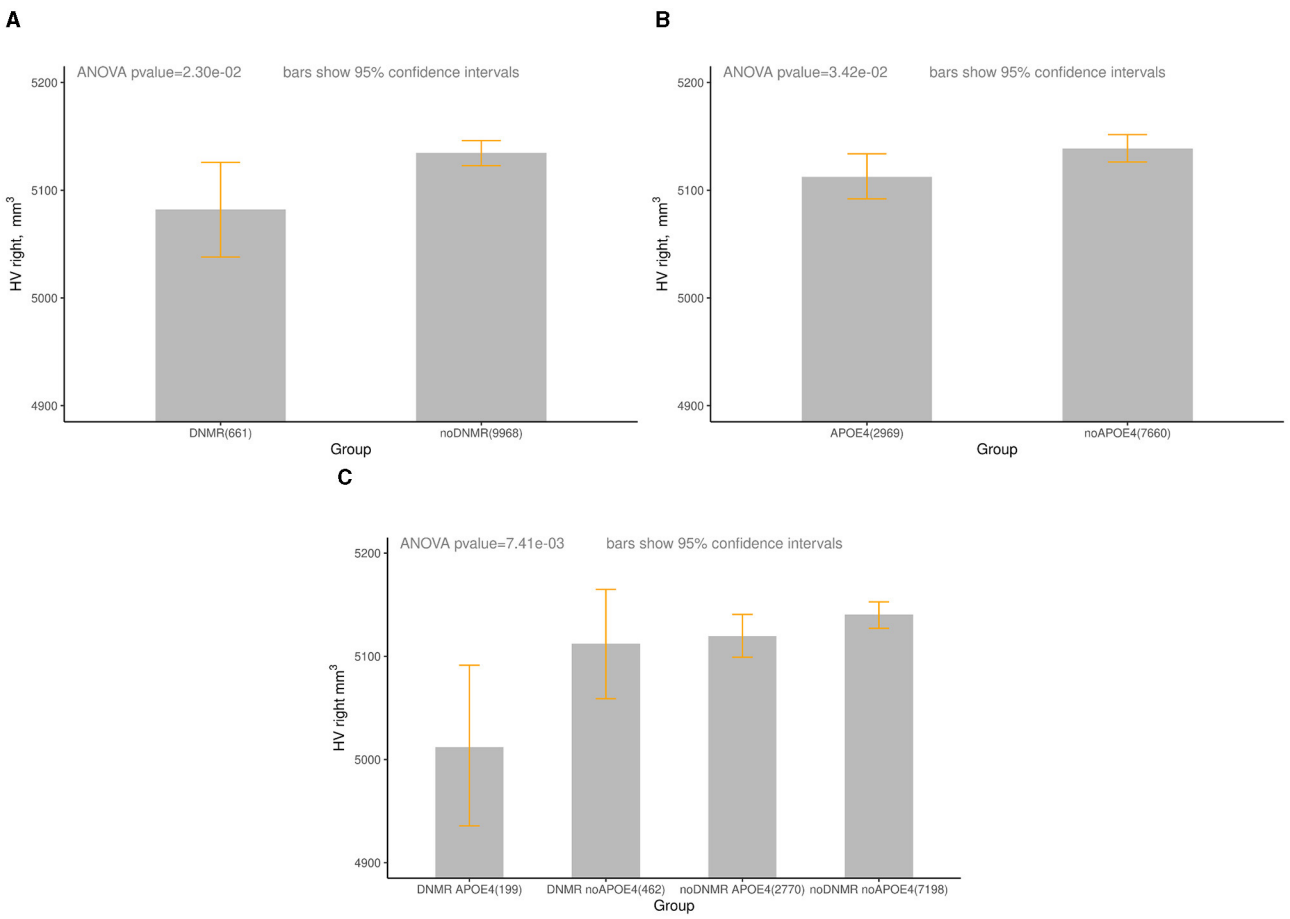

FIGURE 1
The right HV (mm^3) in groups of women aged 60-75 years, by DNMR and APOE4 status. Age—age at the time attending the assessment center during the first imaging visit between January 1, 2014 and October 31, 2019. **(A)** UKB, HV right, DNMR < 50 m, females, aged 60–75 years. DNMR (HV: mean = 5,082, 95% CI: 5,038–5,128), noDNMR (HV: mean = 5,135, 95% CI: 5,123–5,146). **(B)** UKB, HV right, APOE4, females, aged 60–75 years. APOE4 (HV: mean = 5,112, 95% CI: 5,091–5,134), no APOE4 (HV: 5,139, 95% CI: 5,126–5,151). **(C)** UKB, HV right, DNMR < 50m and APOE4, females, age 60–75 years, DNMR_APOE4 (HV: mean = 5,012, 95% CI: 4,934–5,098), DNMR_noAPOE4 (HV: mean = 5,112, 95% CI: 5,059–5,161) noDNMR_APOE4 (HV: mean = 5,120, 95% CI: 5,098–5,140), noDNMR no APOE4 (HV: mean = 5,140, 95% CI: 5,127–5,154). For more detailed statistics, see Table 2.

Results of our study are broadly in line with earlier research that demonstrated that exposure to air pollution (especially to $PM_{2.5}$) is associated with smaller brain/hippocampal volume (Wilker et al., 2015; Hedges et al., 2019; Balboni et al., 2022). Several studies investigated the role of air pollution in dementia and cognitive decline, including in *APOE4* carriers. Chen et al. (2017) reported a modest increase in hazard ratio (1.07 [95% CI: 1.06–1.08]) of dementia in people living <50 meters from a major road. Higher $PM_{2.5}$ exposure was linked to worse cognitive function in *APOE4* carriers, but not in non-carriers (Franz et al., 2023). A paper found that associations of $PM_{2.5}$, PM_{10}, and NO_2 with cognitive function were more pronounced in female *APOE4* carriers (Schikowski et al., 2015). Female *APOE4* carriers were also more at risk for air pollution-induced metabolic alterations in hippocampus and cognitive deficits (Calderón-Garcidueñas et al., 2015, 2016b). Another research that used the Women's Health Initiative Memory Study (WHIMS) data found that exposure to a high level of $PM_{2.5}$ preceded onset of cognitive impairment in older women, and this relationship varied by *APOE* genotype, with the largest adverse effect seen in e4/e4 carriers (Cacciottolo et al., 2017). The authors suggested that exposure to PM in the air may accelerate neurodegeneration through various pathways, amyloidogenic, as well as independent of amyloid deposits. A more recent study tested the interaction between *APOE* genotypes and air pollution and found that the long-term exposure to ambient air pollution was associated with a more rapid cognitive decline in *APOE4* carriers (Kulick et al., 2020). Some studies, however, did not find significant interactions between the air pollution and *APOE4*. For example, a case-control study in northern Taiwan found no differences in susceptibility to air pollution-associated dementia between *APOE* genotypes (Wu et al., 2015).

One should note that DNMR, which was used as an explanatory variable in our analysis, is an indicator of aggregated exposure to various road-related pollutants, not only to those found in car exhaust fumes. Some of these pollutants may also be potentially relevant to AD pathology. E.g., the higher intensity traffic was associated with the higher concentration of airborne fungi in urban air environments. Examples include Alternaria and Cladosporium species which may cause infection and inflammation, potentially contributing to neurodegeneration (Alonso et al., 2017; Phuna and

TABLE 3 Regression analysis, females, age 60–75.

Model/term	Estimate	Std. error	*P*-value
Best model for Set1, HV (mm^3) right, female 60–75			
(Intercept)	6,938.4 (mm^3)	90.6	<1.00e-50
Age	−27.1 (mm^3/year)	1.4	<1.00e-50
Best model for Set2, HV (mm^3) right, female 60–75			
(Intercept)	6,945.9 (mm^3)	90.6	<1.00e-50
Age	−27.1 (mm^3/year)	1.4	<1.00e-50
*Age*snp*	−0.5 (mm^3/year)	0.2	5.55e-03
Best model for Set3, HV (mm^3) right, female 60-75			
(Intercept)	6,947.7 (mm^3)	90.6	<1.00e-50
Age	−27.2 (mm^3/year)	1.4	<1.00e-50
*Age*snp*	−0.4 (mm^3/year)	0.2	3.25e-02
*snp*dnmr*	−106.2 (mm^3)	41.5	1.06e-02
Model 13 in Set3 (reference model)			
(Intercept)	6,954.1 (mm^3)	90.7	<1.00e-50
Age	−27.2 (mm^3/year)	1.4	<1.00e-50
snp	−43.3 (mm^3)	22.7	5.69e-02
dnmr	−32.7 (mm^3)	12.2	7.51e-03

Response variable HV = HV (mm^3) right, independent variables: *dnmr* = 1 (DNMR < 50 meters), *dnmr* = 0 (DNMR ≥ 50 m), *snp* = 1 (APOE4 carrier), *snp* = 0 (APOE4 non-carrier), *Age*—age at the time attending assessment center during the first imaging visit between January 1, 2014 and October 31, 2019. All models in the following three sets of basic linear regression models with pairwise interactions were analyzed: Set 1 = HV~*Age*, *dnmr* (8 models), Set 2 = HV~*Age*, *snp* (8 models), and Set 3 = HV~*Age*, *snp*, *dnmr* (64 models). The optimal, with respect to the minimal AIC criterion significant model was determined for each set and shown in this table. Here, significance means that all regression coefficients were significant ($P < 0.05$) in a specific model, non-significance means the opposite. See Supplementary Tables 6–8 for more detailed information about regression analysis.

Madhavan, 2022; Muafa et al., 2024). The role of exposure to airborne fungi in AD pathology deserves separate investigation, especially in the light of our recent findings suggesting that the impact of recurrent fungal infections on AD risk can be larger than that of other types of infections, including bacterial and viral ones (Ukraintseva et al., 2023). Other road-related pollutants, such as noise (The Lancet Regional Health-Europe, 2023), light pollution (Chepesiuk, 2009; Wyse et al., 2011; Aubrecht et al., 2013), and electromagnetic fields (Ahlbom and Feychting, 2003; Kivrak et al., 2017) might also be relevant to health risks. For instance, noise is currently considered a health problem for citizens of the European Union (European Commission, 2023).

We recognize several study limitations. Since only individuals aged 60–75, who have HV measures, were included in the analysis, the sample size in this study was substantially reduced compared to the total UK Biobank sample. Also, different head-size correction (normalization) strategies might yield various volumetric results across studies (Arndt et al., 1991; Mathalon et al., 1993; Goldstein et al., 1999; Seidman et al., 1999; Sanfilipo et al., 2004; Barnes et al., 2010; O'Brien et al., 2011; Voevodskaya et al., 2014). Also, in our study we evaluated regression models using the Akaike information criterion. One should note that there is no universal procedure by which one can determine the "best model". We applied the AIC approach calculating goodness-of-fit and model variability in order to select the most parsimonious regression model (Burnham and Anderson, 2002; Anderson, 2008; Burnham et al., 2011). Another potential limitation could be that the formal statistical association evaluated from regression analysis may not imply actual causality, which should be further studied using causal inference approaches. Finally, the UK Biobank is volunteer-based study, and so it may not represent general population, therefore, results obtained using this sample should not be extrapolated to the entire UK population, or to other populations, and need further confirmation in additional research.

5 Conclusion

In summary, this study found that the interaction between *APOE4* carrier status and chronic exposure to TRAP (approximated by the closeness of a participant's main residence to a major road) is associated with a significant reduction in hippocampal volume (HV) in female participants of the UK Biobank aged 60–75 years. The results for males didn't reach statistical significance. Our findings suggest that traffic-related air pollution and genetic risk factors for AD (specifically *APOE4*) can synergistically promote neurodegeneration. Living farther from major roads could help reduce the risks of neurodegenerative disorders, including AD, in older female *APOE4* carriers.

Data availability statement

This study used de-identified data provided by the UK Biobank (https://www.ukbiobank.ac.uk). This data is not freely available to the public but can be accessed upon approval of a data request by the UK Biobank. Specific policies governing the process to access the UK Biobank data can be found online at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access.

Ethics statement

The studies involving human subjects were approved by the Duke University Health System Institutional Review Board in accordance with the local legislation and institutional requirements. This publication includes only secondary analyses of existing data collected by the UK Biobank and does not include identifiable human data. Written informed consent for the UK Biobank participants was obtained by the UK Biobank (data holder) in accordance with the UK national legislation and the UK Biobank requirements. The latest (at time of calculations) available information on participants' withdrawal in the UK Biobank was taken into account.

Author contributions

VP: Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. SU: Conceptualization,

Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. HD: Data curation, Investigation, Validation, Writing – review & editing. AY: Investigation, Methodology, Writing – review & editing. KA: Investigation, Methodology, Writing – review & editing.

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Conflict of interest

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Supplementary material

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