Editor summary:

Cities and urbanization concentrate benzene, a carcinogen and brain toxin found in petroleum. This study estimated associations between benzene exposure and brain disorders in urban adults in the UK, finding elevated risks of dementia, major depression, and anxiety disorder at even low benzene levels.

Peer Review Information:

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Item	**Present?**	**Filename** Whole original file name including extension.	**A brief, numerical description of file contents.** i.e.: ***Supplementary Figures 1-4, Supplementary Discussion, and Supplementary Tables 1-4.***
Supplementary Information	Yes	Supplementary_information.pdf	Supplementary Figures 1-6, Supplementary Tables 1-23.
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Parent Figure or Table	Filename	Data description
Source Data Fig. 1	SourceData_Fig1.xls	Map data
Source Data Fig. 2	SourceData_Fig2.xls	Statistical Source Data
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Source Data Fig. 4	SourceData_Fig4.xls	Map data; Trend data; Statistical Source Data
Source Data Fig. 5	SourceData_Fig5.xls	Statistical Source Data
Source Data Fig. 6	SourceData_Fig6.xls	Statistical Source Data

Long-Term Exposure to Ambient Benzene and Brain Disorders Among Urban Adults

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ABSTRACT

Ambient benzene is a volatile anthropogenic pollutant and known carcinogen associated with industrialization and urbanization. Benzene is a natural constituent of petroleum, so cities, which concentrate combustion through industrial activity, transit, and heating, generate a great deal. In addition to causing cancer, theory also predicts that benzene may chronically affect the human brain, even at a low level (<5 $\mu g/m^3$). Here, we estimated associations of ambient benzene exposure, before 2010, with brain disorders (261,909 participants) and brain imaging phenotypes (23,911 participants) in urban residents in the UK (enrolled during 2006-2010 and followed up to 2022). Results showed ambient benzene (per 0.30 $\mu g/m^3$) was associated with elevated risks of dementia (hazard ratio, 1.18; 95% CI, 1.09 to 1.28), major depression (1.09; 1.03 to 1.14), and anxiety disorder (1.16; 1.10 to 1.22). Neuroimaging analyses highlighted the associations with brain structures including the thalamus and the superior temporal gyrus. This study provides population-level evidence of ambient benzene's effect on brain disorders in urban population, critical for risk assessments, air-quality and health guidelines, and sustainable-development efforts as the world urbanizes.

INTRODUCTION

Rapid urbanization is synonymous with higher levels of urban air toxics, including ambient benzene mainly emitted from motor vehicle exhaust, gasoline evaporation, industrial production, domestic combustion, and others[1,2]. Although the contribution from road traffic has decreased as the target of most mitigation legislation, it remains a significant source of benzene in the urban environment, especially in hub cities[3,4]. Additionally, the contribution from domestic combustion (including wood burning) gradually elevated in numerous cities of the United Kingdom (UK), driven by the UK renewable energy strategy[5]. Reductions in ambient benzene have leveled off over time after partially achieving the national pollution targets for emission cuts. However, the remaining low-level benzene in the air is still a pressing public concern as no clear safety limit has been established[6]. Ambient benzene, as one of the toxic air pollutants, may amplify urban vulnerability aligned with other environmental stressors in the context of population aging[7], and its emission inventory in cities is strongly influenced by the development and evolution of the urban form. Catalyzing science-based actions for ambient benzene control is hence challenging but necessary on the path to sustainable and healthy cities. Nevertheless, only 53 countries or states have issued ambient air quality standards for benzene by 2019[8]. With urban crowding and sprawl, more countries and regions should weigh ambient benzene restrictions for the public accordingly.

People in urban living are not only faced with the threat of benzene carcinogenicity, but also identified non-cancer risks involving reproductive, cardiorespiratory, neurological systems, and others[9,10]. With population aging and rapid urbanization, brain health conditions, including neurological and

53 psychiatric disorders, are the leading cause of overall disease burden worldwide and can significantly diminish one's health span[11,12]. It will be tricky to
54 accelerate actions to achieve the Sustainable Development Goals (SDGs) without taking into account the billions of people affected by brain disorders
55 worldwide. A better understanding of the reciprocal relationships between cities and mental health would benefit the promotion of mental health and
56 well-being, as well as enhance the co-benefits of sustainable cities and communities[13,14]. The brain health of urban residents has been linked to numerous
57 verified pollutants and might also be related to various unknown risk factors in the atmosphere[15]. The neurotoxicity and reproductive toxicity of benzene,
58 toluene, ethylbenzene, and xylenes (BTEX), as well as other groups of volatile organic compound (VOC) species, have been well-reported in various
59 occupational settings[16,17]. The documented neurological symptoms include headache, dizziness, drowsiness, confusion, tremors, and loss of
60 consciousness[1,10]. It is reasonably suspected that long-term ambient benzene exposure may be associated with specific brain disorders, even at a low
61 level. Cities are at the forefront of not only the impacts of air pollution but also progress and interventions. However, due to the lack of benzene monitoring
62 data in many cities, the neuropsychiatric effects of ambient benzene on urban residents have not been fully elucidated but are well worth exploring and
63 assessing.

64 To bridge the knowledge gap mentioned above, this study aimed to analyze the linkages of long-term ambient low-level benzene exposure with
65 brain disorders, leveraging the multimodal data of urban residents from the UK biobank. Based on participants with available neuroimaging data, we
66 further identified the potential effects of ambient benzene exposure on brain structures including volumes of cortex and subcortex. In addition, we also

developed structural equation models (SEM) to quantify the potential mechanisms between ambient benzene and brain health driven by peripheral inflammation and glycolipid metabolites. Credible findings in neuropsychiatric effects of ambient benzene might contribute to the update of air quality guidelines in numerous countries and regions. Effective interventions on ambient benzene in the urban context could be beneficial for city health planning and urban sustainable development.

RESULTS

Baseline characteristics of the included urban residents

A total of 261,909 urban residents were included in the primary analysis, after excluding 240,460 participants without data of exposure assessment and potential covariates, those residing in rural areas and prevalent cases of brain disorders at baseline (including dementia, Parkinson's disease (PD), epilepsy, migraine, major depression disorder (MDD) and anxiety disorder) **(Fig. 1**). The data on the incidence of brain disorders was derived via linked electronic health records during the median follow-up of 13.8 years. The follow-up time was computed from the date of attending the baseline assessment center to the earliest date of any brain disorder diagnosis, death, the last available date from either primary care data (UKB field 42040) or hospital inpatient data (UKB field 41280–41281), or December 19, 2022, whichever came first. The brain magnetic resonance imaging (MRI) data, available in 23,911 individuals, were acquired from the UK biobank after 2014. Detailed descriptions of six common brain disorders, brain imaging phenotypes, baseline and lifestyle factors, and other potential covariates are shown in **Supplementary Table 1-9**. The mean age (standard derivation, SD) of included

participants was 56.5 (8.1) years old and 50.5% were females. Statistical characteristics of the analytic sample summarized across three levels of ambient benzene concentrations (low: <0.62 μg/m^3, moderate: 0.62-0.81 μg/m^3, high: >0.81 μg/m^3) are provided in **Supplementary Table 10**. Before December 2022, a total of 3,682 (1.41%) participants were diagnosed with dementia, 1,390 (0.53%) with PD, 1,513 (0.58%) with epilepsy, 1,888 (0.72%) with migraine, 8,463 (3.23%) with MDD and 8,258 (3.15%) with anxiety disorder. The exposure assessment and distributions of benzene and other environmental pollutants are illustrated in **Supplementary Fig. 1-Fig. 3**. The mean (SD) estimate of annual average concentrations for benzene was 0.72 (0.22) μg/m^3. New events, total person year, and incidence rates of brain disorders by sex are displayed in **Supplementary Table 11**.

Ambient benzene and brain disorders

Significant associations were observed between ambient benzene exposure and the risks of brain disorders through Cox proportional hazard models. The hazard ratios (HRs) with 95% confidence intervals (95% CIs) are demonstrated in **Fig. 2**. Several positive associations stood out in particular. First, for participants without any brain disorders at baseline, we observed that per interquartile range (IQR, 0.3 μg/m^3) increase in ambient benzene was significantly related to elevated risks of dementia (HR, 1.18; 95% CI, 1.09 to 1.28), MDD (HR, 1.09; 95% CI, 1.03 to 1.14) and anxiety disorder (HR, 1.16; 95% CI, 1.10 to 1.22) in the model with adjustments for age, sex, index of multiple deprivation (IMD), other environmental risk factors (exposure to ambient fine particulate matter ($PM_{2.5}$), proximity to roadways, high noise exposure), occupational exposure to benzene (measured by the high-risk occupations of benzene exposure), waist-hip rate (WHR), healthy lifestyle (no current smoking, no heavy alcohol intake, healthy sleep pattern, regular

physical activity, and healthy diet), and comorbidities measured by Charlson Comorbidity index (CCI). Compared with participants with low benzene exposure (<0.62 μg/m^3), those with high benzene exposure (>0.81 μg/m^3) had significant HRs of 1.35 (95% CI, 1.20 to 1.51) for dementia, 1.19 (95% CI, 1.01 to 1.39) for migraine, 1.21 (95% CI, 1.12 to 1.30) for MDD, and 1.32 (95% CI, 1.22 to 1.42) for anxiety disorder (**Fig. 2**). Second, for urban residents in the aged society (cities with the share of people aged 65 years or more ⩾14% of the total population), higher incidence risks of dementia (HR, 1.32; 95% CI, 1.17 to 1.48), MDD (HR, 1.19; 95% CI, 1.09 to 1.28), and anxiety disorder (HR, 1.31; 95% CI, 1.21 to 1.42) were also estimated with per IQR increment in ambient benzene with the same adjustments above, compared with those in the aging society (cities with the share of people aged 65 years or more between 7% and 14% of the total population). Third, for dementia subtypes (including Alzheimer's disease (AD), vascular dementia, and frontotemporal dementia), we observed that the incident risk of AD increased by 32% (HR, 1.32; 95% CI, 1.16 to 1.49) with per IQR increment in ambient benzene (**Supplementary Table 12**). Fourth, for subgroup analyses, a stronger association of benzene exposure with MDD was observed for participants with higher low-grade inflammation (calculated by the aggregated inflammation score, INFLA-score) than the counterpart (*P* for interaction =0.021) **(Fig. 3**). Results demonstrated no significant difference in stratification analyses by age, sex, WHR, and metabolic syndrome (MetS) as well as healthy lifestyle, including no heavy alcohol intake, regular physical activity and healthy sleep pattern (**Supplementary Table 13-15, Fig. 3 and Supplementary Fig. 4**). The monotonic increase was distinctly observed in long-term benzene exposure with incidence risks of dementia, migraine, and psychiatric disorders (**Fig. 4**). Our results remained robust in all sensitivity analyses (**Supplementary Table 16**).

Ambient benzene and brain imaging phenotypes

Next, we estimated associations between ambient benzene exposure and brain structure phenotypes including 33 cortical regions and 7 subcortical structures. The descriptive statistics of brain imaging phenotypes are shown in **Supplementary Table 17**. In general, with per 0.3 μg/m^3 increase in ambient benzene, there were 26 out of 33 associations with volumes of cortical regions and 5 out of 7 associations with volumes of subcortical structures remained significant after false discovery rate (FDR) correction (**Fig. 5**). Specifically, ambient benzene exposure was inversely related to the volumes of certain cortical regions, particular the frontal lobe, including the precentral gyrus (β, -0.086; 95% CI, -0.113 to -0.059), paracentral lobule (β, -0.084; 95% CI, -0.113 to -0.056), rostral anterior cingulate cortex (β, -0.076; 95% CI, -0.105 to -0.048), the temporal lobe, including the middle temporal gyrus (β, -0.092; 95% CI, -0.118 to -0.066), superior temporal gyrus (β, -0.086; 95% CI, -0.112 to -0.059), inferior temporal gyrus (β, -0.059, 95% CI, -0.086 to -0.033), and the parietal lobe, including the inferior parietal lobule (β, -0.102; 95% CI, -0.129 to -0.075), postcentral gyrus (β, -0.081; 95% CI, -0.109 to -0.053), and supramarginal gyrus (β, -0.072; 95% CI, -0.099 to -0.045) (**Supplementary Table 18**). For the subcortical volumes, ambient benzene exposure was associated with the shrinkage of dementia-related brain structures including the amygdala (β, -0.054; 95% CI, -0.083 to -0.025), thalamus (β, -0.045; 95% CI, -0.070 to -0.019), caudate nucleus (β, -0.040; 95% CI, -0.069 to -0.012), and others (**Supplementary Table 18**). There was no significant difference between subgroups stratified by age and sex (**Supplementary Table 19-20**). Results of logistic regressions showed potential associations of dementia, MDD, and anxiety disorder with the thalamus, superior temporal gyrus, lateral orbitofrontal cortex, and others (**Fig.6 and**

Supplementary Table 21-Table 23).

Benzene–inflammation–metabolism-brain health pathway

Furthermore, we investigated potential mechanisms of peripheral inflammation and glycolipid metabolites on associations between ambient benzene exposure and brain health. First, confirmatory factor analysis (CFA) was performed to estimate the latent variables in SEM (**Fig. 6**). The counts of neutrophils, monocytes, C-reactive protein (CRP), and lymphocytes were the significant markers for predicting the inflammation latent variable (β =0.550, 0.437, 0.323, and 0.267, respectively; P <0.001). Apolipoprotein A (ApoA), low-density lipoprotein (LDL), and glycated hemoglobin (HbA1c) were the main components of the metabolite latent variable (β =0.703, 0.087, and -0.082, respectively; P <0.001). For the latent variable of brain structure, superior frontal gyrus ranked as the largest effect size, followed by rostral middle frontal gyrus, lateral orbitofrontal cortex, superior temporal gyrus, paracentral lobule, rostral anterior cingulate cortex, thalamus, and amygdala (β =0.831, 0.785, 0.769, 0.752, 0.673, 0.639, 0.628, and 0.306, respectively; P <0.001). The latent variable of brain disorders was constructed by the onset status of MDD, anxiety disorder, and dementia (β =0.082, 0.064, and 0.004 respectively; P <0.001). We further input the prepared latent variables into SEM to estimate the path coefficients for dementia, MDD, and anxiety disorder separately and the model performance was verified by the comparative fit index (CFI). Next, SEM was conducted to evaluate all hypothetical paths (**Fig. 6**). Exposure-inflammation-disease pathways were significant for MDD and anxiety disorder (P <0.05), demonstrating that inflammatory markers mediated the associations of benzene exposure with mental illness.

DISCUSSION

This study benefited from a diverse sociodemographic sample of UK urban residents and revealed the longitudinal relationship between ambient benzene exposure and brain health. To our knowledge, this was the first comprehensive study assessing the relationship above. Results suggested that ambient low-level benzene exposure was a non-negligible contributor to dementia, MDD, and anxiety disorder in urban areas. Likewise, we also found possible effects of ambient benzene on specific brain imaging phenotypes, especially the paracentral lobule, superior temporal gyrus, thalamus, and others. Results from SEM revealed the coherent mediating pathways concerning inflammatory indicators, glycolipid metabolites, and brain structures, supporting the existing hypothesis of multifactorial pathogenesis from ambient benzene exposure to several brain disorders, even at a low level.

Benzene pollution in the urban context

Urban sources from vehicle exhaustion, gasoline evaporation, industrial production, domestic combustion, and others, dominate the emission of ambient benzene in the UK[6]. Other anthropogenic sources intertwined with urban living, such as waste incineration, aircraft, and commercial combustion, also contribute to ambient benzene[6]. The emission sources in the urban context are illustrated in **Supplementary Fig. 5**. The monitoring network to measure benzene in the UK complied with the Air Quality Directive 2008/50/EC, which contained 34 urban traffic, urban background, or urban industrial monitoring stations[18]. As achieving the targets of most mitigation legislation, the contribution from road traffic, a historically most significant contributor

to benzene pollution in the urban environment, has decreased. However, the highest benzene concentration level observed during 2020 has still been seen at roadside and industrial locations. In addition, although the traffic-related benzene emission is decreasing, the monitoring data has stabilized probably because of additional urban sources of benzene, such as the use of wood-burning appliances for domestic and commercial space and water heating. Besides, benzene has been listed as one of the urban air toxics by the United States Environmental Protection Agency due to posing a significant threat to public health in the largest number of urban areas, even at a low level[19]. Investing in green policy, clean air, and sector-based standards for ambient benzene oriented by the source appointments in the urban context is essential for city health planning.

Effects of benzene exposure on brain disorders

Previous studies have found substantial and highly robust healthy effect sizes of low-level ambient benzene. In research focusing on long-term exposure to it, the adjusted HR and 95% CI of mortality risk for all-cause diseases was 1.26 (1.24 to 1.27) with per 0.22 μg/m^3 increase in benzene concentrations[20]. Yansu He et al reported in a study that the effect of benzene on cardiovascular disease remained significant (HR, 1.24; 95% CI, 1.11 to 1.39)[21]. Results from a prospective cohort study demonstrated that a 0.166 μg/m^3 increase in benzene was associated with a 6.9% increased risk of incident type 2 diabetes[22]. Additionally, it was widely documented that chronic inhalation exposure to benzene was associated with neurological symptoms and brain disorders based on animal experiments and studies regarding occupational exposure[23,24]. Our study, revealing the associations with specific brain disorders in a large prospective cohort of urban residents, might trigger renewed attention to latent health hazards of outdoor benzene and promote urban

sustainable strategies to control benzene emission. Results in the study showed that long-term exposure to ambient low-level benzene was significantly associated with the incidence of dementia, particularly AD. A possible explanation was that inhalation of benzene might cross the blood-brain barrier enabled by its high lipophilic nature, interfere with the production and release of acetylcholine by inhibiting acetylcholine esterase, activate the N-methyl-D-aspartic acid receptor abnormally in specific brain regions, and finally induce neurobehavioral disturbances[25,26]. For psychiatric disorders, a cross-sectional study showed that exposure to ambient VOCs was associated with an increased prevalence of depression in US adults[27]. Our findings demonstrated that ambient benzene, the main contributor of VOCs, might elevate the incidence risks of MDD and anxiety disorders in an approximately linear manner. Oxidative stress, cholinergic system, and dopaminergic system disturbed by benzene exposure might play a role in or mediate the driving pathway to psychiatric disorders[28]. Noteworthily, participants with high INFLA-score had a higher risk of MDD after long-term ambient benzene exposure. The latent interaction effects between chronic inflammation and environmental exposures would weaken the effectiveness or confound the assessment of environmental interventions. Distinct neurobiological pathways might mediate the psychiatric influence derived from alternative environmental profiles of urban living, including social deprivation, urban land-use density, street network, and air pollution[29,30]. Relevant studies are highly in demand to deeply dissect the internal relationship. However, based on our results, healthy lifestyles including no heavy alcohol intake, regular physical activity, and healthy sleep patterns might have a limited role in mitigating the neurological effects of ambient benzene exposure. The demographic shift owing to population aging is expected to further exacerbate the burden of neurological disorders that are more common in the elderly. In parallel, it is also exacerbating the negative health effects of air pollution. The urban residents in aged society tended to be more susceptible to the

neuropsychiatric effects of ambient benzene exposure in this study, which addressed the necessity of placing brain health and elderly health at the core of urban environment planning.

Mechanisms linking ambient benzene to brain health effects

We further analyzed the relationships between benzene exposure and specific brain imaging phenotypes. Chronic occupational benzene exposure could result in more extensive injuries to parts of brain regions, including the frontal and temporal lobes[31], which was consistent with our results. Besides these brain regions, we also found inverse associations with the volumes of the imperial parietal lobule, insula, and others. For subcortical regions, results showed that benzene exposure was negatively related to shrunken volumes of the amygdala and thalamus. Notably, we found that the thalamus was associated with the incidence and progression of dementia, MDD, and anxiety disorder. A study suggested that thalamic nuclei might be related to cognition and specific cortical-subcortical regions[32]. Another study indicated that the abnormal connectivity of right thalamic nuclei with cortical regions, related to higher-order cognitive processing, could affect repetitive negative thinking in MDD[33]. Our results of SEM also illustrated the involvement of brain structures, peripheral inflammation, and glycolipid metabolites in associations of long-term ambient benzene exposure with brain disorders, including MDD. Several hypotheses could support the exposure-inflammation-MDD pathway. Benzene could increase pro-inflammatory cytokines and alter immune status by inducing gut microbiota dysbiosis, which corresponds to the role of the microbiota-gut-brain axis in the pathophysiology of MDD[34,35]. Apart from benzene itself, highly reactive benzene metabolites such as hydroquinone and benzoquinones could activate reactive oxygen

194 species (ROS) and cause oxidative stress, which could further trigger inflammatory mechanisms[36]. Increased inflammatory signaling induced by benzene
195 could dysregulate neurotransmitter metabolism, impair neuronal health, and alter neural activity in mood-related brain regions[37]. In addition, although
196 the benzene biotransformation products were not included, it could not be ignored that these products might play important roles in the neurological
197 effects of benzene. During the metabolism and oxidation of benzene, ROS could be produced through the redox cleavage of reactive products, especially
198 hydroquinone and benzoquinone[36]. Excess ROS can cause oxidative stress and damage biomolecules such as lipids, proteins, and genetic material, and
199 then directly or indirectly result in chronic neuropsychiatric effects[38], as shown in **Supplementary Fig. 6**. Further animal experiments were needed to
200 explore the underlying mechanisms by which benzene affects neuropsychiatric disorders.

201 **Potential implications and public health significance**

202 These novel findings bear several potential implications for policy and future research. Understanding the systematic effects of ambient low-level benzene
203 exposure on brain health could facilitate the formulation or update of air quality guidelines in numerous countries and regions, and the implementation
204 of more comprehensive clean air legislation worldwide. Targeted policies supporting healthy transportation, clean energy, and stricter emission standards
205 for benzene-containing products are essential to ambient benzene control in the process of urban sustainable development[1]. The health of its citizens is a
206 city's most important asset. Urban life shapes the brain health of dwellers, and urban environments can promote health or contribute to health risks[14,39].
207 To confront the growing challenges of neurodegenerative diseases in an aging population and mental illness in rapid urbanization, catalyzing

improvements in brain-healthy cities is a promising solution[40]. Policymakers, hence, should pay more attention to the long-term neuropsychiatric effects of both criteria and toxic air pollutants, which would contribute to the resistance, resilience, and stability of urban health as well as public health. Synchronous promotion or systemic coupling of both better urban planning and proactive health may also be worthy of consideration for the development of sustainability.

Strength and limitations

The sample of large size with long-term follow-up provided a substantial number of cases for our study to estimate the association between ambient benzene exposure and brain health in the urban environment. Likewise, the neuroimaging analyses enhanced the understanding of its neurological effects. However, several limitations still need to be acknowledged. First, the ambient benzene concentration data in this study was estimated with a resolution of 1 km×1 km which might not fully apprehend individual-level exposure. Non-differential misclassification was inevitable and might underestimate our results toward the null. Second, in the analyses exploring the relevant mechanism, the pathways were mainly based on peripheral inflammation and glycolipid metabolism, which was not exhaustive due to missing data on indicators related to neurological inflammation and benzene metabolism. Third, due to data inaccessibility, we failed to further estimate the neuropsychiatric effects of toluene, ethylbenzene, and xylenes (TEX) which might co-exist with benzene from vehicle exhaustion, gasoline evaporation, solvent evaporation, and others, and were also related to various human diseases[16,41]. Ambient benzene might be an optimal proxy for BTEX when analyzing the long-term effect since it has a longer half-life time than other benzene series

and is the main component of aged VOCs[42,43]. However, endeavors to estimate the human effects of TEX are still valuable for systematically assessing the overall risk of atmospheric benzene series. Fourth, although occupational exposure to benzene was controlled in the model, there might still be residual confounding from indoor environmental factors, especially environmental tobacco smoke and evaporation of household fuels. Studies are in great demand to further assess the potential influences of indoor benzene exposure on the health effects of outdoor exposure. Fifth, a slight difference in the proportion of no heavy alcohol intake was observed between excluded and included participants (**Supplementary Table 10)**, which might cause mild selection bias. Alcohol metabolism could produce harmful compounds, in particular enzyme cytochrome P450 2E1 (CYP2E1), which might play an important role in the conversion of benzene to benzoquinone. This suggested a possible interaction between drinking and benzene on human health[44]. Hence, the effects of interaction on the risks of brain disorders were further estimated in this study, and the results were not statistically significant. Sixth, the underestimation in observed effect sizes would also be likely since the brain disorders could be risk factors for each other, and participants with brain disorders at baseline were excluded before analysis. Specifically, a bidirectional relationship was evidenced between epilepsy and depression. It has been reported that depression can directly increase the seizure frequency of epilepsy, while it also worsens with antiepileptic medication[45]. Therefore, excluding patients with brain disorders at baseline might reduce the number of new cases, and further lead to an underestimation of the effect estimates. Finally, this study was conducted within a database from the UK, and participants were more likely to be healthier residents of white ancestry, which may bias the representativeness and restrict the generalizability of our findings. Further studies across different countries are encouraged to validate the results.

CONCLUSION

In conclusion, long-term ambient benzene exposure was associated with elevated incidence risks of dementia and psychiatric disorders including MDD and anxiety disorder. These relationships were complemented by alterations in several cortical and subcortical structures that related to specific brain disorders. This study further demonstrated the involvement of peripheral inflammation and glycolipid metabolites in the associations above. The findings about neuropsychiatric effects of ambient benzene, with a low-level but long-term exposure, would arouse a spreading public concern towards the urban air toxic, and also increase a weight for the formulation of quality guidelines for ambient benzene globally and the clean energy for sustainable and healthy cities.

MATERIALS AND METHODS

Study population

This study used data from the UK Biobank, a large-scale ongoing prospective cohort including more than half a million participants across the UK recruited in 2006–2010 with a response rate of 5.47% in recruitment (https://www.ukbiobank.ac.uk/). Participants (aged 37-73 years) were asked to

provide information on their demographic, lifestyle, physical, and health conditions at baseline or during the follow-up, with their biological samples and imaging information collected. UK Biobank has received ethical approval from the North West Multicenter Research Ethics Committee (reference 16/NW/0274), and informed consent was provided by all participants through electronic signature. This study utilized the UK Biobank Resource under application number 99001. After excluding participants residing in rural areas, those without data of exposure assessment and potential covariates, and those with prevalent brain disorders at baseline, a total of 261,909 urban residents were included in the study, where 23,911 participants were further included for association analysis of brain imaging (**Fig. 1**). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Assessment of exposure

The annual mean benzene concentrations from 2003 to 2010 were derived from the UK-wide air pollution maps modeled on a 1 km×1 km grid square provided by the UK's Department for Environment, Food and Rural Affairs (DEFRA). The maps were developed by the pollution climate mapping (PCM) model (a collection of models designed to fulfill part of the UK's EU Directive (2008/50/EC) requirements) based on data from the National Atmospheric Emission Inventory (NAEI), measurements, road traffic counts, and others. The measurements used for benzene exposure assessment were derived from the automatic (6 monitoring stations) and non-automatic (34 monitoring stations situated in urban locations) hydrocarbon network sites in the UK[18]. The air sampling method conformed to the European Standard (EN14662:2005). Specifically, the ambient benzene monitoring method for the

non-automatic hydrocarbon network involved drawing ambient air alternately through two tubes containing a carbon-based sorbent (Carbopack X). Each tube sampled air at a controlled rate (nominally 10 mL/min) for 8 minutes for a nominal two-week period. The tubes were then sent to the laboratory for subsequent analysis of benzene by gas chromatography-mass spectrometry. The Limit of Detection (LOD) for the benzene on a desorption tube from the non-automatic hydrocarbon network was about 0.05 $\mu g/m^3$ from a 14-day sampling period. Meanwhile, the automatic hydrocarbon network monitored hourly ambient benzene using automatic Perkin Elmer ozone precursor analyzers with advanced automatic gas chromatography. Following a 40-minute sampling at a flow rate of 15 mL/min, components were desorbed from the cold trap and were transferred to the capillary column where they were separated using gas-chromatography and subsequently detected by a flame ionizing detector, which achieved the LOD of 0.03 $\mu g/m^3$ for benzene[46]. Furthermore, for benzene modeling, contributions were estimated at both background sites and roadside sites, where background sites included area sources, point sources, and regional rural sources[47]. The area source benzene emission (excluding combustion in the industry) maps were calculated from the NAEI emissions maps by applying a dispersion kernel. The modeled benzene concentrations from area sources were calibrated using monitoring data from one site within the national automatic hydrocarbon network (London Eltham) and 17 non-automatic hydrocarbon sites in the UK. The calibration coefficient was derived by linear regression of a corrected measured annual mean background benzene concentration versus the modeled uncalibrated area source contribution. The calibrated area source contribution for each grid square in the country was then calculated by multiplying the modeled area source contribution (excluding combustion in the industry) with the calibration coefficient. The point benzene sources were modeled using the air dispersion model and the regional rural benzene concentrations were estimated based on the concentrations of other gaseous pollutants. Subsequently,

the contributions of combustion in industry, point source, and regional rural concentration were added to the calibrated area source contribution, resulting in a map of the total background annual mean benzene concentrations. In addition, contributions from road traffic sources were added to locations at roadside sites. Comparisons of modeled and measured annual benzene concentrations for background and roadside sites were conducted to ensure the reliability of models. For background sites, the mean of measurement and model estimates were 0.47 μg/m^3 and 0.45 μg/m^3; for roadside sites, the mean of measurement and model estimates were 0.61 μg/m^3 and 0.55 μg/m^3, which showed great agreement between the monitoring data and modeled values. The annual average benzene concentrations before baseline were assigned to each participant based on the 1 km×1 km grid square in which their address was located. Furthermore, the benzene concentration estimates were scaled to IQR (0.30 μg/m^3) and categorized into three monotonically increasing exposure levels (low: <0.62 μg/m^3, moderate: 0.62-0.81 μg/m^3, high: >0.81 μg/m^3) based on the quartile. The flowchart of the PCM model for benzene is shown in **Supplementary Fig. 1**.

Ascertainment of outcomes

The primary outcomes covered a range of incident brain disorders, including neurological diseases (dementia, PD, epilepsy, and migraine) and psychiatric disorders (MDD and anxiety disorder). The health-related outcome dataset's summary diagnoses of health outcomes (category 2002) and self-reported medical conditions (category 20002) of the UK Biobank were utilized to extract the selected outcomes above. The neurological and psychiatric diseases were ascertained and classified based on the International Classification of Diseases (ICD-9 and ICD-10) system codes. The definition of each brain

disorder on ICD-10 codes were as follows: dementia (F00, F01, F02, F03, F05.1, F10.6, G30, G31, and I67.3), PD (G20), epilepsy (G40, G41), migraine (G43), MDD (F32, F33), and anxiety disorder (F40, F41). Information in detail for the definition of brain disorders in the UK Biobank is presented in **Supplementary Table 1**. Besides all-cause dementia, we further considered specific dementia subtypes including AD (ICD-10 codes: F00, G30), vascular dementia (ICD-10 codes: F01, I67.3), and frontotemporal dementia (ICD-10 codes: F02.0, G31.0).

The secondary outcome included multiple brain imaging phenotypes, with the brain MRI data acquired after 2014. Among 502,369 original UK biobank participants, 63,696 individuals underwent brain MRI (with each individual scanned once) at dedicated assessment centers fitted with the standard Siemens Skyra 3T scanner with a 32-channel receiver head coil. The image acquisition protocols were freely provided and sequence parameters have been published previously[48]. All brain MRI data were available as image-derived phenotypes (IDPs) in the UK Biobank. The T1-weighted imaging data, which derived from a structural technique with a high-resolution depiction of brain anatomy, were processed through an image processing pipeline with tools called FSL and FreeSurfer. The cortical surface was modeled using FreeSurfer and the IDPs relating to standard atlas regions' volumes were extracted via surface atlases. The volumes of subcortical structures modeled using FIRST were also generated as IDPs in the UK Biobank. FreeSurfer desikan white (category 192) and subcortical volumes (FIRST) (category 1102) were used to extract the volumes of brain cortical and subcortical regions in this study. All continuous indices of brain structures were standardized using Z-transformation for interpretation and comparison. Among included

261,909 participants, brain imaging information was available in 23,911 individuals. Detailed information for brain phenotype used in this study is presented in **Supplementary Table 2**.

Covariates

Values for all covariates were collected at baseline including demographics, lifestyle factors, socioeconomic status, and anthropometric measurements. Based on the previous evidence, we considered age, sex, IMD, WHR, healthy lifestyle, occupational exposure to benzene, CCI, and other traffic-related factors ($PM_{2.5}$, proximity to roadways, noise pollution) as potential confounders. Specifically, healthy lifestyle factors consisted of no current smoking, no heavy alcohol intake, healthy sleep pattern, regular physical activity, and healthy diet[49]. No heavy alcohol intake was defined as the average daily intake $\leqslant$16 g of pure alcohol (2 units of alcohol) for both men and women[50]. The components and assembling procedures of no heavy alcohol intake healthy sleep pattern, regular physical activity, and healthy diet can be found in **Supplementary Table 3**. **Supplementary Table 4** displays the identified high-risk occupations for benzene exposure[51-53]. Occupations such as printing trades personnel, vehicle spray painters, painters and decorators, leather and related trades personnel, and rubber process operatives were not classified as high-risk occupations because the use of benzene in relevant industries has been gradually reduced or replaced by non-benzene containing substitutes since the 1950s[51]. Of note, CCI scores were incorporated to account for major comorbidities. The CCI covers a range of concurrent comorbidities divided into 17 categories, each condition is assigned a score of 1, 2, 3, or 6,

depending on the risk of dying associated with each one[54]. Patients who are 50 years old or older get additional points. Detailed calculation for CCI is shown in **Supplementary Table 5**.

The high-resolution data on annual average concentrations of $PM_{2.5}$ and NO_x at baseline were derived from UK-wide air pollution maps developed by the PCM model. The modeled estimates for $PM_{2.5}$ and NO_x were calibrated using automatic monitoring data from the national network. Additionally, at locations close to urban roads, an additional roadside contribution was added to account for contributions from road traffic sources. Based on the high-resolution air pollution data described above, the annual average concentration was linked to each participant according to the geocoded home address and the corresponding grid cell for further analysis. Proximity to roadways was measured by the inverse distance, which was derived based on a local road network with traffic intensity greater than 5000 motor vehicles per 24 hours. Noise pollution was classified as low and high exposure according to the L_{den} (weighted average noise sound level for 24 hours, with a penalty of 5 dB for evening hours and 10 dB for night hours) of 65 dB. Information in detail is demonstrated in **Supplementary Table 6.**

We conducted subgroup analyses by population aging level, INFLA-score, and MetS as well. According to the World Health Organization and the United Nations, cities with an aged society were defined as cities where more than 14% of residents are over the age of 65, while cities with an aging society were defined as those with a share of people aged 65 years or more between 7% and 14% of the total population. The INFLA-score, which contains CRP, total white blood cell count, platelet count, and the neutrophil-to-lymphocyte ratio (NLR), was recognized as a systematic marker of low-grade inflammation. A higher score suggests a greater degree of low-grade inflammation. The MetS was defined as the presence of three or more of the

following quantitative criteria: unhealthy waist circumference, high blood pressure, abnormal blood lipids, hypertriglyceridemia, and hyperglycemia. Information on population aging level, INFLA-score, and MetS are presented in **Supplementary Table 7 and Table 8**.

Inflammation markers and metabolites

Peripheral inflammatory markers were collected from blood count data (category 100081) and blood biochemistry data (category 17518). The baseline count data consisted of neutrophils, monocytes, platelets, lymphocytes, and the concentration data of CRP. Based on the blood cell counts above, we further calculated four ratios including NLR, platelet-to-lymphocyte ratio (platelets/lymphocyte, PLR), systemic immune inflammation index (neutrophil × platelets/lymph, SII), and lymphocyte-to-monocyte ratio (lymph/mono, LMR).

Glycolipid metabolites were extracted from blood biochemistry data (category 17518). In this study, a total of 9 indicators were selected, including glucose, HbA1c, and lipids traits that related to cardiometabolic diseases. The lipids traits mentioned above consisted of ApoA, apolipoprotein B (ApoB), high-density lipoprotein (HDL), LDL, total cholesterol, lipoprotein (a), and triglyceride. Another three ratios including HDL/ApoA, LDL/ApoB, and ApoB/ApoA ratios were then derived based on the lipid traits above. More detailed information on inflammatory markers and metabolites was exhibited in **Supplementary Table 9**.

Statistical analysis

Statistical characteristics of participants were exhibited with percentages for categorical variables as well as mean and SD for normally distributed continuous variables. Cox proportional hazard regression models, with follow-up time as the underlying time metric, were utilized to examine the longitudinal association of ambient benzene exposure with risks of brain disorders. The missing data were deleted in the analyses, and the proportional hazard assumption was confirmed for all Cox proportional hazard regression models using the Scaled Schoenfeld Residual. Three strategies of model adjustment were adopted for restricting potential confounding: i) the basic model without adjustment (model 1); ii) adjusted for age, sex, IMD and other environmental risk factors including ambient exposure to $PM_{2.5}$, proximity to roadways, high noise exposure (model 2); and iii) additionally adjusted for occupational exposure to benzene, WHR, healthy lifestyle factors (no current smoking, no heavy alcohol intake, healthy sleep pattern, regular physical activity, and healthy diet) and CCI (model 3). Furthermore, we performed the analyses stratified by age (<65 and ≥65), sex (male and female), WHR (poor and ideal), healthy lifestyle including no heavy alcohol intake (yes and no), regular physical activity (yes and no) and healthy sleep pattern (yes and no), population aging level (cities with aging society and aged society), INFLA-score (low and high) as well as MetS (yes and no) separately to assess the vulnerable population. Effect values were presented by HRs with corresponding 95% CIs for moderate and high exposure concentrations (low as the reference) as well as HRs per IQR increment. *P* values for trend (*P* for trend) were calculated by treating categorical exposure variables as ordinal in Cox regression models. Exposure-response curves for associations of benzene exposure with primary outcomes were assessed by nature cubic spline regression models controlling for all potential covariates that were adjusted in model 3, with three knots placed at fixed quantile (i.e., the 1st, 50th, and 99th percentiles).

Multiple linear regression models were used to estimate associations between ambient benzene exposure and brain structure phenotypes, including volumes of cortical and subcortical regions, with the full adjustment in model 3. Before modeling, each phenotype was standardized to maintain the same scale. Stratification analyses by age and sex were further conducted. Effect values were shown with the βs and corresponding 95% CIs, and we compensated for multiple comparisons for all *P* values using FDR control. Logistic regression models were utilized to investigate associations of brain imaging phenotypes with incident brain diseases.

The SEM was performed to determine the directional dependencies of benzene exposure with brain health including brain disorders and related imaging phenotypes, which were mediated by peripheral inflammation and glucolipid metabolism paths. Before modeling, four latent variables of brain disorders, brain structures, inflammatory markers, and metabolites were estimated using the CFA. The latent variable of brain disorders was constructed by the onset status of dementia, MDD, and anxiety disorders, which were significantly associated with ambient benzene exposure. The latent variables of peripheral inflammation and glucolipid metabolites were measured in the model using those significantly correlated with ambient benzene. Finally, the latent variable for brain structures was derived from the 8 cortical and subcortical volumes significantly related to ambient benzene and the incidence of dementia or psychiatric disorders. The estimates of benzene, inflammatory markers, and metabolites were scaled before inputting into SEM to estimate the path coefficients. Additionally, the SEM was also performed to determine the directional dependencies of benzene exposure with dementia, MDD, and anxiety disorder separately in the same manner.

Several sensitivity analyses were conducted to test the robustness of the results. First, since non-White participants only constitute ~3% of this dataset, we restricted the study to individuals with racial/ethnic backgrounds of white. Second, to alleviate the influence of the extreme values, benzene concentration estimates were trimmed on extreme values (1% below and 99% above), respectively. Third, we excluded participants who experienced any target event within the first 2 years of follow-up. Fifth, considering the COVID-19 outbreak, we further conducted the analysis after advancing the follow-up deadline to December 31, 2019[55]. Finally, we adjusted NO_x additionally due to the potential confounding of this environmental risk factor. Two-tailed *P* value <0.05 were considered statistically significant and an FDR correction was applied when appropriate. R software version 4.2.2 was used for all analyses.

Data availability: The data used in the present study are available from the UK Biobank with restrictions applied. Access to the UK Biobank data can be requested through a standard protocol (https://www.ukbiobank.ac.uk/register-apply/). This research has been conducted using the UK Biobank Resource under Application Number 99001. The data on ambient benzene exposure concentration used in this study were provided by the UK's Department for Environment, Food and Rural Affairs (DEFRA), which can be obtained at https://uk-air.defra.gov.uk/data/pcmdata.

Code availability: The main codes are available on GitHub at: https://github.com/Rlab2020/BZandBH.git. Other codes in detail for statistical analysis are available upon request from Dr. Jinjun Ran.

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Author contributions: J.R. and L.H. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. J.R. and L.H. conceived and designed the project. Y-X.L., Y.B., and J.R. acquired, analyzed, or interpreted data. Y.B., Y-X.L., and N.Q. generated all the figures. Y-X.L., Y.B., N.Q., and M.Z. wrote the initial draft of the manuscript. Z.H., Y-Y.L., Y.Z., J.Z., X.D., C.S., L.H., and J.R. contributed to subsequent versions of the manuscript. J.R., L.H., C.S., and X.D. provided administrative, technical, or material support. All authors critically reviewed the paper, all authors have a clear understanding of the content, results, and conclusions of the study, and agree to submit this

manuscript for publication.

Competing interests: The authors declare no competing interests.

FIGURE LEGENDS

Fig. 1 Study workflow. Top left: the distribution of ambient benzene in the UK, participant flowchart, and the UK Biobank variables in the analysis. Bottom left: emission sources of benzene in the urban context. The illustration was designed by Freepik (www.freepik.com). Top right: the main and subgroup associations between benzene exposure and brain disorders. Bottom right: relationships of benzene exposure with brain structures and framework of structural equation model (SEM).

Fig. 2 Associations between ambient benzene exposure and incidence risks of brain disorders among all included urban residents, residents in the aging society/aged society. a, A total of 261,909 participants were utilized to assess the relationship of benzene exposure with specific brain disorders by the Cox proportional hazards regression model, with no adjustment in model 1, adjustment for age, sex, IMD, and other environmental risk factors in model 2 and additional adjustment for occupational exposure to benzene, WHR, healthy lifestyle, and CCI in model 3. **b**, The associations among the residents in the cities with aging society and aged society are shown on the right, respectively. Results were presented as hazard ratios (HRs) ± 95% confidence intervals (CIs). The error bars represent the 95% CIs of HRs. Benzene concentrations were categorized into three levels (low: <0.62 μg/m^3, moderate: 0.62-0.81 μg/m^3, high: >0.81 μg/m^3), with the low level as a reference. The '*P* for trend' value was calculated by a trend test for categorical

414 results. Additionally, the risks of brain disorders per IQR increment (0.30 μg/m^3) of benzene concentration were also estimated. The two-sided *P* value
415 (<0.05) marked with the asterisk indicates the association of statistical significance.
416
417 **Fig. 3 Associations between ambient benzene exposure and incidence risk of brain disorders stratified by status of peripheral inflammation and**
418 **metabolic syndrome.** A total of 261,909 participants were utilized to assess the relationship of benzene exposure with specific brain disorders. **a**, The
419 analysis stratified by INFLA-score (low/high) was performed utilizing Cox proportional hazards regression models with adjustment for age, sex, IMD,
420 ambient exposure to $PM_{2.5}$, proximity to roadways, high noise exposure, occupational exposure to benzene, WHR, healthy lifestyle, and CCI. **b**, The
421 analysis stratified by MetS (yes/no) was performed utilizing Cox proportional hazards regression models with the same adjustment strategy. The error
422 bars represent the 95% confidential intervals of hazard ratios (HRs). HRs per IQR increment of ambient benzene were shown. HRs for high level (>0.81
423 μg/m^3) were estimated with the lowest level of ambient benzene (<0.62 μg/m^3) as a reference. *P* for interaction for each subgroup was calculated to
424 evaluate comparability through the multiplicative term in the model. The two-sided *P* value (<0.05) marked with the asterisk indicates a statistically
425 significant difference.
426

Fig. 4 The distribution of benzene concentrations over the UK from 2003-2010 and exposure-response relationships of long-term ambient benzene exposure with brain disorders. a, The spatial distribution of ambient benzene across the UK with concentrations categorized into three levels (low: <0.62 μg/m^3, moderate: 0.62-0.81 μg/m^3, high: >0.81 μg/m^3). **b**, The temporal trend of annual mean benzene concentrations from 2003 to 2010. **c**, The exposure-response relationships between ambient benzene exposure and brain disorders, among 261,909 participants, were derived by natural cubic spline regression models, with three knots placed at fixed quantiles (i.e., the 1st, 50th, and 99th percentiles). Results were presented as hazard ratios.

Fig. 5 Associations between long-term ambient benzene exposure and brain imaging phenotypes. The brain imaging phenotypes included the volumes of the cortex and subcortex. The associations between ambient benzene exposure and brain structures were estimated among 23,911 participants with available neuroimaging data, utilizing multiple linear regression models. Data were presented as the *βs*. The *P* values were adjusted using the FDR method to control for the rate of false discoveries in multiple comparisons, with a two-sided *P* value FDR <0.05 (bold font) suggesting statistical significance.

Fig. 6 Associations of brain imaging phenotypes with brain disorders and the results of structural equation models. a, Among 23,911 participants with available neuroimaging data, the associations between brain imaging phenotypes and brain disorders were estimated through logistic regression

models. Results were presented as odds ratios. **b**, Among 23,911 participants with available data on neuroimaging, inflammation, and metabolites, the structural equation models were constructed for brain disorders, dementia, MDD, and anxiety disorder, respectively. Latent variables including brain disorders, brain structure, inflammation, and metabolites were estimated in models. Standardized coefficients are shown in tables. *Wald* tests were used in the SEM analyses to obtain the two-sided *P* values. The asterisk indicates the association of statistical significance ($P < 0.05$).

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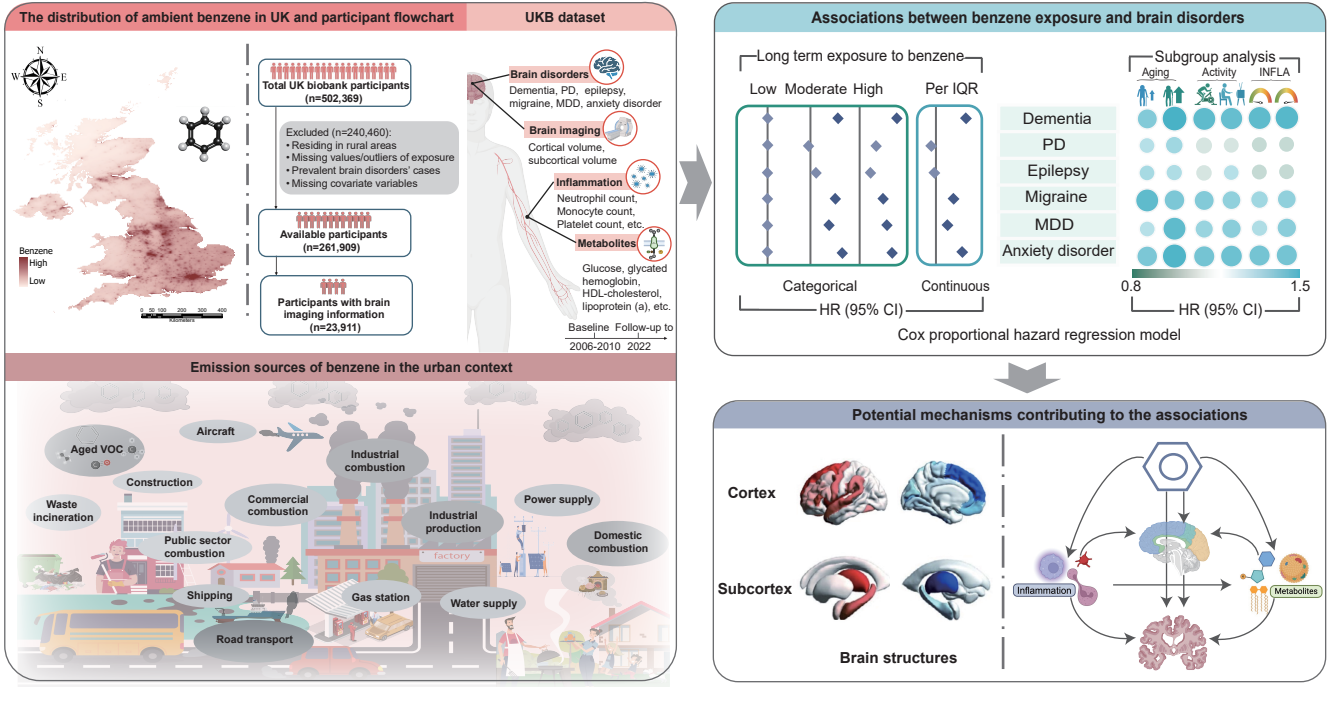
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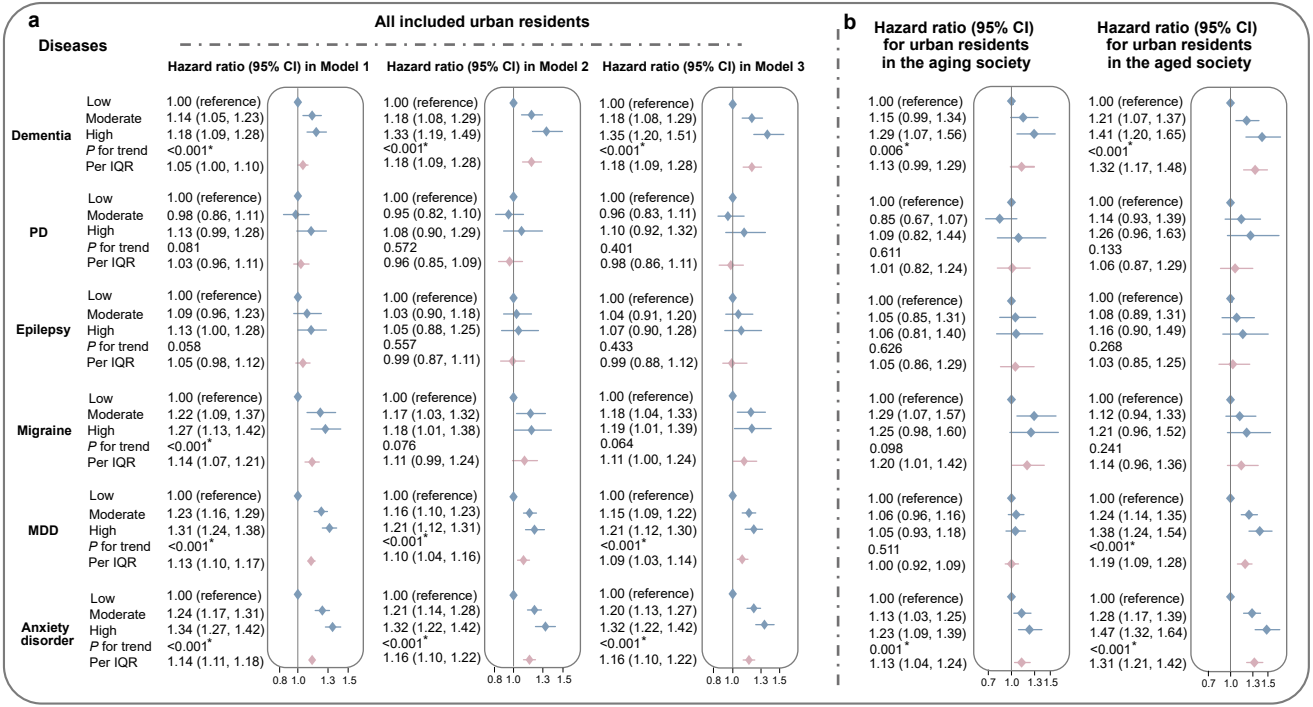
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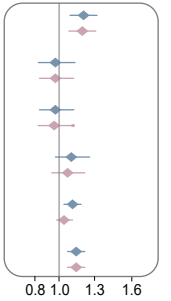
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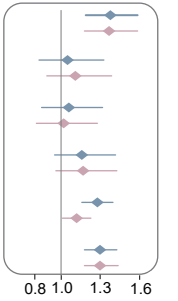

The distribution of ambient benzene in UK and participant flowchart
UKB dataset
N
W
E
S
Benzene
High
Low
0 50 100 200 300 400
Kilometers
Total UK biobank participants (n=502,369)
Excluded (n=240,460):
• Residing in rural areas
• Missing values/outliers of exposure
• Prevalent brain disorders' cases
• Missing covariate variables
Available participants (n=261,909)
Participants with brain imaging information (n=23,911)
Brain disorders
Dementia, PD, epilepsy, migraine, MDD, anxiety disorder
Brain imaging
Cortical volume, subcortical volume
Inflammation
Neutrophil count, Monocyte count, Platelet count, etc.
Metabolites
Glucose, glycated hemoglobin, HDL-cholesterol, lipoprotein (a), etc.
Baseline
Follow-up to
2006-2010
2022
Emission sources of benzene in the urban context
Aged VOC
Aircraft
Industrial combustion
Construction
Waste incineration
Commercial combustion
Power supply
Industrial production
Public sector combustion
Domestic combustion
factory
Shipping
Gas station
Water supply
Road transport
Associations between benzene exposure and brain disorders
Long term exposure to benzene
Low Moderate High
Per IQR
Categorical
Continuous
HR (95% CI)
Dementia
PD
Epilepsy
Migraine
MDD
Anxiety disorder
Subgroup analysis
Aging
Activity
INFLA
0.8
1.5
HR (95% CI)
Cox proportional hazard regression model
Potential mechanisms contributing to the associations
Cortex
Subcortex
Brain structures
Inflammation
Metabolites


a
All included urban residents
Diseases
Hazard ratio (95% CI) in Model 1
Hazard ratio (95% CI) in Model 2
Hazard ratio (95% CI) in Model 3
Dementia
Low 1.00 (reference) 1.00 (reference) 1.00 (reference)
Moderate 1.14 (1.05, 1.23) 1.18 (1.08, 1.29) 1.18 (1.08, 1.29)
High 1.18 (1.09, 1.28) 1.33 (1.19, 1.49) 1.35 (1.20, 1.51)
P for trend <0.001* <0.001* <0.001*
Per IQR 1.05 (1.00, 1.10) 1.18 (1.09, 1.28) 1.18 (1.09, 1.28)
PD
Low 1.00 (reference) 1.00 (reference) 1.00 (reference)
Moderate 0.98 (0.86, 1.11) 0.95 (0.82, 1.10) 0.96 (0.83, 1.11)
High 1.13 (0.99, 1.28) 1.08 (0.90, 1.29) 1.10 (0.92, 1.32)
P for trend 0.081 0.572 0.401
Per IQR 1.03 (0.96, 1.11) 0.96 (0.85, 1.09) 0.98 (0.86, 1.11)
Epilepsy
Low 1.00 (reference) 1.00 (reference) 1.00 (reference)
Moderate 1.09 (0.96, 1.23) 1.03 (0.90, 1.18) 1.04 (0.91, 1.20)
High 1.13 (1.00, 1.28) 1.05 (0.88, 1.25) 1.07 (0.90, 1.28)
P for trend 0.058 0.557 0.433
Per IQR 1.05 (0.98, 1.12) 0.99 (0.87, 1.11) 0.99 (0.88, 1.12)
Migraine
Low 1.00 (reference) 1.00 (reference) 1.00 (reference)
Moderate 1.22 (1.09, 1.37) 1.17 (1.03, 1.32) 1.18 (1.04, 1.33)
High 1.27 (1.13, 1.42) 1.18 (1.01, 1.38) 1.19 (1.01, 1.39)
P for trend <0.001* 0.076 0.064
Per IQR 1.14 (1.07, 1.21) 1.11 (0.99, 1.24) 1.11 (1.00, 1.24)
MDD
Low 1.00 (reference) 1.00 (reference) 1.00 (reference)
Moderate 1.23 (1.16, 1.29) 1.16 (1.10, 1.23) 1.15 (1.09, 1.22)
High 1.31 (1.24, 1.38) 1.21 (1.12, 1.31) 1.21 (1.12, 1.30)
P for trend <0.001* <0.001* <0.001*
Per IQR 1.13 (1.10, 1.17) 1.10 (1.04, 1.16) 1.09 (1.03, 1.14)
Anxiety disorder
Low 1.00 (reference) 1.00 (reference) 1.00 (reference)
Moderate 1.24 (1.17, 1.31) 1.21 (1.14, 1.28) 1.20 (1.13, 1.27)
High 1.34 (1.27, 1.42) 1.32 (1.22, 1.42) 1.32 (1.22, 1.42)
P for trend <0.001* <0.001* <0.001*
Per IQR 1.14 (1.11, 1.18) 1.16 (1.10, 1.22) 1.16 (1.10, 1.22)
0.8 1.0 1.3 1.5
0.8 1.0 1.3 1.5
0.8 1.0 1.3 1.5
b
Hazard ratio (95% CI) for urban residents in the aging society
Hazard ratio (95% CI) for urban residents in the aged society
1.00 (reference) 1.00 (reference)
1.15 (0.99, 1.34) 1.21 (1.07, 1.37)
1.29 (1.07, 1.56) 1.41 (1.20, 1.65)
0.006* <0.001*
1.13 (0.99, 1.29) 1.32 (1.17, 1.48)
1.00 (reference) 1.00 (reference)
0.85 (0.67, 1.07) 1.14 (0.93, 1.39)
1.09 (0.82, 1.44) 1.26 (0.96, 1.63)
0.611 0.133
1.01 (0.82, 1.24) 1.06 (0.87, 1.29)
1.00 (reference) 1.00 (reference)
1.05 (0.85, 1.31) 1.08 (0.89, 1.31)
1.06 (0.81, 1.40) 1.16 (0.90, 1.49)
0.626 0.268
1.05 (0.86, 1.29) 1.03 (0.85, 1.25)
1.00 (reference) 1.00 (reference)
1.29 (1.07, 1.57) 1.12 (0.94, 1.33)
1.25 (0.98, 1.60) 1.21 (0.96, 1.52)
0.098 0.241
1.20 (1.01, 1.42) 1.14 (0.96, 1.36)
1.00 (reference) 1.00 (reference)
1.06 (0.96, 1.16) 1.24 (1.14, 1.35)
1.05 (0.93, 1.18) 1.38 (1.24, 1.54)
0.511 <0.001*
1.00 (0.92, 1.09) 1.19 (1.09, 1.28)
1.00 (reference) 1.00 (reference)
1.13 (1.03, 1.25) 1.28 (1.17, 1.39)
1.23 (1.09, 1.39) 1.47 (1.32, 1.64)
0.001* <0.001*
1.13 (1.04, 1.24) 1.31 (1.21, 1.42)
0.7 1.0 1.3 1.5
0.7 1.0 1.3 1.5

a

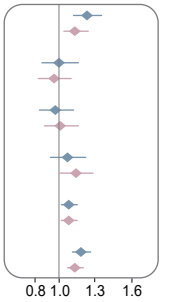
Diseases	INFLA-score	Hazard ratio per IQR (95% CI)	*P* for interaction	Hazard ratio for high level (95% CI)	*P* for interaction
Dementia	High	1.20 (1.09, 1.31)	0.871	1.38 (1.19, 1.59)	0.950
	Low	1.19 (1.08, 1.30)		1.37 (1.18, 1.59)	
PD	High	0.97 (0.83, 1,13)	0.995	1.05 (0.83, 1.33)	0.689
	Low	0.97 (0.84, 1.12)		1.11 (0.89, 1.39)	
Epilepsy	High	0.97 (0.84, 1.12)	0.942	1.06 (0.85, 1.32)	0.768
	Low	0.96 (0.83, 1.11)		1.02 (0.81, 1.28)	
Migraine	High	1.10 (0.97, 1.25)	0.624	1.16 (0.95, 1.42)	0.948
	Low	1.07 (0.94, 1.21)		1.17 (0.96, 1.43)	
MDD	High	1.11 (1.04, 1.18)	0.051	1.28 (1.16, 1.40)	0.021*
	Low	1.04 (0.98, 1.11)		1.12 (1.01, 1.23)	
Anxiety disorder	High	1.14 (1.07, 1.21)	0.955	1.30 (1.18, 1.43)	0.971
	Low	1.14 (1.07, 1.21)		1.30 (1.18, 1.44)	

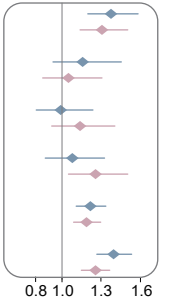


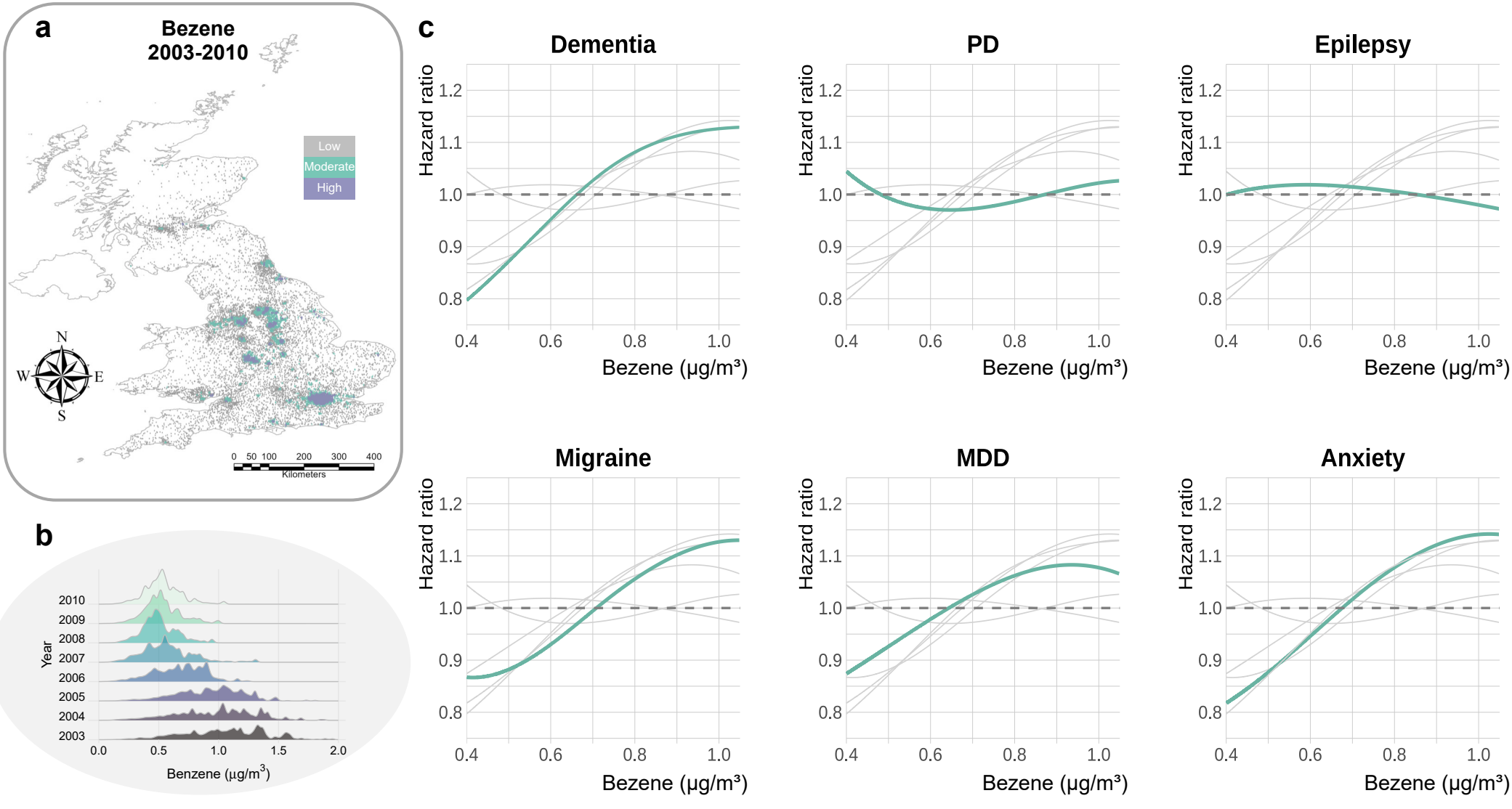


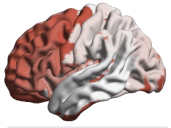
b

Diseases	MetS	Hazard ratio per IQR (95% CI)	*P* for interaction	Hazard ratio for high level (95% CI)	*P* for interaction
Dementia	Yes	1.23 (1.12, 1.35)	0.075	1.38 (1.20, 1.59)	0.526
	No	1.13 (1.04, 1.24)		1.31 (1.14, 1.51)	
PD	Yes	1.00 (0.86, 1.16)	0.531	1.16 (0.93, 1.46)	0.459
	No	0.96 (0.83, 1.10)		1.05 (0.85, 1.31)	
Epilepsy	Yes	0.97 (0.84, 1.12)	0.569	0.99 (0.80, 1.24)	0.275
	No	1.01 (0.88, 1.16)		1.14 (0.92, 1.41)	
Migraine	Yes	1.07 (0.93, 1.22)	0.306	1.08 (0.87, 1.33)	0.187
	No	1.14 (1.01, 1.28)		1.26 (1.05, 1.51)	
MDD	Yes	1.08 (1.02, 1.15)	0.944	1.22 (1.11, 1.34)	0.608
	No	1.08 (1.02, 1.15)		1.19 (1.09, 1.30)	
Anxiety disorder	Yes	1.18 (1.11, 1.26)	0.145	1.40 (1.27, 1.54)	0.056
	No	1.13 (1.07, 1.20)		1.26 (1.15, 1.37)	

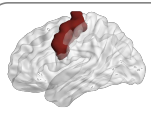




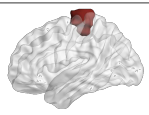

a
Bezene
2003-2010
Low
Moderate
High
N
W
E
S
0 50 100 200 300 400
Kilometers
b
2010
2009
2008
2007
2006
2005
2004
2003
Year
0.0 0.5 1.0 1.5 2.0
Benzene (μg/m3)
c
Dementia
PD
Epilepsy
Migraine
MDD
Anxiety
Hazard ratio
0.8 0.9 1.0 1.1 1.2
0.4 0.6 0.8 1.0
Bezene (μg/m³)



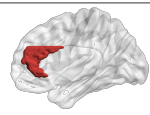
Frontal lobe



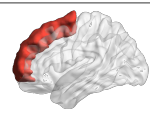
Precentral gyrus



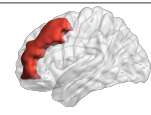
Paracentral lobule



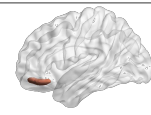
Rostral anterior cingulate cortex



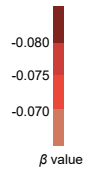
Superior frontal gyrus

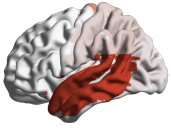


Rostral middle frontal gyrus



Lateral orbitofrontal





Temporal and Insular lobes



Middle temporal gyrus



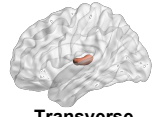
Superior temporal gyrus



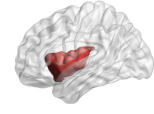
Inferior temporal gyrus



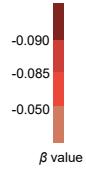
Fusiform gyrus

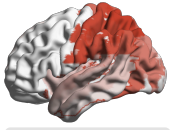


Transverse temporal gyrus

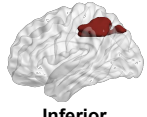


Insula

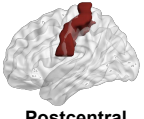




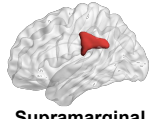
Parietal lobe



Inferior parietal lobule



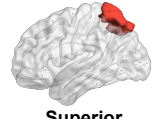
Postcentral gyrus



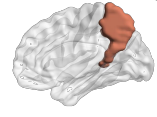
Supramarginal gyrus



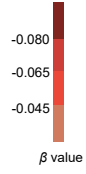
Posterior cingulate cortex



Superior parietal lobule

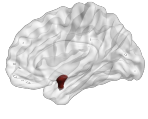


Precuneus

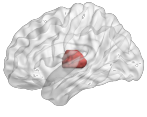




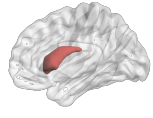
Subcotex



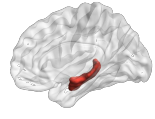
Amygdala



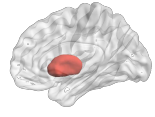
Thalamus



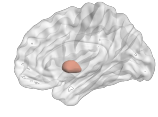
Caudate nucleus



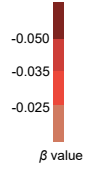
Hippocampus

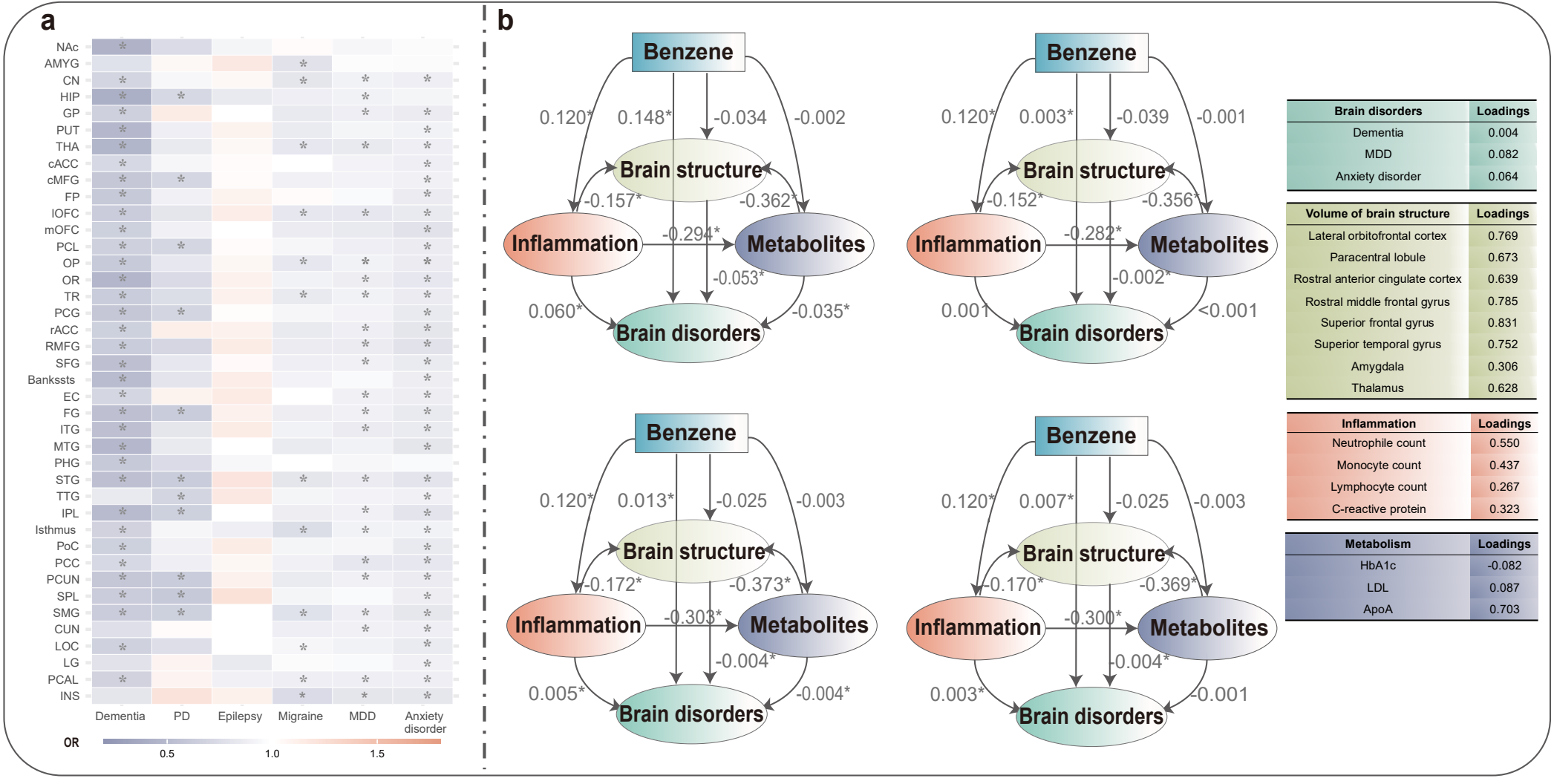


Putamen



Globus pallidus





Brain disorders	Loadings
Dementia	0.004
MDD	0.082
Anxiety disorder	0.064

Volume of brain structure	Loadings
Lateral orbitofrontal cortex	0.769
Paracentral lobule	0.673
Rostral anterior cingulate cortex	0.639
Rostral middle frontal gyrus	0.785
Superior frontal gyrus	0.831
Superior temporal gyrus	0.752
Amygdala	0.306
Thalamus	0.628

Inflammation	Loadings
Neutrophile count	0.550
Monocyte count	0.437
Lymphocyte count	0.267
C-reactive protein	0.323

Metabolism	Loadings
HbA1c	-0.082
LDL	0.087
ApoA	0.703