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Personality traits and brain health: a large prospective cohort study

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Personality has recently emerged as a critical determinant for multiple health outcomes. However, the evidence is less established for brain health, and the underlying mechanisms remain unclear. Here, utilizing data of 298,259 participants from the UK Biobank, five personality traits, including warmth, diligence, nervousness, sociability and curiosity, were constructed, and their relationships with brain disorders were examined with Cox regression and Mendelian randomization analyses. The results revealed consistent deleterious roles of nervousness, while the protective roles of warmth, diligence, sociability and curiosity in brain disorders were emphasized. Neuroimaging analyses highlighted the associations of personality traits with critical brain regions including the frontal cortex, temporal cortex and thalamus. Exploratory analyses revealed the mediating effects of neutrophil and high-density lipoprotein, indicating the contribution of inflammation and lipid metabolism to the associations between personality and brain health. This study provides a foundation for personality-oriented interventions in brain health, and it is necessary to validate our findings in other populations.

Brain disorders, the disturbance of brain health characterized by structural damage and/or functional impairment in the brain, are the leading cause of disability and the second leading cause of death worldwide[1,2]. The burden of brain disorders is an unquestionable emergency with increasing prevalence of dementia, Parkinson's disease (PD) and stroke driven by an ageing population, and increasing incidence of schizophrenia, bipolar affective disorder, major depressive disorder (MDD) and anxiety disorders driven by the coronavirus disease 2019 pandemic[3]. However, most brain disorders are incurable or irreversible, so primary prevention is still the critical way to maintain brain health. Multiple modifiable risk factors, such as smoking, alcohol consumption, physical activities, obesity, hypertension and diabetes[4–6], have been identified as key components of any prevention strategy. Further efforts to alleviate the disease burden of brain disorders require a search for additional factors. Recently, personality has been receiving interest due to its impact on brain health through processes such as physiological responses, engagement of risky behaviours, coping mechanisms and, potentially, shared genetic risks[7–9]. Elucidating the role of personality

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in brain disorders would enhance our understanding of brain health and provide new perspectives to establish prevention strategies for brain disorders.

Personality represents relatively stable patterns of thoughts, feelings and behaviours that reflect the tendency to respond in a specific way under particular circumstances. It is believed that personality originates in infancy and continues through late life periods[10,11]. Personality science seeks to study individual differences of personality that persist over time and place, and one of the core analysis units in the field is personality traits[12]. Trait-based personality theories and predictive tests have been widely adopted as objective measurements of personality traits, such as the Big Five Inventory (BFI)[13], which organizes personality traits into the five broad domains of extraversion, agreeableness, conscientiousness, neuroticism and openness. The organized personality traits measurement makes it possible to study the connections of personality psychology with other fields[12], such as brain health.

Growing evidence indicates that personality traits can predict the incidence of dementia[7], PD[8], bipolar affective disorder and schizophrenia[9], with a common direction of effect that a higher degree of nervousness is associated with increased disease risk. The other four personality traits, extraversion, agreeableness, conscientiousness and openness, were found as potential protective factors for brain disorders, although some studies did not acquire statistically significant results. However, personality has been traditionally viewed as a separate discipline, and its importance is often overshadowed, resulting in studies with small sample sizes narrowly focused on single outcomes that fail to capture the full range of brain health. Heterogeneity of cohort populations, study designs and personality scales is also encountered across studies. Among previous studies[14,15], the sample sizes usually ranged from tens to thousands of participants, the follow-up duration varied across 1 to 10 years and inconsistent methods were incorporated to measure the personality traits, including BFI, Midlife Development Inventory, Temperament and Character Inventory, and so on. These issues increase the uncertainty of the relationship between personality traits and brain health. Additionally, all previous studies only considered the role of individual personality traits in single brain disorders. Actually, most of the inventories are broad and inclusive taxonomies so that the personality traits are not discrete or independent dimensions but are overlapping and complicated groups of facets[12]. More efforts should be made to investigate the interaction of different personality traits in various brain disorders' development.

Although many studies tried to detail the relationship between personality traits and brain health, they rarely explored the underlying mechanisms. It has been reported that personality traits were related to cortex volume[16], and the shared genetic basis existed between personality traits and cortical structures[17]. Additionally, there is evidence that inflammation[18] and metabolism[19,20] are key elements in the pathobiology of brain disorders, and systemic inflammatory markers contribute to the role of personality traits in health[21], thus shedding light on these peripheral markers as bridges between personality traits and brain health. Clarifying the influence of personality traits on central brain structure, peripheral inflammation and metabolism may help uncover the contribution of personality traits to brain health.

In this Article, to address the gaps in the literature, we conducted a prospective cohort study leveraging data from the UK Biobank (UKB) to unravel the linkages between personality traits and brain health (Fig. 1). First, we performed the Cox proportional hazards model and Mendelian randomization (MR) to investigate the longitudinal and causal associations of five personality traits with seven common brain disorders. Next, by neuroimaging, we quantified the effect of brain health-related personality traits on brain structures involving the cortex, subcortex and white matter. Finally, we explored the potential mechanisms of personality in brain disorders driven by inflammatory markers and metabolites. Taking advantage of the large sample size (N = 298,259), a long follow-up time (9.49 years) and the multimodal data of consistent psychological assessment, disease outcomes, imaging, genomics, inflammatory and metabolic markers in UKB, we aim to establish robust evidence for the differential roles of five personality traits in brain disorders and deepen our understanding of the potential mechanisms of personality traits in brain health.

Results

Baseline characteristics of the participants

At baseline, a total of 298,259 participants were included in the primary analyses (mean and standard deviation (s.d.) age, 60.32 (5.41) years; 53.97% women). During a median of 9.49 (Q1, 7.56; Q3, 11.26) years of follow-up, 6,041 individuals were diagnosed with dementia, 2,239 with PD, 9,199 with stroke, 183 with schizophrenia, 309 with bipolar affective disorder, 8,832 with MDD and 11,346 with anxiety disorder. The baseline demographic and personality characteristics of participants stratified by incident brain disorder are presented in Table 1. We calculated descriptive statistics as mean (s.d.) for continuous variables and number (percentage) for categorical variables.

Personality traits longitudinally predict brain disorders

Significant associations were observed between the five separate personality traits and the risk of brain disorders in Cox proportional hazards models (Fig. 2a). Three trends particularly stood out. First, after false discovery rate (FDR) correction for 30 tests (five personality traits multiplied by six brain disorders) using the Benjamini–Hochberg method, we found that the risks conferred by personality traits were ubiquitous across diagnoses. Levels of warmth, sociability and curiosity were significantly associated with the incidence of all studied neurological and psychiatric disorders (warmth: FDR-Q <0.001 for dementia, stroke, schizophrenia, bipolar affective disorder and MDD, and FDR-Q of 0.017 for PD; sociability: FDR-Q <0.001 for dementia, stroke, schizophrenia, bipolar affective disorder and MDD, and FDR-Q of 0.002 for PD; curiosity: FDR-Q <0.001 for dementia, PD, schizophrenia, bipolar affective disorder and MDD, and FDR-Q of 0.001 for stroke). Strong evidence also supported the associations of diligence and nervousness with all brain disorders except PD (diligence: FDR-Q <0.001 for dementia, stroke and MDD, FDR-Q of 0.049 for schizophrenia, and FDR-Q of 0.004 for bipolar affective disorder; nervousness: FDR-Q <0.001 for all five disorders). Second, the directions of the effect of these personality traits on brain disorders were entirely consistent, where higher levels of warmth, diligence, sociability and curiosity were associated with decreased risk of brain disorders, with hazard ratios (HRs) and 95% confidence intervals (CIs) ranging from 0.52, 0.41–0.66 (schizophrenia ~ curiosity) to 0.95, 0.91–0.99 (PD ~ warmth), while nervousness was associated with increased risk (HR, 95% CI ranges from 1.05, 1.04–1.07 for stroke to 1.53, 1.33–1.76 for schizophrenia). Third, despite the relative homogeneity in statistical significance and direction, the effect sizes varied considerably across brain disorders. Personality conferred larger risks towards psychiatric disorders than neurological diseases. In particular, each point increase of nervousness score was associated with a 7% higher hazard for dementia (HR, 95% CI: 1.07, 1.04–1.10, FDR-Q <0.001), 5% for stroke (1.05, 1.04–1.07, FDR-Q <0.001), but with a 53% increased hazard for schizophrenia (1.53, 1.33–1.76, FDR-Q <0.001), 40% for bipolar affective disorder (1.40, 1.27–1.54, FDR-Q <0.001) and 48% for MDD (1.48, 1.45–1.51, FDR-Q <0.001). Sex-stratified models were also performed (Supplementary Table 1). Although most of the associations remained significant (FDR-Q <0.05 for 60 tests (five personality traits multiplied by six brain disorders multiplied by two sexes)) in both sexes, the effect of personality traits on neurological diseases was slightly more notable in females, while the effect on psychiatric disorders was relatively more apparent in males.

While common trends among relationships between separate personality traits and brain disorders were discovered, psychometric

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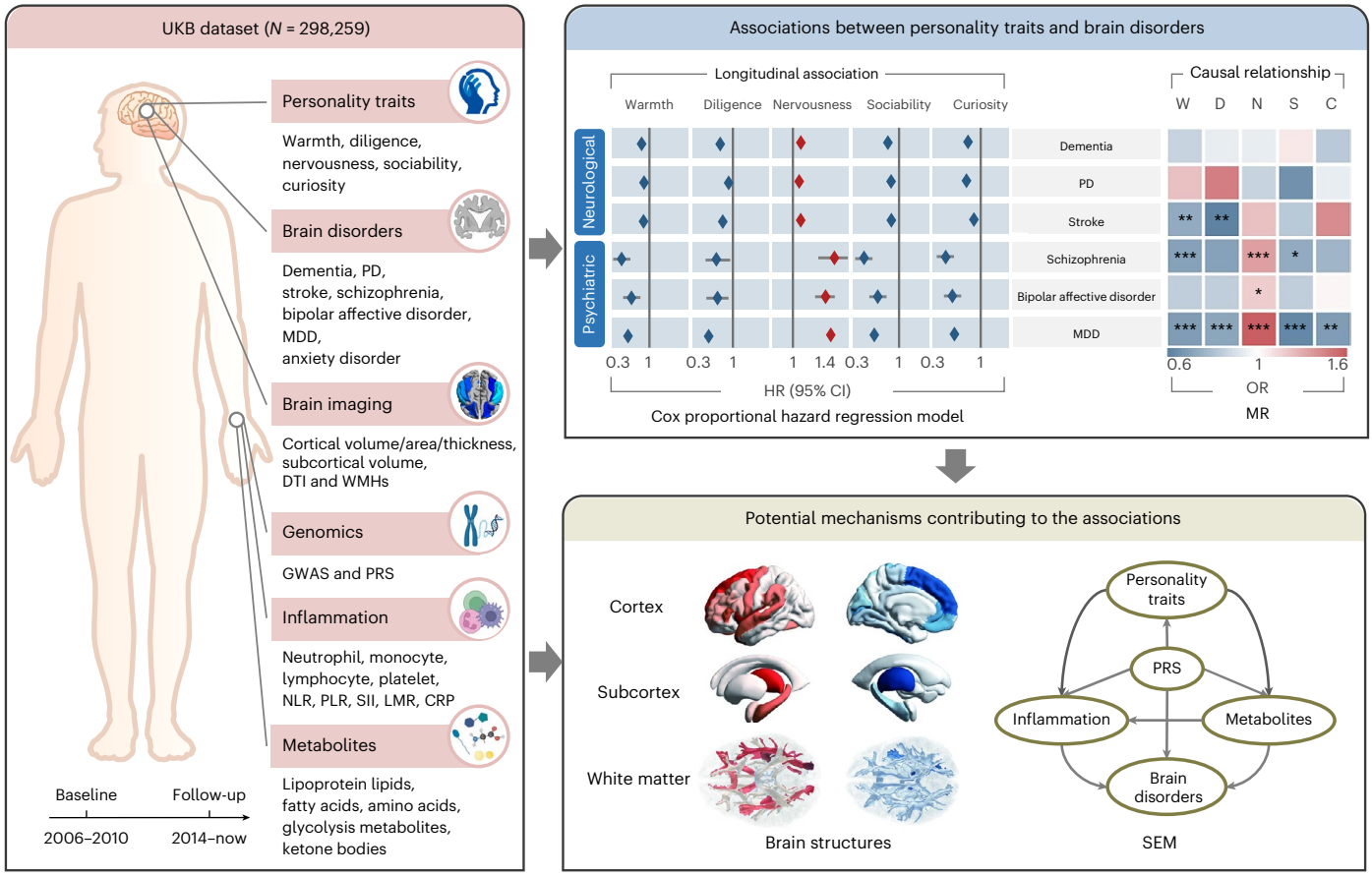

Fig. 1 | Study workflow. Left: the data used in the study from UKB include personality traits, brain disorders, brain imaging, genomics, inflammation and metabolites. Top right: longitudinal and causal associations between personality traits and brain disorders. Data are presented as HR ± 95% CI for Cox regression, and Wald test was utilized to obtain the two-sided *P* values. Data are presented as OR ± 95% CI for MR, and *t*-test was utilized to obtain the two-sided *P* values. FDR correction was applied, and FDR-*Q* value of 0.844, 0.573, 0.638, 0.764 and 0.278 for warmth, diligence, nervousness, sociability and curiosity, respectively, in dementia group; 0.554, 0.640, 0.750, 0.569 and 1.015 in PD group; 0.009, 0.004, 0.074, 0.119 and 0.442 in stroke group; 1×10^{-7}, 0.124, 3×10^{-4}, 0.041 and 0.550 in schizophrenia group; 0.129, 0.645, 0.022, 0.552 and 0.736 in bipolar affective disorder group; 2×10^{-30}, 4×10^{-4}, 1×10^{-29}, 8×10^{-15} and 8×10^{-4} in major depressive disorder group. *FDR-*Q* <0.05, **FDR-*Q* <0.01, ***FDR-*Q* <0.001. Bottom right: potential mechanisms contributing to the associations between personality traits and brain disorders.

properties are complicated and an individual may possess more than one dominant personality trait. With this in mind, we included the participants with complete data of five personality traits in a cluster analysis. A three-cluster solution was found and tested for whether the trends of single personality traits still held for personality clusters (Fig. 2b). Cluster 1 was labelled 'nervous-dominant', cluster 2 was labelled 'warm-social-curious' and cluster 3 was labelled 'warm-social-diligent'. In comparison with the 'nervous-dominant' cluster, the 'warm-social-curious' cluster showed significant protective effects on psychiatric disorders (HR, 95% CI is 0.30, 0.16–0.55 for schizophrenia, 0.49, 0.33–0.73 for bipolar affective disorder and 0.51, 0.47–0.55 for MDD; FDR-*Q* <0.001 for all mentioned associations), and the 'warm-social-diligent' cluster showed significant protective effects on brain disorders except for PD (0.79, 0.72–0.87 for dementia, 0.81, 0.77–0.87 for stroke, 0.28, 0.17–0.47 for schizophrenia, 0.45, 0.32–0.62 for bipolar affective disorder and 0.33, 0.31–0.35 for MDD; FDR-*Q* <0.001 for all mentioned associations) (Fig. 2b and Supplementary Table 2). Consistent with the results of the separate personality traits, the effect sizes for different clusters were generally larger in psychiatric disorders than neurological diseases, and there was little heterogeneity among different sex groups (only the associations between cluster 2 and bipolar affective disorder disappeared in the male group; FDR-*Q* of 0.054) (Supplementary Table 3).

Causal relationships between personality traits and brain disorders

Leveraging personality trait scores and genotype data from UKB participants, we performed a genome-wide association study (GWAS) to investigate the genetics of personality traits (Fig. 3a). A total of 31 genetic loci for warmth, 10 for diligence, 39 for nervousness, 6 for sociability and 5 for curiosity reached the genome-wide significance level of $P < 5 \times 10^{-8}$; further details are presented in Supplementary Table 4. Next, MR analysis (Fig. 3b and Supplementary Table 5) was conducted to estimate the causal relationships between personality traits and brain disorders using the GWAS data of personality traits obtained above and GWAS data of brain disorders based on exogenous samples[22–27]. Under an inverse variance-weighted (IVW) model, we found potential causal relationships of warmth (odds ratio (OR), 95% CI: 0.65, 0.49–0.85, FDR-*Q* of 0.009) and diligence (0.40, 0.24–0.67, FDR-*Q* of 0.004) with stroke, nervousness with all psychiatric disorders (schizophrenia: 1.50, 1.24–1.82, FDR-*Q* <0.001; bipolar affective disorder: 1.31, 1.09–1.58, FDR-*Q* of 0.022; MDD: 1.79, 1.62–01.98, FDR-*Q* <0.001), all personality traits (warmth: 0.56, 0.50–0.61, FDR-*Q* <0.001; diligence: 0.61, 0.48–0.78, FDR-*Q* <0.001; nervousness: 1.79, 1.62–01.98, FDR-*Q* <0.001; sociability: 0.45, 0.37–0.54, FDR-*Q* <0.001; curiosity: 0.56, 0.41–0.75, FDR-*Q* <0.001) with MDD, as well as warmth (0.57, 0.47–0.69, FDR-*Q* <0.001) and sociability (0.63, 0.44–0.89, FDR-*Q* of 0.041) with schizophrenia.

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Table 1 | Baseline characteristics of the study population

Characteristics	Non-brain disorders	Dementia	Parkinson's disease	Stroke	Schizophrenia	Bipolar affective disorder	Major depressive disorder	Anxiety disorder
Sample size	266,224	6,041	2,239	9,199	183	309	8,832	11,436
Age, years	60.16 (5.39)	64.66 (4.03)	63.47 (4.48)	62.40 (5.08)	60.11 (6.06)	59.98 (5.70)	60.38 (5.65)	60.58 (5.51)
Female, *n* (%)	143,060 (53.73)	2,916 (48.27)	805 (35.95)	4,177 (45.41)	78 (42.62)	181 (58.58)	5,445 (61.65)	7,762 (67.87)
Ethnicity white, *n* (%)	255,260 (96.19)	5,799 (96.38)	2,157 (96.77)	8,828 (96.31)	164 (90.61)	298 (97.07)	8,501 (96.60)	10,962 (96.23)
Education								
1, *n* (%)	79,560 (38.46)	1,219 (32.58)	639 (39.40)	2,327 (35.76)	40 (34.78)	101 (42.26)	1,962 (31.95)	2,721 (33.39)
2, *n* (%)	27,052 (13.08)	483 (12.91)	201 (12.39)	805 (12.37)	21 (18.26)	26 (10.88)	783 (12.75)	1,056 (12.96)
3, *n* (%)	54,532 (26.36)	1,105 (29.53)	430 (26.51)	1814 (27.87)	29 (25.22)	56 (23.43)	1761 (28.68)	2,391 (29.34)
4, *n* (%)	10,466 (5.06)	131 (3.50)	58 (3.58)	306 (4.70)	3 (2.61)	12 (5.02)	414 (6.74)	499 (6.12)
5, *n* (%)	19,072 (9.22)	421 (11.25)	171 (10.54)	700 (10.76)	10 (8.70)	27 (11.30)	692 (11.27)	804 (9.87)
6, *n* (%)	16,181 (7.82)	383 (10.24)	123 (7.58)	556 (8.54)	12 (10.43)	17 (7.11)	528 (8.60)	677 (8.31)
SBP, mmHg	140.52 (18.50)	144.41 (19.24)	142.84 (18.43)	145.15 (19.39)	138.88 (19.69)	136.63 (17.12)	139.08 (18.47)	139.80 (18.74)
DBP, mmHg	82.62 (9.97)	81.66 (10.15)	82.24 (9.75)	83.62 (10.41)	83.20 (11.68)	80.41 (9.44)	81.92 (10.16)	81.95 (10.12)
Personality traits								
Warmth	3.70 (1.30)	3.54 (1.33)	3.63 (1.33)	3.61 (1.33)	2.58 (1.45)	2.98 (1.54)	3.05 (1.44)	3.04 (1.47)
Diligence	2.66 (0.91)	2.56 (0.92)	2.64 (0.89)	2.58 (0.94)	2.35 (1.01)	2.41 (0.98)	2.38 (0.99)	2.50 (0.98)
Nervousness	1.40 (1.28)	1.46 (1.31)	1.39 (1.31)	1.45 (1.29)	2.22 (1.48)	2.08 (1.44)	2.06 (1.36)	2.04 (1.40)
Sociability	2.73 (0.99)	2.69 (0.99)	2.73 (0.98)	2.71 (0.99)	2.15 (1.11)	2.30 (1.03)	2.38 (1.01)	2.41 (1.02)
Curiosity	1.94 (0.73)	1.87 (0.77)	1.88 (0.76)	1.94 (0.75)	1.52 (0.91)	1.62 (0.84)	1.70 (0.86)	1.65 (0.85)
Personality cluster[#]								
Cluster 1	52,809 (25.69)	1,169 (28.22)	426 (26.31)	1,911 (27.52)	67 (54.47)	106 (47.11)	2,910 (45.74)	3,788 (46.05)
Cluster 2	50,809 (24.71)	1,052 (25.39)	384 (23.72)	1,855 (26.71)	21 (17.07)	43 (19.11)	1,472 (23.14)	1,573 (19.12)
Cluster 3	101,977 (49.60)	1,922 (46.39)	809 (49.97)	3,179 (45.77)	35 (28.46)	76 (33.78)	1,980 (31.12)	2,864 (34.82)

SBP, systolic blood pressure; DBP, diastolic blood pressure. [#]Cluster: Cluster 1, nervous-dominant; cluster 2, warm-social-curious; cluster 3, warm-social-diligent.

Personality traits are associated with brain structures

To further investigate the underlying mechanism between personality and brain health, we evaluated the associations between personality traits and brain structures in a subgroup of 23,090 participants with available neuroimaging data acquired approximately 4 years after personality assessment. In general, 305 out of 1,020 associations of personality traits with cortical regions, 18 out of 80 associations with subcortical structures and 26 out of 270 associations with white matter tracts remained significant after FDR correction. White matter hyperintensities (WMHs) were significantly associated with warmth ($R = -0.026$, FDR-Q of 0.001), diligence ($R = -0.033$, FDR-Q of 4×10^{-5}), nervousness ($R = 0.023$, FDR-Q of 0.003) and sociability ($R = -0.017$, FDR-Q of 0.022) (Fig. 4 and Supplementary Table 6).

Specifically, most personality traits affected cortical regions including medial orbitofrontal cortex (all five personality traits; the smallest FDR-Q is 8×10^{-5}), superior frontal cortex (all five; the smallest FDR-Q is 1×10^{-5}), supra marginal cortex (all five; the smallest FDR-Q is 1×10^{-4}), insula (four out of five; the smallest FDR-Q is 3×10^{-6}), inferior temporal cortex (all five; the smallest FDR-Q is 1×10^{-4}) and middle temporal cortex (four out of five; the smallest FDR-Q is 3×10^{-5}) and so on. In addition to these shared brain regions, each personality trait was also related to specific regions. A higher warmth score was related to a larger volume of cortex in rostral anterior cingulate ($R = 0.033$, FDR-Q of 2×10^{-5}). In contrast, a higher nervousness score was related to a smaller cortex in this region ($R = -0.034$, FDR-Q of 2×10^{-5}). Diligence was predominantly associated with the thickness in regions including the insula ($R = 0.036$, FDR-Q of 3×10^{-6}), temporal pole ($R = 0.037$, FDR-Q of 3×10^{-6}) and superior frontal sulcus ($R = 0.030$, FDR-Q of 1×10^{-4}). Sociability was positively related to the area around the inferior parietal sulcus ($R = 0.021$, FDR-Q of 0.015) and curiosity was positively associated with the area of middle temporal sulcus ($R = 0.034$, FDR-Q of 3×10^{-5}). The results for subcortical volumes showed that warmth, diligence and nervousness were associated with the left thalamus (warmth: $R = 0.035$, FDR-Q of 3×10^{-6}; diligence: $R = 0.030$, FDR-Q of 1×10^{-4}; nervousness: $R = -0.034$, FDR-Q of 6×10^{-6}) and left hippocampus (warmth: $R = 0.017$, FDR-Q of 0.039; diligence: $R = 0.025$, FDR-Q of 0.001; nervousness: $R = -0.021$, FDR-Q of 0.008), while curiosity was related to the left ($R = 0.028$, FDR-Q of 3×10^{-4}) and right ($R = 0.028$, FDR-Q of 2×10^{-4}) lateral ventricle. In terms of white matter, higher levels of warmth and diligence showed elevated fractional anisotropy (FA) or mean diffusion (MD) values of tracts, including the anterior/posterior thalamic radiation, whereas a higher level of nervousness represented an effect in the opposite direction.

Personality traits–inflammation–metabolism–brain disorders pathway

Next, we investigated the potential mechanisms of peripheral inflammation and metabolism on associations between personality traits and brain health. First, confirmatory factor analysis was performed to estimate the latent variables in a structural equation model (SEM) that included inflammatory markers, metabolites, and the status of incident brain disorders (Fig. 5). The results demonstrated that neutrophil counts, the neutrophil-to-lymphocyte ratio (NLR), and the systemic immune-inflammation index (SII) were the main components of the inflammation latent variable. Four high-density lipoprotein (HDL)-related metabolites, including average diameter for HDL particles

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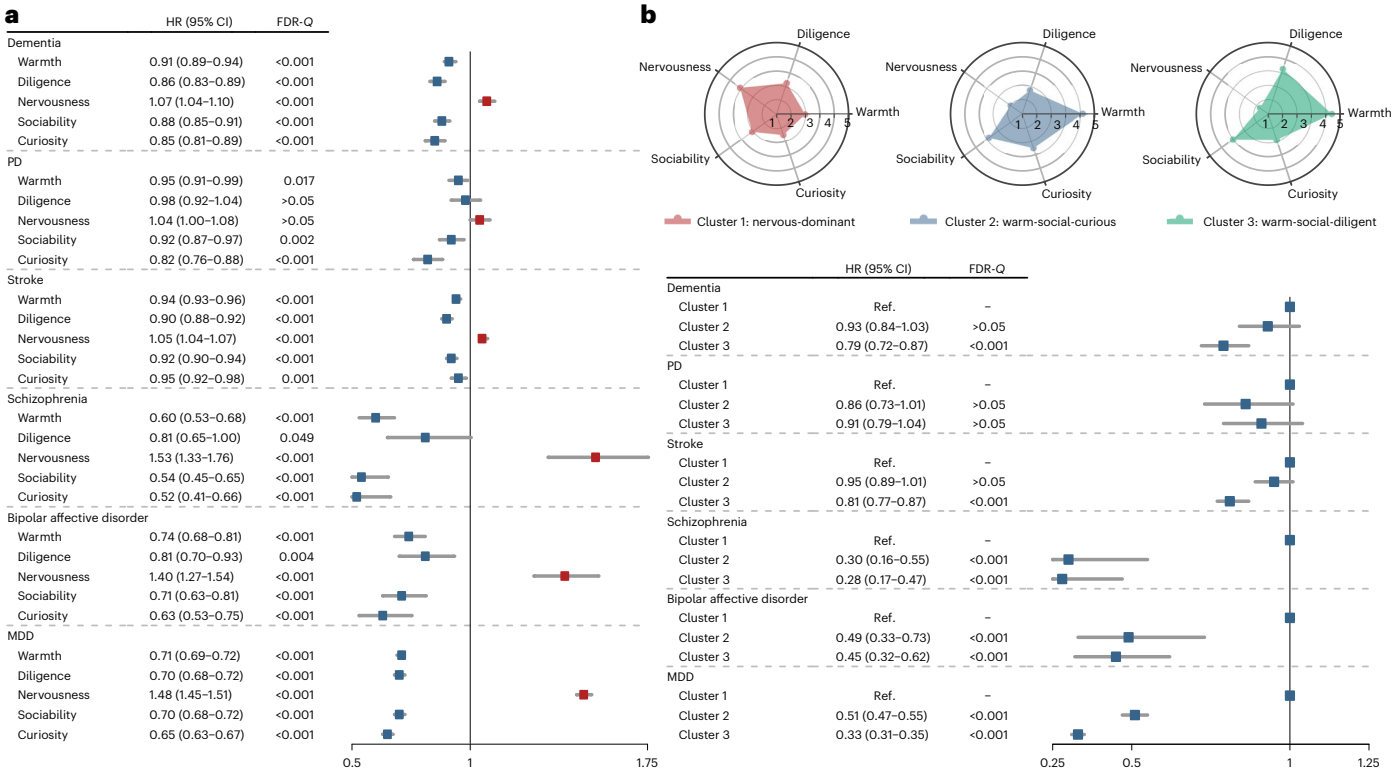

Fig. 2 | Risk for incident brain disorders according to personality traits and clusters. a, Personality traits (in dementia group, n = 191,178, 189,139, 190,035, 200,631 and 195,327 participants for warmth, diligence, nervousness, sociability and curiosity, respectively; in PD group, n = 189,163, 187,132, 188,951, 198,426 and 193219 participants, respectively; in stroke group, n = 219,121, 217,061, 218,114, 229,493, and 225,182 participants, respectively; in schizophrenia group, n = 187,921, 185,934, 186,820, 197,092 and 191,934 participants, respectively; in bipolar affective disorder group, n = 187,729, 185,729, 186,612, 196,876 and 191,713 participants, respectively; in major depressive disorder group, n = 179,063, 177,081, 177,971, 187,960 and 182,960 participants, respectively). **b**, Personality clusters (n = 166,392, 164,740, 188,301, 163,697, 156,145 and 163,534 participants in dementia, PD, stroke, schizophrenia, bipolar affective disorder and major depressive disorder group, respectively). For neurodegenerative and psychiatric disorders, age at baseline, sex, ethnicity and education were adjusted; for stroke, age at baseline, sex, ethnicity, and systolic and diastolic blood pressure were adjusted in Cox proportional hazards regression models. Data are presented as HR ± 95% CI for Cox regression, and Wald test was utilized to obtain the two-sided P values.

(HDL-D), cholesterol in very large HDL (XL-HDL-C), phospholipids in large HDL (L-HDL-PL) and cholesteryl esters in large HDL (L-HDL-CE), were the main components of the metabolite latent variable. As for the brain disorder latent variable, dementia ranked as the largest effect size, followed by PD, stroke and MDD.

SEM was then conducted to evaluate the mediation effects of inflammatory markers and metabolites on the associations between personality traits and brain disorders (Fig. 5). Each personality trait score was significantly associated with their polygenic risk scores (PRSs) (P < 0.001). For warmth and diligence, all paths were significant (P < 0.05), demonstrating that inflammatory markers and metabolites mediated the associations between the phenotypic score and PRS of personality with brain disorders. For nervousness, mediation effects were also observed, except for the PRS–inflammation–brain disorder pathway. For sociability and curiosity, the PRS-related pathways were not significant, while inflammatory markers and metabolites partially mediated the effects of high levels of personality scores on a lower incidence of brain disorders. There is a relatively good fit for the SEM, with comparative fit index of 0.95, root mean squared error of approximation <0.05, standardized root mean squared residual <0.08 (detailed statistical parameters in Supplementary Table 7).

Discussion

Here we presented a systematic study investigating the longitudinal and causal relationships between personality traits and brain health. Utilizing a large population-based cohort, our results suggested that lower levels of warmth, diligence, sociability and curiosity and a higher level of nervousness are predictive of both neurological diseases (dementia, PD and stroke), and psychiatric disorders (schizophrenia, bipolar affective disorder and MDD). We also discovered possible underlying mechanisms by identifying the associations between personality traits and brain structures, including regions in the cortex, subcortex, white matter tracts and WMHs, and revealed the involvement of metabolic and inflammatory factors.

Previous research involving personality trait and brain health

In recent years, the roles of different personality traits in facilitating overt medical health conditions have been extensively studied, and their associations with brain disorders including dementia[14,28,29], PD[30–32], stroke[33] and depression[34,35] have been highlighted. The additional findings mainly concerned the influence of personality on the incidence of schizophrenia and bipolar affective disorder, which has hardly been investigated as personality traits are often overlooked or treated as part of the psychiatric disorders[36]. We found that lower levels of warmth, diligence, sociability and curiosity, and a higher level of nervousness, increased the future risk of schizophrenia and bipolar affective disorder. Together with emerging research suggesting genetic and causal correlations between personality with schizophrenia and bipolar affective disorder[37,38], our study indicated that personality traits established before the expression of illness might be independent risk factors for psychiatric disorders. Another important finding lies in the significant associations between lower levels of warmth and curiosity and a higher

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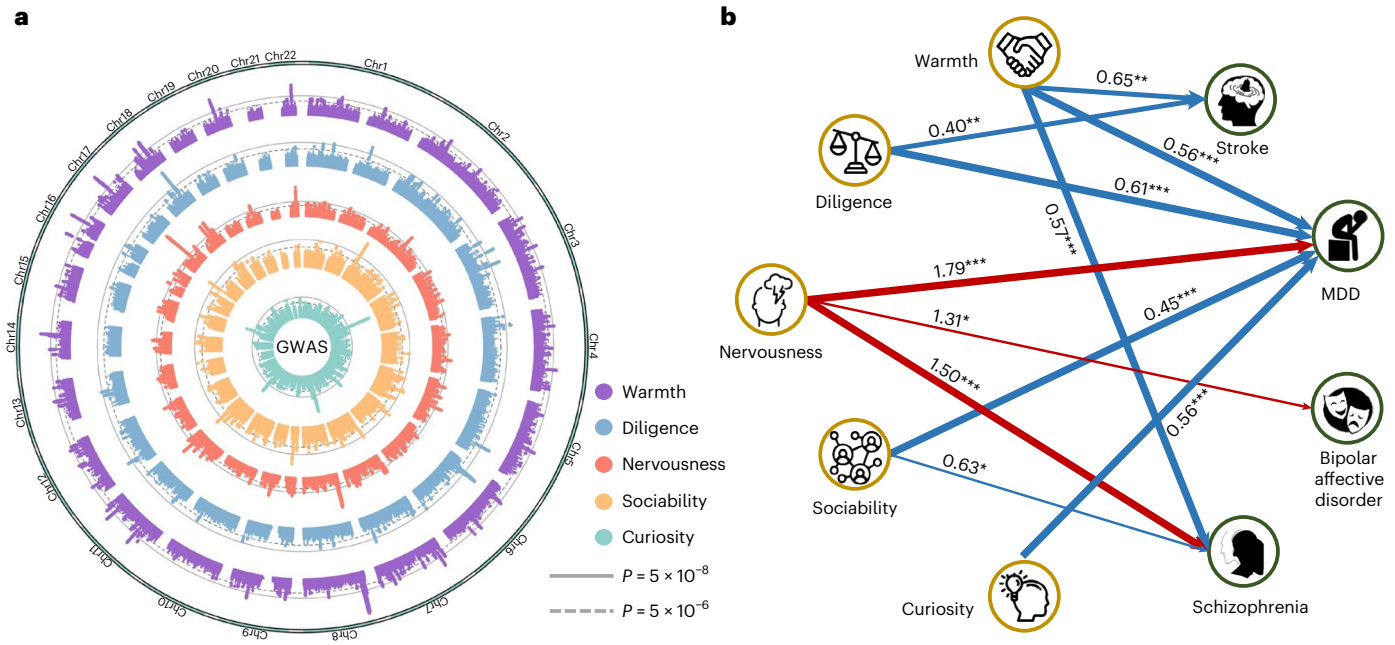

Fig. 3 | The causal relationship between personality traits and brain disorders. a, Circular Manhattan plots of personality traits GWAS. **b**, MR study of personality traits and brain disorders presented with ORs. Data are presented as OR ± 95% CI for MR, and *t*-test was utilized to obtain the two-sided *P* values. FDR correction was applied and FDR-*Q* value of $0.009, 1 \times 10^{-7}, 2 \times 10^{-30}$ for warmth; $0.004, 4 \times 10^{-4}$ for diligence; $3 \times 10^{-4}, 0.022, 1 \times 10^{-29}$ for nervousness; 8×10^{-15}, 0.041 for sociability; 8×10^{-4} for curiosity. *FDR-*Q* <0.05, **FDR-*Q* <0.01, ***FDR-*Q* <0.001.

risk of PD, filling in the gap in the literature on the associations between warmth and curiosity and risk of PD[8,30,39]. Consistent with previous studies[8,30,39], we showed that higher nervousness was related to increased risk of PD at the very edge of significance. Meanwhile, it is important to note that we did not observe a longitudinal and genetic association between diligence and PD risk, which requires further research to verify, as it has not been studied before this work. Moreover, the result that a lower level of sociability was related to a higher risk of stroke is in contrast to a previous study showing higher extraversion was associated with an increased risk of stroke[33], although most previous studies argued that better sociability is protective against cardiovascular risk[40,41]. The possible explanation for high sociability and stroke risk is that the assertive aspects of sociability prompting individuals to maintain social dominance might pose psychosocial stress, which increases cardiovascular adverse outcomes[33]. However, a recent study found that extraverted individuals showed lower anxiety levels when faced with psychosocial stress[42]. Thus, we suspect that better sociability is protective against stroke risk. Finally, regarding the findings on dementia and depression, the effect directions of five personality traits are consistent with previous studies[14,29].

Mechanisms on the association of personality trait and brain health

Concerning potential mechanisms underlying the associations between personality and brain health, previous studies have proposed the predisposition model that personality influences disease incidence via a cascade of effects on health conditions, such as physical inactivity, obesity, stress and so on[43,44]. The results of our mechanism analysis supported the predisposition model and extended the potential mediators. Consistent with previous research, our results suggested that different personality traits can profoundly affect brain structures, indicating the neuropathological burden of personality, which could possibly contribute to the personality–brain health associations[45]. Specifically, in subcortical regions, the associations between personality traits and the volume of the thalamus indicate the potential involvement of personality in processing and transmitting information throughout cortical regions[46,47], whereas associations with hippocampal volume imply a role in cognition processing[48,49]. For white matter tracts, we suggested thalamic radiation as a key structure in these relationships considering previous reports of alterations of posterior thalamic radiation in the presence of brain disorders such as PD[50] and schizophrenia[51]. WMHs, typical markers of cerebral small vessel disease[52], also demonstrated significant associations with personality traits, thus extending the scope of previous research[53]. WMHs reflect demyelination and Wallerian degeneration of neurons after cerebral ischaemia[54], partly explaining the effect of personality on stroke discovered in this analysis.

Next, since inflammation has been emphasized in pathological mechanisms of socio-psychological behaviours and brain disorders[55–58], we explored whether the associations between personality and brain health are driven, at least in part, by peripheral inflammatory markers. As indicated by the SEM analysis, peripheral inflammation markers, including neutrophil count, NLR and SII, mediated the relationship between personality and brain health. We found support for this result from several prior investigations suggesting that cytokines derived from chronic systemic inflammation could serve as mediators of certain social, environmental and lifestyle factors in the incidence of diseases and mortality across the lifespan[59], as well as in major depression[23]. Given that inflammation and lipid metabolism are closely related to each other and both act as modulators of homeostasis and immunity[60], we also examined the effects of lipids and found significant results. We found that HDL, expressing antioxidative and anti-inflammatory activity[61], was positively associated with extraversive personality traits, such as warmth, diligence, sociability and curiosity, while negatively related to introversive traits like nervousness. A possible link between personality and inflammation could be found in physical activity levels and obesity. People with introverted personality traits tend to have a lower exercise frequency and thus benefit less from exercise-induced anti-inflammatory effects[62,63]. Compounding this, obesity increases the risk of inflammation and oxidative stress[62–64]. Peripheral inflammation can impact brain function as the blood–brain

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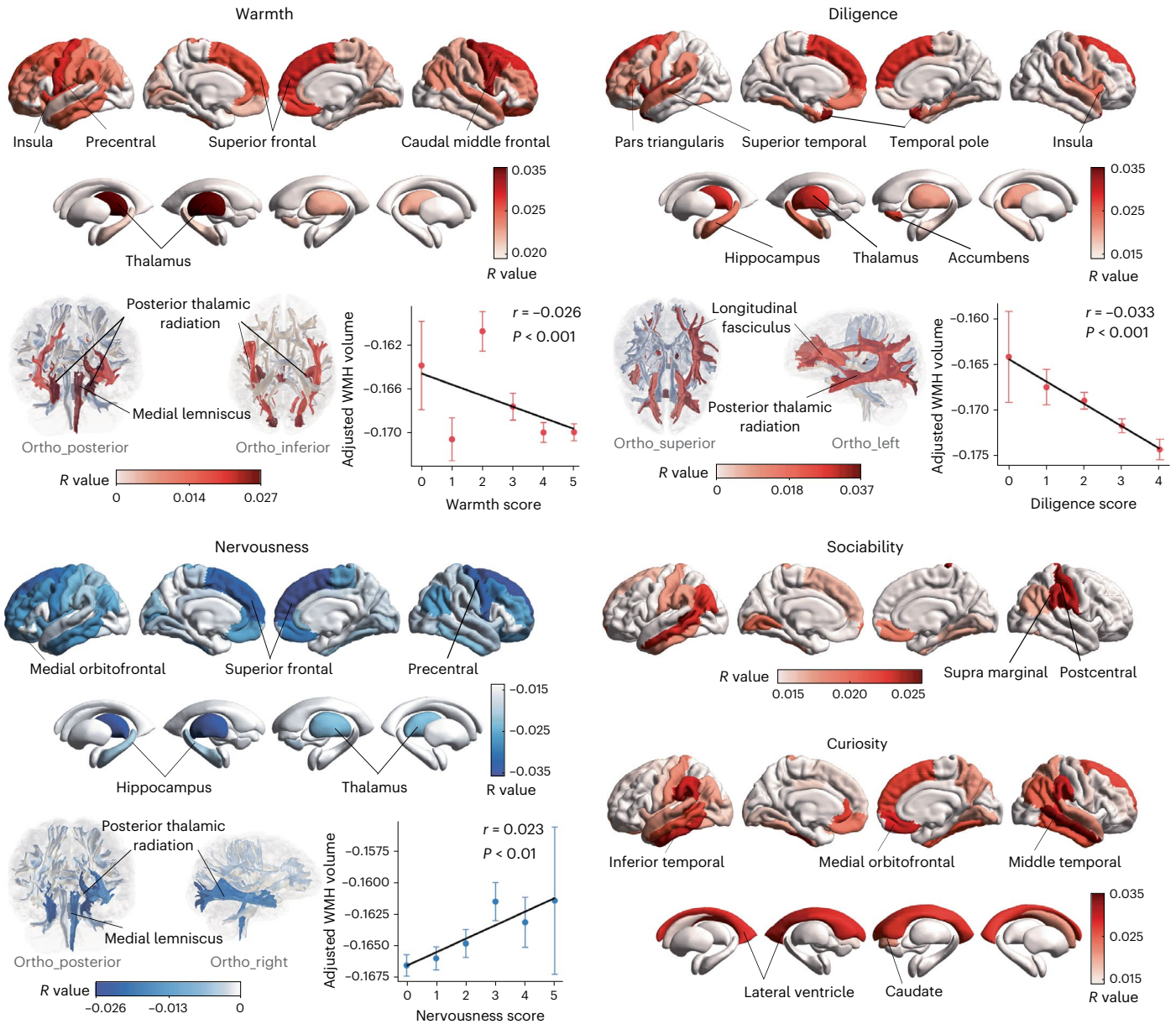

Fig. 4 | Associations of personality traits with brain structures. For each personality trait, the brain structures including cortical regions (volume for warmth, nervousness, sociability, curiosity and thickness for diligence, n = 22,419, 22,232, 23,090, 22,704 and 22,115 participants, respectively), subcortical structures (volume, n = 22,419, 22,232, 23,090, 22,704 and 22,115 participants, respectively), white matter tracts (FA value, n = 21,070, 20,891, 21,695, 21,312 and 20,783 participants, respectively) and WMHs (n = 18,294, 18,120, 18,751, 18,461 and 17,972 participants, respectively) were estimated by linear regression adjusted for covariate age at baseline, sex, ethnicity, education, systolic blood pressure, diastolic blood pressure and imaging scanning sites. Data are presented as mean ± s.d. for the linear regression analyses of WMHs and personality traits, and t-test was utilized to obtain the two-sided P values. $P = 5 \times 10^{-4}$ for warmth, 7×10^{-6} for diligence and 0.002 for nervousness.

barrier is necessary to maintain proper neuronal function[65,66]. Furthermore, inflammation has been shown to impact neural circuits in certain brain structures altered in brain disorders[67]. Therefore, together with our brain imaging analysis, we suggest that inflammation may mediate some of the effects of personality traits on brain health.

Potential implications, strengths and limitations

Based on the present findings, there are several practical implications and potential applications for future research. First, understanding the relationship between personality traits and brain disorders could contribute to the identification of at-risk individuals. Furthermore, as revealed by recent studies, there are intervention strategies to modify personality. If the modification of personality toward a lower risk direction could decrease the incidence of brain disorders, corresponding targeted prevention trials could be conducted. Then, elucidating the biological indicators in the pathways between personality traits and brain disorders could provide new clues for the aetiology of brain disorders.

The major strengths of our study include a dataset of large size, a prospective design with long-term follow-up, multiple phenotypes and genotypes and the incorporation of brain morphometric measures, peripheral inflammatory markers and serum metabolomics.

We acknowledge several limitations of our study. First, the definitions of personality traits are not strictly based on standard BFI assessment scales. However, UKB questionnaires provide effective estimates

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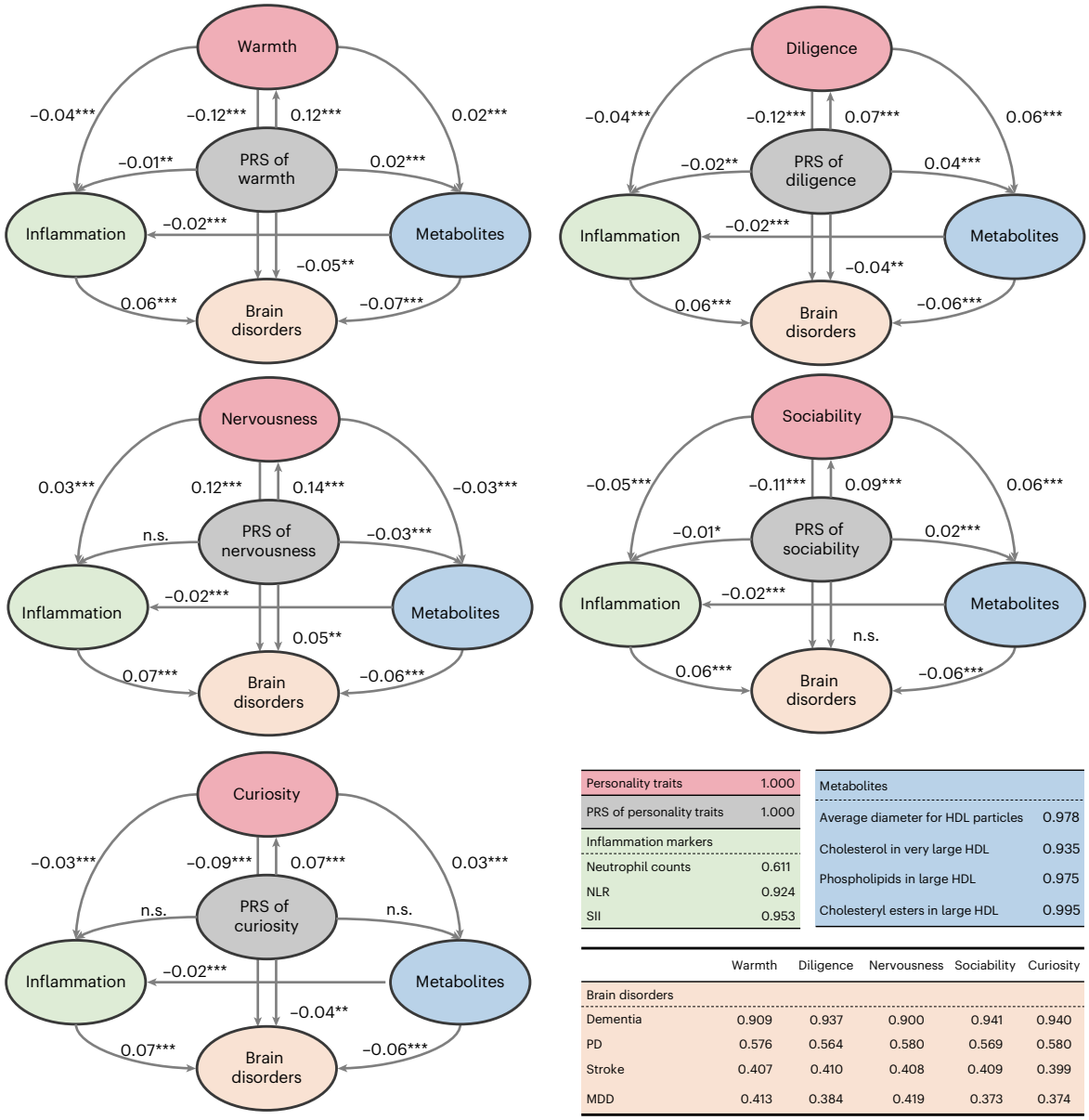

Personality traits	1.000
PRS of personality traits	1.000
Inflammation markers	
Neutrophil counts	0.611
NLR	0.924
SII	0.953

Metabolites	
Average diameter for HDL particles	0.978
Cholesterol in very large HDL	0.935
Phospholipids in large HDL	0.975
Cholesteryl esters in large HDL	0.995

	Warmth	Diligence	Nervousness	Sociability	Curiosity
Brain disorders					
Dementia	0.909	0.937	0.900	0.941	0.940
PD	0.576	0.564	0.580	0.569	0.580
Stroke	0.407	0.410	0.408	0.409	0.399
MDD	0.413	0.384	0.419	0.373	0.374

Fig. 5 | Structural equation model results. Standardized coefficients are shown. Latent variables including personality traits, brain disorders, PRS of personality traits, inflammation markers and metabolites were estimated in the model, which are shown with magenta, pink, grey, green and blue tables, respectively. Wald tests were used in the SEM analyses to obtain the two-sided *P* values. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. n.s., not significant.

of BFI for participants that have been validated elsewhere[68,69]. Second, the brain imaging data were acquired 4 years after the personality data were obtained. The relationship between personality and brain structure should be interpreted with caution. Third, this analysis only included inflammatory cells and C-reactive protein (CRP) captured in the UKB, but this is not exhaustive of inflammatory markers. Therefore, future investigations would benefit from a more comprehensive panel. Fourth, although we conducted longitudinal analyses and excluded brain disorder cases within the first 5 years of follow-up, the possibility that personality change is a prodromal feature rather than a risk factor for brain disorders still exists. Fifth, in SEM analysis, we excluded schizophrenia and bipolar affective disorder due to the small case number, which might limit the comprehensiveness of our work. Sixth, network modelling may reveal other inter-relationships between personality traits, brain health and biological indicators, which could be applied in future research. Seventh, we did not perform the external validation because comprehensive data of personality traits, brain disorders, brain imaging, genomics, inflammation and metabolites in a large population with a long follow-up time period from other cohorts are unavailable. Thus, our findings were limited to a specific dataset, country and admixtures, which might lack global representativeness. Meanwhile, we focused primarily on participants of white ancestry, which may limit the generalizability of our findings to other ethnic groups. Future research with different settings is encouraged to validate our findings. Finally, selection bias existed, as participants from UKB are more affluent and healthier than the general UK population[70], which might lead to a more conservative effect size.

Conclusion

All in all, personality traits predict brain health. For brain disorders, nervousness is deleterious, while the other four personality traits, including warmth, diligence, sociability and curiosity, have protective

effects. The relationships are complemented by the analyses targeting underlying mechanisms, in which nervousness is associated with alterations in the structure of the cortex and subcortex, lower connectivity of white matter tracts and higher WMHs. The other four personality traits have significant associations but with effects in the opposite direction. We have also demonstrated that personality traits can involve peripheral pathways through inflammatory cells and metabolites. Together, our study has pin-pointed a critical role of personality in brain disorders, providing new perspectives to develop strategies for maintaining brain health. However, some key questions remain: (1) can personality traits be fundamentally changed, and (2) will the change help maintain brain health?

Methods

Participants

Our study adopted data from UKB, a large-scale longitudinal cohort database containing in-depth genetic and health information of half a million UK participants (https://www.ukbiobank.ac.uk/). The UKB enroled the participants aged 40–69 years between 2006 and 2010 for baseline assessments in 22 centres across the United Kingdom[71]. The assessment visits comprised interviews and questionnaires covering lifestyles and health conditions, physical measures, biological samples, imaging and genotyping. The database is linked to national health datasets, including primary care, hospital inpatient, death and cancer registration data. Ethics approval for the UKB study was obtained from the North West Multicenter Research Ethical Committee (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics). This study utilized the UK Biobank Resource under application number 19542. All included participants gave written informed consent. Firstly, we included 497,091 participants with available personality traits facets information. Then we excluded participants with dementia, PD, stroke, schizophrenia, bipolar affective disorder, MDD and anxiety disorder at baseline (N = 60,500), participants with follow-up duration less than 5 years until July 2022 (N = 5,676), and participants aged under 50 (N = 82,656). Finally, we included 298,259 participants in the primary analysis. The mean age of the included participants was 60.32 years and 53.97% of them were women. The demographical information among different incident brain disorder groups is presented in Table 1.

Personality traits

We investigated the score-level personality traits in primary analyses. A variety of structural frameworks for personality have been proposed in recent years. One study integrating frequently-used personality models indicated that a model of five personality traits comprising agreeableness, conscientiousness, neuroticism, extraversion and openness occupied an important, unique position in the hierarchy of personality[72]. The model has demonstrated strong psychometric properties and accounts for substantial variance in normal-range personality and personality disorders[73]. Since there is no specific validated personality scale within the UKB, we incorporated a hierarchy method[68] to generate proxies for the five personality traits, including warmth (agreeableness), diligence (conscientiousness), nervousness (neuroticism), sociability (extraversion) and curiosity (openness), by utilizing data from touchscreen questionnaires on psychological factors, mental health and social support completed by the participants at the baseline assessment. The selected questions and corresponding field identification for the five personality traits were summarized in Supplementary Table 8. Each question accounts for one point in generating the score of personality traits; based on the score, the proxies of warmth and nervousness were between 0 and 5, and the proxies of diligence, sociability and curiosity were between 0 and 4. These personality trait proxies were initially established in a study focusing on personality and myocardial infarction in UKB[68], the validity of which in predicting disease was proven by another study focusing on strokes[69]. We also evaluated the longitudinal stability of five personality trait proxies by calculating the linear associations of the baseline personality traits scores (2006–2010) with their corresponding follow-up scores (2014+) and adjusting for covariates of age, sex, ethnicity, socioeconomic status, education, body mass index, smoking and drinking status. We found that baseline personality trait scores were nicely correlated with their corresponding follow-up scores, including warmth (β = 0.62, P < 0.001), diligence (β = 0.44, P < 0.001), nervousness (β = 0.62, P < 0.001), sociability (β = 0.46, P < 0.001) and curiosity (β = 0.48, P < 0.001), which also validate the reliability of our personality trait proxies. In addition, we estimated the phenotypic correlations among five personality trait proxies in UKB and compared them with correlations among the standard BFI personality traits in the Human Connectome Project (N = 1,206) using Pearson correlation analyses. All phenotypic correlations among the personality trait proxies in UKB were significant (P < 0.001), which were consistent with that among the standard BFI personality traits in Human Connectome Project, except for curiosity - nervousness (P = 0.582) (Supplementary Table 9). Additionally, the correlation directions were consistent in two cohorts, which further validated the reliability of our personality scale. All participants (N = 298,259) were included in primary analyses with at least one personality trait score available, comprising participants with data of warmth (N = 268,476), diligence (N = 266,062), nervousness (N = 267,350), sociability (N = 280,546) and curiosity (N = 276,105).

In secondary analyses, we stratified the participants into groups with different dominant personality traits by K-means clustering[74,75], an unsupervised machine learning algorithm that splits the sample into collections of aggregated data points based on pre-defined similarities. The algorithm started by randomly choosing k observations from the dataset and taking them as the initial centroids for the clusters. It then performed iterative calculations to optimize the positions of the centroids until stabilization. Specifically, the optimization procedure was mathematically processed to minimize the within-cluster sum of square distances between the standardized five personality traits. The determination of the optimal number of clusters leveraged the Elbow method by sequentially adding another cluster until there was no substantial drop of within-cluster sum of squares. Overall, participants with all five personality traits scores available (N = 228,865) in our study were grouped into three clusters based on the similarities shared across the five personality traits. Cluster 1 was labelled 'nervous-dominant' for its notably higher level of nervousness (N = 61,432). Compared to cluster 1, clusters 2 and 3 had higher scores of warmth and sociability, which were labelled together as 'warm-social'. When comparing cluster 2 with cluster 3, cluster 2 had a higher curiosity score and a lower diligence score. Hence, cluster 2 was labelled 'warm-social-curious' (N = 56,236), while cluster 3 was labelled 'warm-social-diligent' (N = 111,197).

Brain disorders

The selected outcomes covered a variety of brain disorders, including neurological diseases (dementia, PD and stroke) and psychiatric disorders (schizophrenia, bipolar affective disorder, MDD and anxiety disorder). The brain disorders were ascertained and classified according to the corresponding three-character International Classification of Diseases codes (Supplementary Table 8), extracted from UKB health outcome datasets' first occurrences of health outcomes (category 1712) and algorithmically defined outcomes (category 42). Specifically, the dementia cases were defined as all-cause dementia containing Alzheimer's disease, vascular dementia, frontotemporal dementia, dementia with Lewy bodies and dementia in other neurodegenerative or specified diseases. The stroke cases consisted of ischaemic stroke (transient cerebral ischaemic attacks and cerebral infarction), haemorrhagic stroke (intracerebral haemorrhage and subarachnoid haemorrhage) and stroke not specified as haemorrhage or infarction. Follow-up visits began from the date of attending the assessment centre (field 53) to the earliest date of any brain disorder diagnosis, date of death (field 40000) or the last available date from the hospital

inpatient data (field 41280–41281) or primary care data (field 42040), whichever occurred first. Among included 298,259 participants, 32,035 participants were diagnosed with at least one brain disorder during the follow-up time period, comprising dementia (N = 6,041), PD (N = 2,239), stroke (N = 9,199), schizophrenia (N = 183), bipolar affective disorder (N = 309), MDD (N = 8,832) and anxiety disorder (N = 11,346).

Brain imaging

UKB brain magnetic resonance imaging data were acquired in 23,090 participants approximately 4 years after personality assessment on a standard Siemens Skyra 3 T scanner with a 32-channel head coil. The sequence parameters have been published previously[76], and the protocol is accessible[77].

The brain structural data were derived from quality-controlled T1-weighted neuroimaging data, which was processed with FreeSurfer. The cortical regions' surface areas, volumes and mean thickness were extracted via FreeSurfer's surface templates derived atlas phenotypes[78]. The subcortical regions' volumes were extracted via FreeSurfer's aseg tool[79]. FreeSurfer aparc (category 192) and aseg (category 190) atlases corresponding to 68 cortical regions and 40 subcortical regions were used in this study. The Qoala-T approach was used to check FreeSurfer outputs, supplemented by manual checking of outputs close to the threshold. Any FreeSurfer outputs that failed to pass quality control were excluded from the FreeSurfer imaging-derived phenotypes. Among included 298,259 participants, brain structural data were available in 23,090 participants.

The diffusion tensor imaging (DTI) data were pre-processed and analysed by the UKB brain imaging team using the FMRIB Software Library (FSL) version 6.0. The DTI data were corrected using FSL Diffusion Toolbox for diffusion modelling and tractography analysis. The DTI measures included FA and MD values, corresponding to the directionality of diffusion and the overall diffusivity accordingly in 27 white matter tracts (category 135). Among the included 298,259 participants, DTI data were available in 21,695 participants.

The total volume of WMHs was calculated from the T2-weighted fluid-attenuated inversion recovery images using Brain Intensity Abnormality Classification Algorithm[80] (field 25781). The WMHs load was logit-transformed to normalize and stabilize the variance. Among included 298,259 participants, WMH volume data were available in 21,296 participants.

Genomics

GWAS of personality traits. To understand the genetic basis of personality traits, we performed GWAS of the five personality traits using the same standards for phenotype construction. There were 488,377 participants with available genotype data in UKB. The genetic analysis was restricted to samples with white British ancestry as determined by the 'in.white.British.ancestry.subset' column in the quality control file 'ukb_sqc_v2.txt'. Individuals with self-reported (field 31) and genetic-inferred sex (field 22001) mismatches, putative sex chromosome aneuploidy ('putative.sex.chromosome.aneuploidy' column), heterozygosity outliers ('het.missing.outliers' column), relatedness ('excess.relatives' column), not used in principal component calculation ('used_in_pca_calculation' column) and missing genotype rate of more than 5% were excluded. Finally, we included 337,156 participants in personality traits GWAS comprising warmth (N = 304,135), diligence (N = 301,291), nervousness (N = 302,916), sociability (N = 318,867) and curiosity (N = 311,512). We next applied standard quality control procedures to the imputed variants (call rate >0.95, minor allele frequency >0.005, imputation quality score >0.8 and Hardy–Weinberg $P > 1 \times 10^{-6}$) provided by UKB[81] and tested their associations with personality scales by linear regression assuming an additive model using PLINK 2.0 (ref. 82). The adjusted covariates included age, sex, socioeconomic status, genotype array type and the top ten genetic principal components.

The genomic risk loci characterization and variant annotation were conducted using the FUMA platform (http://fuma.ctglab.nl/)[83]. Briefly, FUMA first identified independent significant variants at the Bonferroni corrected threshold ($r^2 < 0.6$, $P < 5 \times 10^{-8}$). Lead variants were then chosen on the basis of independent significant variants in linkage equilibrium with each other at $r^2 < 0.1$. Genomic risk loci were identified by merging lead variants closer than 250 kb. ANNOVAR annotations were used to map variants to the nearest genes[84]. The single nucleotide polymorphism-based heritability was calculated using linkage disequilibrium score regression and the pre-calculated European 1000 Genomes Project phase 3 linkage disequilibrium scores were obtained as linkage disequilibrium reference[85].

PRS of personality traits. To avoid sample overlap between the base and the target data, we split the participant samples into two parts. Briefly, we re-performed the personality-specific GWAS using the participants not included in the SEM analysis with the same parameter and quality control criteria used in the GWAS mentioned above (N = ~271,464–302,654). We calculated the personality-specific PRS for those included in the SEM analysis (N = 40,549) by summing the product of the number of risk alleles by the effect size of each risk allele. The classic clumping and thresholding method was used to generate PRS in PRSice2 using the default parameter (–clump-kb 250 kb–clump-r2 0.1) (ref. 86). For each participant, we used 14 different P value thresholds to select variants ($P < 5 \times 10^{-8}$, 1×10^{-6}, 5×10^{-6}, 1×10^{-5}, 5×10^{-5}, 1×10^{-4}, 5×10^{-4}, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5 and 1).

Inflammation. Inflammatory markers were collected from blood count data (category 100081) and blood biochemistry data (category 17518). The detailed blood sample processing and analysing steps can be found in the UKB data sources (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100080). We extracted baseline count data of neutrophils, monocytes, platelets, lymphocytes and the concentration data of CRP. Furthermore, we calculated four ratios based on blood cell counts including NLR (neutrophils/lymphocytes), platelet-to-lymphocyte ratio (PLR) (platelets/lymphocytes), SII (neutrophils × platelets/lymphocytes) and lymphocyte-to-monocyte ratio (LMR) (lymphocytes/monocytes). Among included 298,259 participants, inflammatory marker data were available in 291,477 participants.

Metabolites. Nuclear magnetic resonance metabolic biomarkers were generated by Nightingale Health. A total of 249 metabolic biomarkers (category 220) were measured from randomly selected ethylenediaminetetraacetic acid plasma samples using a high-throughput nuclear magnetic resonance-based metabolic biomarker profiling platform developed by Nightingale Health Ltd. The biomarkers span multiple metabolic pathways, including lipoprotein lipids, fatty acids, fatty acid compositions and various low molecular weight metabolites, such as amino acids, glycolysis metabolites and ketone bodies quantified in molar concentration units. Among the included 298,259 participants, metabolic biomarkers data were available in 70,198 participants.

Statistical analysis. Baseline characteristics of participants were summarized for those with and without incident brain disorder status as mean and s.d. for continuous variables and as a number and percentage for categorical variables.

Multivariable time-varying Cox proportional hazards regression models were used to estimate longitudinal associations for each personality trait with risks of each brain disorder and the results were presented with HR and 95% CI. The missing data were deleted in the analyses. For neurodegenerative and psychiatric disorders, age at baseline, sex, ethnicity and education were adjusted; for stroke, age at baseline, sex, ethnicity, and systolic and diastolic blood pressure were adjusted. Multiple comparisons were corrected by FDR corrections (α = 0.05) and proportional hazards of the associations were

tested using Schoenfeld's residuals without indicating a violation of the model assumptions except for associations between personality traits and anxiety disorder. The relationships between personality clusters and brain disorder risks were examined separately with clusters 1 or 2 as a reference. Wald test were utilized in the Cox proportional hazard regression to test whether the beta was 0 and obtained the two-sided *P* values. Then we performed the sex-stratified analysis to investigate whether heterogeneity existed between men and women with regard to the influence of personality on disease risks.

We performed MR to estimate the association between genetically predicted personalities and the risks of brain disorders. The summary statistics of dementia[22], stroke[23], PD[24], schizophrenia[25], bipolar affective disorder[26] and MDD[27] were obtained from large consortia with European samples that did not overlap with ours. We selected genetic instruments for personality traits based on the genome-wide significance threshold $P < 5 \times 10^{-6}$. Linkage disequilibrium clumping ($r^2 > 0.001$) was performed to select independent instrumental variables associated with the exposure based on the 1000 Genomes European reference panel. We then harmonized the exposure and outcome datasets and pooled the MR estimates for each variant using the IVW, weighted median, weighted mode and Egger methods, and the results were presented with OR and 95% CI. IVW method was implemented as the primary method[87]. However, the results of IVW method can be biased when there is horizontal pleiotropy. Under this circumstance, we would further conduct sensitivity analyses using weighted median[88], weighted mode[89] and Egger methods[90]. The *t*-test was utilized in the MR analyses to derive the two-sided *P* values. The heterogeneity was assessed by IVW *Q* statistic and the pleiotropy was quantified with the Egger intercept. All MR analyses were performed by the R package TwoSampleMR[91].

Linear regression models were utilized to investigate the associations of personality traits with brain morphometric measures involving cortical structures areas, volumes and thickness, subcortical structures volumes, FA and MD values of white matter tracts revealed in DTI and the total volume of WMHs, adjusting for covariates of age at baseline, sex, ethnicity, education, systolic blood pressure, diastolic blood pressure and imaging scanning sites. We also incorporated the linear regression model to examine the associations of personality traits with inflammatory and metabolic biomarkers levels, adjusting for covariate age at baseline, sex, ethnicity, education, systolic blood pressure and diastolic blood pressure. The *t*-test was used in the linear regression to derive the two-sided *P* values. The correlation coefficients (*R* values) were obtained for the linear associations, and FDR-corrected *Q* values ($\alpha = 0.05$) were reported.

The SEM was performed to determine the directional dependencies of personality traits and their PRS with brain disorders, which were mediated by inflammation and metabolite paths. We included 40,549 participants with data of personality traits and their PRS and brain disorders status, as well as inflammatory and metabolic biomarkers at the same time. The latent variables were estimated in the model using confirmatory factor analysis. PRS of personality traits were estimated via the corresponding score of warmth, diligence, nervousness, sociability and curiosity. The latent variable of brain disorders was constructed by the onset status of dementia, PD, stroke and MDD, after excluding schizophrenia and bipolar affective disorder due to the small case number. The latent variable of inflammation and metabolites was measured in the model using the inflammatory markers and metabolites significantly correlated with personality traits, of which the correlation was pre-estimated by linear regression models mentioned before. Wald tests were used in the SEM analyses to derive the two-sided *P* values. Cutoff values, comparative fit index of 0.95, root mean squared error of approximation <0.05 and standardized root mean squared residual <0.08 (ref. 92), were needed to achieve a relatively good fit between the hypothesized model and the observed data for SEM.

The statistical analyses were performed using R statistical software (http://www.r-project.org/). Statistical significance was determined by a two-tailed *P* value <0.05. An FDR correction was applied when appropriate.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The main data used in this study were accessed from the publicly available UK Biobank Resource under application number 19542, which cannot be shared with other investigators. The GWAS data of brain disorders were retrieved from the exogenous population which is publicly available (dementia: https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_DEMENTIA/, PD: https://gwas.mrcieu.ac.uk/datasets/ieu-a-812/, stroke: http://megastroke.org/download.html, schizophrenia: https://pgc.unc.edu/for-researchers/download-results/, bipolar affective disorder: https://pgc.unc.edu/for-researchers, and MDD: https://pgc.unc.edu/for-researchers/download-results/).

Code availability

Packages including survival 3.2, TwoSampleMR and lavaan 0.8 in R version 4.0.0 were used to perform Cox proportional hazards regression model, MR study and structural equation model, respectively. PLINK 2.0 was used to perform genome-wide association analysis and PRSice2 was used to calculate the PRS. Freesurfer v6.0 and FSL 6.0 were used to process the imaging data, and MATLAB 2018b was used to perform corresponding linear association analysis. Scripts used to perform the analyses are available at https://github.com/yuzhulineu/UKB_personality.

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Author contributions

All authors had full access to the data in the study and accepted responsibility to submit them for publication. J.-T.Y. designed the study. Y.-R.Z. and Y.-T.D. conducted the primary analyses and drafted the manuscript. Y.-Z.L., R.-Q.Z., Y.-J.G., B.-S.W., W.Z. and K.K. contributed to imaging, SEM and genetic data analyses. J.-T.Y., W.C., J.-F.F., B.J.S., J.S. and A.D.S. critically revised the manuscript, and all authors approved the final version.

Competing interests

The authors declare no competing interests.

Additional information

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Software and code

Policy information about availability of computer code

Data collection	No software was involved in data collection (data used is all directly available from UK Biobank, as described in detail in the paper)
Data analysis	R version 4.0.0 packages: survival 3.2 was used to perform Cox proportional hazard regression model; TwoSampleMR 0.5.6 was used to perform Mendelian randomization study; lavaan 0.8 was used to perform structural equation model. PLINK 2.0 and PRSice2 were used to perform genome-wide association analysis and calculate the polygenic risk score respectively; Freesurfer v6.0 and FSL 6.0 were used to process the imaging data and Matlab 2018b was used to perform corresponding linear association analysis. FSL v5.0.10 BIANCA (Brain Intensity AbNormality Classification Algorithm) were utilized for automated segmentation of white matter hyperintensities. Scripts used to perform the analyses are available at https://github.com/yuzhulineu/UKB_personality.

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The main data used in this study were accessed from the publicly available UK Biobank Resource under application number 19542, which cannot be shared with other investigators. The GWAS data of brain disorders were retrieved from exogenous population which is publicly available (Dementia: https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_DEMENTIA/, PD: https://gwas.mrcieu.ac.uk/datasets/ieu-a-812/, stroke: http://megastroke.org/download.html, Schizophrenia: https://pgc.unc.edu/for-researchers/download-results/, bipolar affective disorder: https://pgc.unc.edu/for-researchers, and MDD: https://pgc.unc.edu/for-researchers/download-results/).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	We took sex into considerations in our study and our findings could apply to both male and female. Sex (Field ID 31) in the UK Biobank was determined based on self-reporting data via questionaire, and all included 298,259 participants gave written informed consent for sharing of individual-level data.
Population characteristics	At baseline, a total of 298,259 participants were included in the main analyses (mean (SD) age, 60.32 (5.41) years; 53.97% women). During a median 9.49 (Q1, 7.56; Q3, 11.26) years of follow-up, 6041 individuals were diagnosed with dementia, 2239 with PD, 9199 with stroke, 183 with schizophrenia, 309 with bipolar affective disorder, 8832 with MDD, and 11,346 with anxiety disorder. The baseline demographic and personality characteristics of participants stratified by incident brain disorder is presented in Table 1. We calculated descriptive statistics as mean (SD) for continuous variables and number (percentage) for categorical variables.
Recruitment	The UKB enrolled the participants aged 40-69 years between 2006 and 2010 for baseline assessments in 22 centers across the UK. The assessment visits comprised interviews and questionnaires covering lifestyles and health conditions, physical measures, biological samples, imaging, and genotyping. The database is linked to national health datasets, including primary care, hospital inpatient, death, and cancer registration data. We included all participants with available personality traits facets information. Previous investigation showed UK biobank subject to a healthy sample bias.
Ethics oversight	UK Biobank has approval from the North West Multi-centre Research Ethics Committee (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics) as a Research Tissue Bank approval and provides oversight for this study. Written informed consent was obtained from all participants.

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Life sciences study design

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Sample size	No statistical methods were used to predetermine sample sizes. Firstly, we included 497,091 participants with available personality traits facets information. Then we excluded participants with dementia, PD, stroke, schizophrenia, bipolar affective disorder, MDD, and anxiety disorder at baseline (N: 60,500); participants with follow-up duration less than five years until July 2022 (N: 5676); participants aged under 50 (N: 82,656). Finally, 298,259 participants over 50 years old with available personality data who had at least five years of follow-up until July 2022 were included. These sample sizes are sufficient for the analyses according to the previous published studies using data from UK Biobank.
Data exclusions	Participants with dementia, PD, stroke, schizophrenia, bipolar affective disorder, MDD, and anxiety disorder at baseline were excluded. Considering that the personality trait change could be one of the preclinical symptom of brain disorders, we excluded the ones diagnosed with any of the studied brain disorder to avoid the reverse causality, which is consistent with previous studies.
Replication	All available data were used to maximize statistical power of the analysis therefore we did not repeat the analysis.

Randomization	Covariates including age at baseline, sex, ethnicity, education, scanning site of imaging, and systolic and diastolic blood pressure were adjusted in the study.
Blinding	Blinding was not applicable to this study as this study is observational.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
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☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Magnetic resonance imaging

Experimental design

Design type	Structural MRI
Design specifications	UK Biobank designed the imaging acquisition protocals including 6 modalities, covering structural, diffusion and functional imaging. The collection order is T1-weighted structural image, resting-state functional MRI, task functional MRI, T2-weighted FLAIR structural image, Diffution MRI and susceptibility-weighted imaging. T1-weighted structural image was acquired using straight sagittal orientation for 5 minutes.
Behavioral performance measures	Proxies for the five personality traits were generated by utilizing data from touchscreen questionnaires on psychological factors, mental health and social support completed by the participants at the baseline assessment. The selected questions and corresponding Field ID for the five personality traits were summarized in Supplementary Table 1.

Acquisition

Imaging type(s)	T1-weighted structural imaging, T2-weighted FLAIR structural imaging, Diffusion imaging
Field strength	3T
Sequence & imaging parameters	T1-weighted structural imaging Resolution: 1x1x1 mm Field-of-view: 208x256x256 matrix Duration: 5 minutes 3D MPRAGE, sagittal, in-plane acceleration iPAT=2, prescan-normalise The superior-inferior field-of-view is large (256mm), at little cost, in order to include reasonable amounts of neck/ mouth, as those areas will be of interest to some researchers. T2-weighted FLAIR structural imaging Resolution: 1.05x1x1 mm Field-of-view: 192x256x256 matrix Duration: 6 minutes 3D SPACE, sagittal, in-plane acceleration iPAT=2, partial Fourier = 7/8, fat saturation, elliptical k-space scanning, prescannormalise After early piloting, a standard T2/PD-weighted acquisition was dropped due to a combination of factors such as overall value and timing practicalities. However a T2-weighted FLAIR image is acquired, which is generally of good quality and which shows strong contrast for white matter hyperintensities.
Area of acquisition	Whole brain

Diffusion MRI ☒ Used ☐ Not used

Parameters: Resolution: 2x2x2 mm

Parameters	Field-of-view: 104x104x72 matrix Duration: 7 minutes (including 36 seconds phase-encoding reversed data) 5x b=0 (+3x b=0 blip-reversed), 50x b=1000 s/mm2 , 50x b=2000 s/mm2 Gradient timings: δ=21.4 ms, Δ=45.5 ms; Spoiler b-value = 3.3 s/mm2 SE-EPI with x3 multislice acceleration, no iPAT, fat saturation For the two diffusion-weighted shells, 50 distinct diffusion-encoding directions were acquired (and all 100 directions are distinct). The diffusion prepraration is a standard ("monopolar") Stejskal-Tanner pulse sequence. This enables higher SNR due to a shorter echo time (TE=92ms) than than a twice-refocused ("bipolar") sequence. This improvement comes at the expense of stronger eddy current distortions, which are removed in the image processing pipeline.

Preprocessing

Preprocessing software	Imaging derived phenotypes (IDP) generated by an imaging-processing pipeline developed and run on behalf of UK Biobank were used in the study. T1 images were processed with Freesurfer, surface templates were utilized to extract imaging derived phenotypes (IDP) referring to atlas regions' surface area, volume and mean cortical thickness42. Subcortical regions were extracted via FreeSurfer's aseg tool. The full processing pipeline is openly available here: http://doi.org/10.1016/j.neuroimage.2017.10.034. The diffusion tensor imaging (DTI) data were preprocessed and analyzed by the UK Biobank brain imaging team using the FMRIB Software Library (FSL) version 6.0. The DTI data was corrected using FSL Diffusion Toolbox for diffusion modeling and tractography analysis. The DTI measures included FA and MD values, corresponding to the directionality of diffusion and the overall diffusivity accordingly in 27 white matter tracts. The total volume of WMHs was calculated from the T2-weighted fluid-attenuated inversion recovery images using Brain Intensity Abnormality Classification Algorithm. The WMHs load was logit-transformed to normalize and stabilize the variance.
Normalization	see above
Normalization template	fsaverage
Noise and artifact removal	see above
Volume censoring	see above

Statistical modeling & inference

Model type and settings	Linear regression models
Effect(s) tested	The correlation coefficients (R values) were obtained for the linear regression models

Specify type of analysis: ☒ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016)	Voxel-wise association
Correction	False discovery rate (FDR) correction

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis