

1 **Nine Neuroimaging-AI Endophenotypes Unravel Disease** 2 **Heterogeneity and Partial Overlap across Four Brain Disorders: A** 3 **Dimensional Neuroanatomical Representation**

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31 **Abstract**

32 Disease heterogeneity poses a significant challenge for precision diagnostics. Recent work
33 leveraging artificial intelligence has offered promise to dissect this heterogeneity by identifying
34 complex intermediate brain phenotypes, herein called dimensional neuroimaging
35 endophenotypes (DNEs). We advance the argument that these DNEs capture the degree of
36 expression of respective neuroanatomical patterns measured, offering a dimensional
37 neuroanatomical representation for studying disease heterogeneity and similarities of neurologic
38 and neuropsychiatric diseases. We investigate the presence of nine such DNEs derived from
39 independent yet harmonized studies on Alzheimer's disease (AD1-2)¹, autism spectrum disorder
40 (ASD1-3)², late-life depression (LLD1-2)³, and schizophrenia (SCZ1-2)⁴, in the general
41 population of 39,178 participants in the UK Biobank study. Phenome-wide associations revealed
42 prominent associations between the nine DNEs and phenotypes related to the brain and other
43 human organ systems. This phenotypic landscape aligns with the SNP-phenotype genome-wide
44 associations, revealing 31 genomic loci associated with the nine DNEs (Bonferroni corrected P-
45 value < $5 \times 10^{-8}/9$). The DNEs exhibited significant genetic correlations, colocalization, and causal
46 relationships with multiple human organ systems and chronic diseases. A causal effect (odds
47 ratio=1.25 [1.11, 1.40], P-value= 8.72×10^{-4}) was established from AD2, characterized by focal
48 medial temporal lobe atrophy, to AD. The nine DNEs, along with their polygenic risk scores,
49 significantly enhanced the predictive accuracy for 14 systemic disease categories, particularly for
50 conditions related to mental health and the central nervous system, as well as mortality
51 outcomes. These findings underscore the potential of the nine DNEs to capture the expression of
52 disease-related brain phenotypes in individuals of the general population and to relate such
53 measures with genetics, lifestyle factors, and chronic diseases. All results are publicly available
54 at <https://labs-laboratory.com/medicine/>.

55 Main

56 Disease heterogeneity^{2,3,5-10} has been a significant challenge for precision medicine¹¹. A new era
57 powered by artificial intelligence (AI) and large-scale, multi-omics biomarkers may enable us to
58 quantify individualized liability for various brain diseases^{12,13}. Recent work has leveraged semi-
59 supervised clustering methods (**Fig. 1a** and **Supplementary eMethod 1**) to tackle this challenge.
60 These methods characterize disease heterogeneity by constructing a mapping or transformation
61 from a reference group (e.g., healthy controls) to a target group (i.e., patients with a specific
62 disease). In clinical neuroscience, these methods can quantify deviation from typical brain
63 structure measured by T1-weighted magnetic resonance imaging (MRI)¹⁻⁴. They represent
64 disease-related neuroanatomical heterogeneity via multiple low-dimensional categorical subtypes
65 associated with specific patterns of brain change relative to the reference group. Instead of
66 focusing on the categorical subtypes, we investigated their corresponding continuous phenotypes
67 (i.e., dimensions)¹⁴, given that many chronic brain diseases develop along a continuous
68 spectrum. Each neuroanatomical pattern's level of expression, therefore, serves as a dimensional
69 AI-derived biomarker pertinent to the respective disease.

70 Previous heterogeneity research has primarily focused on within-disease
71 heterogeneity^{2,3,5-10}. However, this approach neglects the shared disease mechanisms, genetics,
72 and clinical manifestations among different brain diseases. Conversely, while several studies
73 have investigated the shared genetic components across various brain diseases, they have
74 overlooked the important aspect of disease heterogeneity within each condition^{15,16}. As such, a
75 broad perspective is required to investigate disease heterogeneity simultaneously, spanning
76 multiple neurodegenerative and neuropsychiatric disorders. This holistic approach aids in
77 understanding the commonalities and interrelationships between these brain diseases and the
78 multi-organ systems of humans¹⁷. Such an effort could simultaneously capture neurobiological
79 heterogeneity within disorders and explain shared features, mechanisms, and risk factors across
80 disorders. Ultimately, unraveling neurobiological heterogeneity within neuropsychiatric
81 syndromes and explaining co-morbidity among them promises to accelerate more effective
82 diagnosis, treatment, and prevention strategies.

83 These AI-derived biomarkers capture disease-specific neuroanatomic heterogeneity.
84 However, whether these biomarkers are present in the general population, potentially
85 simultaneously, remains unknown. Here, we sought to measure the presence of multiple AI-
86 based signatures in the general population, delineate common mechanisms among them, and
87 shed light on their relationship with other human organ systems^{18,19}. To do this, we capitalized
88 on nine imaging biomarkers recently derived from regional gray matter (GM) volumetrics
89 derived from several large-scale disease-focused consortia, including ADNI²⁰ for Alzheimer's
90 disease (AD1-2¹), ABIDE²¹ for autism spectrum disorder (ASD1-3²), LLD for late-life
91 depression older than 60 years old (LLD1-2³), and PHENOM⁴ for schizophrenia (SCZ1-2⁴).
92 Utilizing semi-supervised clustering and representation learning methodologies²², we obtained
93 nine imaging biomarkers capturing the neuroanatomical diversity across the four distinct brain
94 diseases. AD1 and AD2 illustrate distinct atrophy patterns in the overall brain and medial
95 temporal lobe, respectively¹. ASD1, ASD2, and ASD3 showcase reduced overall volume,
96 expanded subcortical volume, and increased cortical volume². LLD1 and LLD2³ exhibit
97 augmented subcortical volume and overall brain atrophy, respectively. Finally, SCZ1 and SCZ2⁴
98 display global brain atrophy and expanded basal ganglia volume. We first conceptualized these
99 biomarkers as the dimensional neuroimaging endophenotypes (DNE), seeking to test the
100 endophenotype hypothesis in psychiatry²³⁻²⁵, which suggests that such measurable intermediate

101 biomarkers (i.e., the endophenotypes) serve as intermediate phenotypes between genetics and
102 clinical symptoms of the disease. They are thought to be more closely related to the underlying
103 etiology and genetics than the complex clinical symptoms or the disease itself. Furthermore, the
104 concept of dimensional representation reinforces the idea that diseases like AD progress along a
105 continuous spectrum. As such, categorizing disease heterogeneity into distinct subtypes
106 overlooks the presence of co-existing patterns within the same individuals (refer to **Method 2a**
107 and **Supplementary eMethod 1a** for details).

108 We evaluated the manifestation of the nine DNEs in the general population using the
109 neuroimaging and genetic data available in the UK Biobank study²⁶ (UKBB, **Method 1**). The
110 four pre-trained disease-specific AI models (**Method 2**) were applied to the 39,178 UKBB
111 participants with both brain MRI²⁷ and genetic²⁸ data. To delineate the phenotypic landscape of
112 the nine DNEs, we first tested whether the neuroanatomical patterns of the nine DNEs are
113 present in the UKBB general population. Subsequently, we conducted a phenome-wide
114 association study (PWAS, **Method 3**) to establish associations between the nine DNEs and 611
115 UKBB phenotypes, including brain imaging-derived phenotypes (IDPs), traits related to multiple
116 human organ systems, cognition, and lifestyle factors. We performed a genome-wide association
117 study (GWAS, **Method 4**) linking the nine DNEs to 6,477,810 quality-checked common single
118 nucleotide polymorphisms (SNPs) to depict their genetic architecture. Furthermore, we
119 conducted analyses to investigate genetic correlations, colocalization, and causal relationships
120 between the nine DNEs, nine human organ systems¹⁷, and several chronic diseases. Finally, we
121 assessed the ability of the nine DNEs and their corresponding polygenic risk score (PRS) to
122 predict 14 systemic disease categories, 8 cognitive scores, and mortality (**Method 5**).

123

124 **Results**

125 Our analytic framework involves computational genomics, statistical methods, and machine
126 learning to elucidate the phenotypic landscape and genetic architecture of the nine DNEs, as
127 illustrated in **Fig. 1**.

128

144 (PWAS) were conducted to associate the nine DNEs with phenotypes across nine organ systems,
145 cognition, and lifestyle factors. Genome-wide association studies (GWAS) were performed to
146 investigate associations between the nine DNEs and common genetic variants (SNPs). Finally,
147 the nine DNEs and their polygenic risk scores predicted 14 disease categories (ICD-10-based), 8
148 cognitive scores, and mortality. CN: healthy control; PT: patient.

149

150 **All nine DNEs are evident in the general population**

151 We tested whether the neuroanatomical patterns defined in the four disease populations could be
152 found in the general population. We applied the DNE models pre-trained for each disease
153 population to the UKBB general population to measure the degree of expression of each DNE at
154 the individual level. The imaging data from the four disease populations and the UKBB general
155 population were first statistically harmonized via the iSTAGING consortium³⁰ and then linearly
156 corrected in the AI models for common confounders like demographics to alleviate potential
157 domain shifts³¹.

158 We first summarize the neuroanatomical patterns of the nine DNEs (**Fig. 2a** and **Method**
159 **3b**). Overall, the original patterns identified in the disease populations¹⁻⁴ manifest in the general
160 population. AD1 exhibits a pattern of brain atrophy (i.e., negative correlation) across various
161 brain volumes, while AD2 involves focal atrophy of the medial temporal lobe. ASD1 captures a
162 pattern of lower GM volumes in several subcortical regions, including the pallidum, amygdala,
163 and putamen, whereas ASD2 reflects a pattern of relatively larger GM volumes (i.e., positive
164 correlation) in subcortical regions. ASD3, conversely, is characterized by relatively larger GM
165 volumes in several cortical areas, including the insula. LLD1 (positive correlation) and LLD2
166 (negative correlation) are characterized by concomitant patterns of regional GM volumes,
167 prominently involving the middle frontal gyrus, the insula, and the thalamus. For schizophrenia,
168 a widespread pattern of reduced brain volumes (e.g., insula) is associated with SCZ1, whereas
169 SCZ2 displays increased volumes of the putamen and pallidum. The details of the P-value,
170 sample sizes, and β values of the linear regression are presented in **Supplementary eFile 1** (from
171 disease-specific populations¹⁻⁴) and **2** (from UKBB).

172 The nine DNEs showed different strengths of expression in the general population
173 relative to what is seen in the disease populations from which they were derived. These
174 differences were statistically significant except for ASD2, after correcting for multiple
175 comparisons using the Bonferroni method (**Fig. 2b**). For instance, AD1, characterized by diffuse
176 brain atrophy in the ADNI data, showed a significant under-expression (i.e., a smaller mean of
177 the DNE score) in the general population. Conversely, the subcortical atrophy pattern originally
178 identified in ASD1 from the ABIDE data displayed a significant over-expression (i.e., a larger
179 mean of the DNE score) in the participants from the general population.

180 We then tested whether the nine DNEs differed between the healthy control and disease
181 groups (AD, ASD, LLD, and SCZ; refer to **Method 1** for detailed definitions) in the general
182 UKBB population. Compared to the healthy control group ($N=6390$), a small proportion of
183 patients with the four brain diseases showed significant differences (two-sample t-test) for AD1-
184 2 ($N=23$), LLD1-2 ($N=1329$), and SCZ1-2 ($N=23$), except for ASD1-3 (only 6 ASD patients in
185 this population). For example, AD2, characterized by focal medial temporal lobe atrophy, had a
186 significantly lower mean of DNE in the healthy control (0.29 ± 0.19) compared to the AD patient
187 groups (0.45 ± 0.27 ; $P\text{-value}=1.1\times 10^{-4}$). Detailed statistics for all nine DNEs are presented in
188 **Supplementary eTable 1**.

189 These results proved that the nine DNEs manifest in the general population and convey
190 disease-specific information about the four brain diseases. The contrast in their expression (i.e.,
191 over- and under-expression) between the disease-specific and UKBB general populations is
192 expected and underscores their potential relevance as sub-clinical or vulnerability quantitative
193 indices.

194

195 **The nine DNEs exhibit phenotypic associations with traits beyond the brain**

196 To delineate their phenotypic landscape, we associated the nine DNEs with 611 phenotypes in
197 UKBB. To avoid circularity, the PWAS did not include the 119 GM ROIs derived from T1-
198 weighted MRI, from which the nine DNEs were derived. Out of the 611 additional clinical traits
199 spanning multiple organ systems, cognition, and lifestyle factors, we discovered 1818 significant
200 associations after applying the Bonferroni correction (P-value < 0.5/611) (**Fig. 2c**,
201 **Supplementary eFile 3**, and **Method 3c**).

202 Of the 1818 significant associations, 91% were related to the brain. For example, the
203 mean intracellular volume fraction in the superior frontal-occipital fasciculus derived from the
204 multi-shell NODDI³² model was significantly associated with AD1 [$\beta=-0.67\pm0.02$, $-\log_{10}(\text{P-}$
205 $\text{value}) > 300$]. Multiple DNEs were significantly associated with the biological age gap (BAG:
206 AI-predicted age minus chronological age) of the brain [e.g., SCZ2: $\beta=0.19\pm0.01$, $-\log_{10}(\text{P-}$
207 $\text{value})=50.10$]. Furthermore, 2% of the phenotypes related to the musculoskeletal system were
208 associated with the nine DNEs. The nine DNEs were also largely associated with many
209 phenotypes related to mental health (1%). For example, the neuroticism score was significantly
210 associated with LLD2 [$\beta=-1.09\times10^{-2}\pm2.42\times10^{-3}$, $-\log_{10}(\text{P-value})=5.20$] (**Supplementary eFile 3**).
211 A previous study suggests distinct neural mechanisms between older individuals with neurotic
212 and non-neurotic depression, indicating diverse biological pathologies contributing to varying
213 clinical presentations of LLD³³.

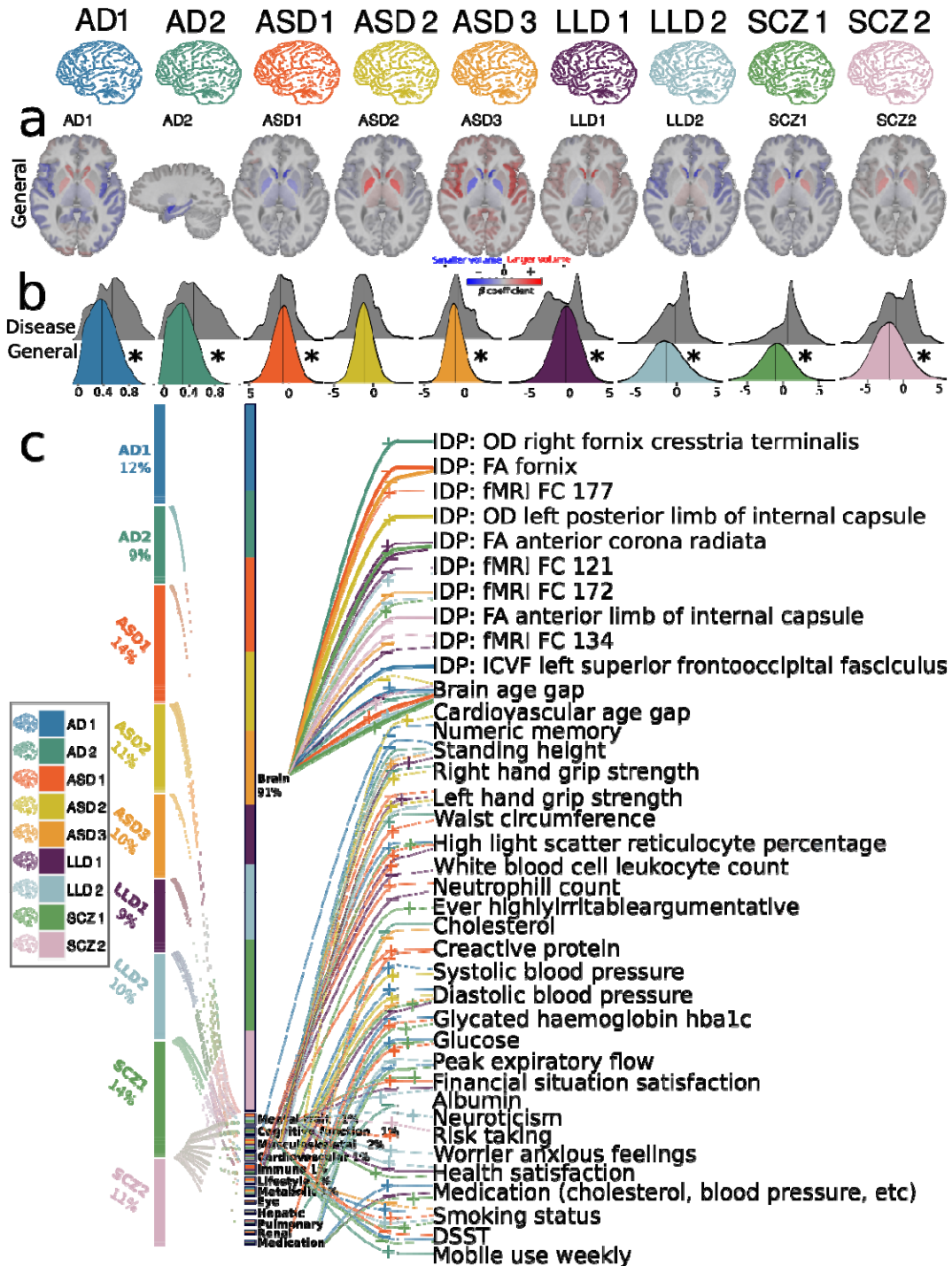
214 We conducted two sensitivity analyses to validate the main PWAS results. We obtained
215 high concordance rates in split-sample (98.03%) and sex-stratified analyses (93.98%). Detailed
216 results can be found in **Supplementary eText 1** and **Supplementary eFile 4** and **5** for split-
217 sample and sex-stratified analyses.

218 As anticipated, 91% of the significant associations were linked to the brain, given that the
219 DNEs were derived from regional brain volumetrics in brain disease-specific populations.
220 However, it is noteworthy that these phenotypic associations extended beyond the brain,
221 providing evidence for the significant associations between the brain and other organ systems.
222 This brain-body connection was consistent with previous literature on multi-organ research using
223 imaging and genetic data^{17,34,35}.

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Figure 2: Phenome-wide associations of the nine DNEs



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a) The neuroanatomical patterns of the nine DNEs were manifested in the UKBB general population and were concordant with the patterns initially derived from the original disease populations¹⁻⁴. A linear regression model was applied to the 119 gray matter regions of interest (ROIs) derived from T1-weighted MRI data while accounting for various covariates (**Method 3b**). We present the β coefficients of the ROIs that withstood the Bonferroni correction. Positive

232 correlations are depicted using warm reddish colors, while cold blue colors represent negative
233 correlations. For AD2, we showed the sagittal view to visualize the hippocampus and medial
234 temporal lobe. **b**) The nine DNEs are over-expressed (i.e., a higher mean of the DNE score in the
235 population) and under-expressed (i.e., a lower mean of the DNE score) in the general population
236 compared to the disease populations. The kernel density estimates of the nine DNEs are shown
237 for both the training dataset (gray-colored in patients) and the independent test dataset from the
238 UK Biobank (UKBB). Significant differences that survived the Bonferroni corrections between
239 the training and independent test datasets (two-sampled t-test) are denoted with the symbol *. **c**)
240 Phenome-wide associations (PWA) between the nine DNEs (left panel) and 611 phenotypes
241 (middle panel) are dominated by brain phenotypic measures. The right panel shows
242 representative phenotypes linked to multiple phenotype categories with the highest statistical
243 significance after the Bonferroni correction ($P\text{-value} < 0.05/611$). A thicker colored line
244 corresponds to a higher value of $-\log_{10}(P\text{-value})$. The symbols "+" and "-" represent positive and
245 negative correlations. IDP: imaging-derived phenotype; OD: orientation dispersion; FA:
246 fractional anisotropy; ICVF: intracellular volume fraction; FC: functional connectivity; DSST:
247 digit symbol substitution test.

248

249 **Genome-wide associations identify 66 genomic loci associated with the nine DNEs**

250 At the genome-wide significance level ($P\text{-value} < 5 \times 10^{-8}$), GWAS using PLINK for a linear
251 regression model (**Method 4a**) identified 10, 8, 5, 21, 9, 1, 3, 3, and 6 genomic loci significantly
252 associated with AD1, AD2, ASD1, ASD2, ASD3, LLD1, LLD2, SCZ1, and SCZ2, respectively
253 (66 in total, **Fig. 3a**, and **Supplementary eFile 6**). At a more stringent significance level ($P\text{-}$
254 $\text{value} < 5 \times 10^{-9}$), 31 loci passed the Bonferroni correction. Notably, 4 loci linked to LLD1-2 and
255 SCZ1 are new – their top lead SNP was not associated with any clinical traits in the EMBL-EBI
256 GWAS Catalog³⁶ and not presented in **Fig. 3b** for our phenome-wide query, as annotated in **Fig.**
257 **3a (Method 4c**, query date: 2nd June 2023, via FUMA version: v1.5.4). To support the
258 robustness of our GWAS, we estimated the intercept of linkage disequilibrium score regression
259 (LDSC)³⁷ and obtained intercepts of 0.9997 ± 0.0093 , 1.0325 ± 0.0091 , 0.9962 ± 0.0095 ,
260 1.0172 ± 0.0099 , 1.0117 ± 0.0085 , 1.0135 ± 0.008 , 1.0162 ± 0.0094 , 1.0101 ± 0.0087 , and
261 1.0124 ± 0.0095 for the nine DNEs. All intercepts were close to 1, indicating no substantial
262 genomic inflation in our GWASs. The Manhattan and QQ plots of the nine GWASs are
263 presented in **Supplementary eFigure 1-9** and are also publicly available on the MEDICINE
264 knowledge portal: <https://labs-laboratory.com/medicine/>.

265 All DNEs are significantly heritable ($0.24 < h^2 < 0.66$, $P\text{-value} < 1 \times 10^{-10}$) after Bonferroni
266 correction (**Fig. 3a**, **Supplementary eTable 2**, and **Method 4b**). We employed the GCTA³⁸
267 software to estimate h^2 , acknowledging that previous research has demonstrated variations in the
268 magnitude of h^2 estimates based on the choice of methods. The h^2 estimates obtained through
269 GCTA or similar methods may underestimate SNP-based heritability (i.e., missing heritability),
270 potentially due to unaccounted factors such as gene-environment interactions, epistasis, and rare
271 variant effects.

272 We further investigated the significant genomic loci by mapping them to protein-
273 encoding genes and examining their functional implications through expression quantitative trait
274 loci (eQTL) mapping. **Supplementary eFigure 10** presents the regional Manhattan plot for the
275 most significant genomic locus associated with each DNE. For example, we identified a locus
276 associated with ASD2 (top lead SNP: rs3068507 at 20q11.21) and a neighboring locus associated
277 with SCZ1 (top lead SNP: rs6088962 at 20q11.21), both of which mapped to the *MYLK2* gene

278 **(Supplementary eFigure 10d and h)**. *MYLK2* encodes a myosin light chain kinase primarily
279 expressed in adult skeletal muscle.

280 We conducted seven sensitivity analyses to validate the main GWAS results (**Method**
281 **4a**). We obtained perfect concordant rates (100%) and similar genomic inflation factors using
282 fastGWA^{39,40} for a generalized linear mixed model in the nine GWAS. Specifically, we excluded
283 the related individuals (up to 2nd-degree) in our genetic quality check pipeline; mixed effect
284 models like fastGWA can detect additional genetic relatedness without excluding individuals by
285 using a sparse genomic relationship matrix, significantly reducing the computational burden for
286 large-scale GWAS. This sensitivity check further supports that no substantial genomic inflation
287 exists in our main GWASs. We also observed high concordance rates in split-sample, sex-
288 stratified (63.26-92.54%), and longitudinal GWAS analyses (100%, $N=1116$), but the
289 concordance rates were relatively low in non-European ancestry GWAS, independent ADNI
290 whole-genome sequencing GWAS, and six case-control GWAS⁴¹⁻⁴⁶ of neurodegenerative and
291 neuropsychiatric disorders from the Psychiatric Genomics Consortium (PGC)⁴⁷ (**Supplementary**
292 **eTable 3a**). The sample sizes for the non-European ($N=4783$) and ADNI ($N=1555$) samples are
293 small; the case-control GWAS from the PGC may overlook the heterogeneity within each
294 disease. Detailed results are presented in **Supplementary eText 2** for the sensitivity results,
295 **Supplementary eFile 7-13** for replicated SNPs/loci, and **Supplementary eFigure 1-9** for
296 Manhattan and QQ plots and the LDSC intercepts. In conclusion, our GWASs were robust across
297 several scenarios and identified 4 new genomic loci that previous case-control GWASs might
298 have missed.

299

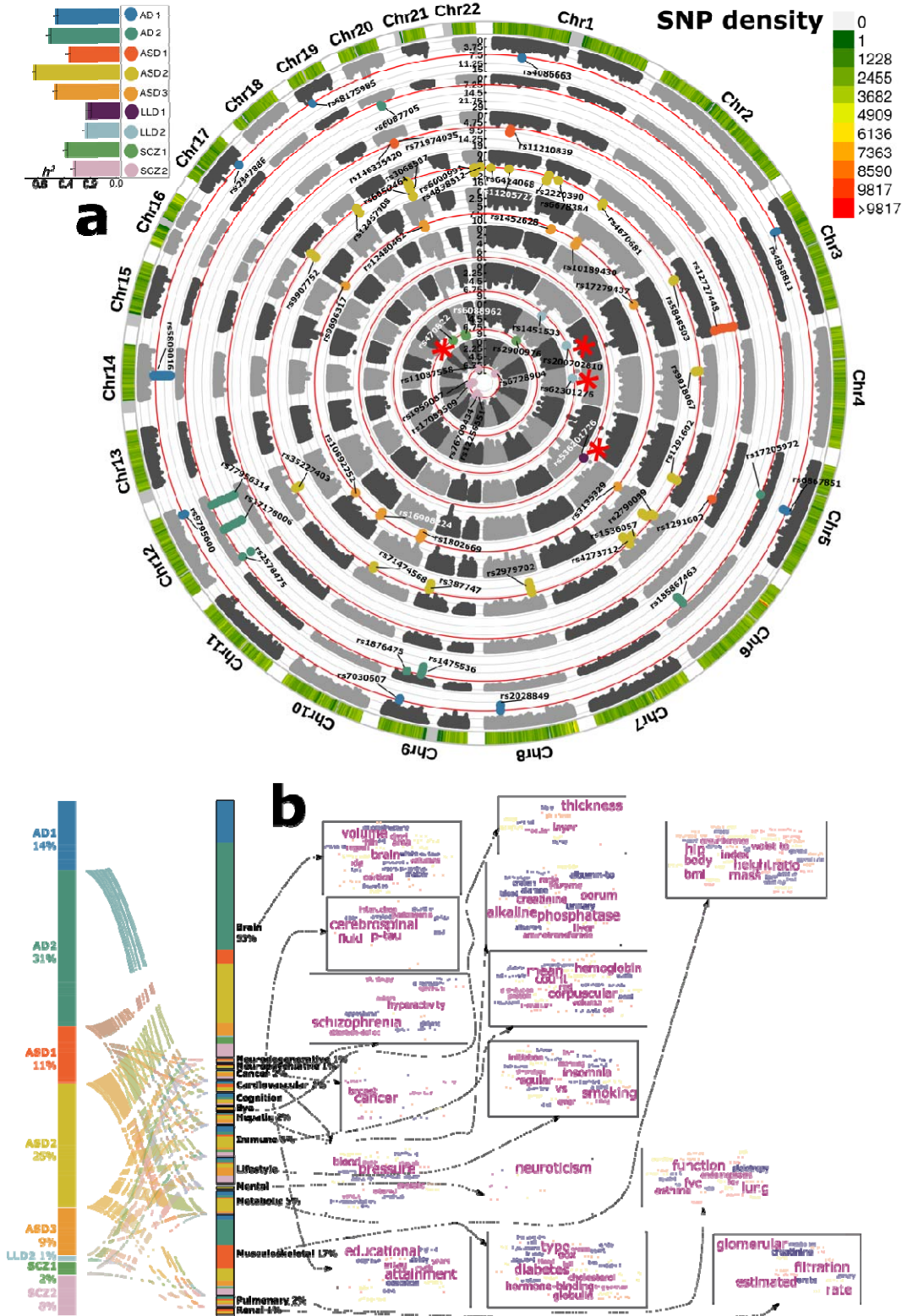
300 **The genetic associations of the nine DNEs parallel their phenotypic associations**

301 We performed a phenome-wide look-up analysis (**Method 4d**) to understand the phenotypic
302 associations in the literature for the identified genomic loci in our GWAS.

303 In total, 2525 clinical traits were associated with genetic variants in our GWAS,
304 including traits linked to multiple organ systems, cognition, and lifestyle factors (**Fig. 3b** and
305 **Supplementary eFile 14**). The genomic loci were largely associated with clinical traits of the
306 brain (53%), musculoskeletal (17%), immune system (6%), neurodegenerative (1%), and
307 neuropsychiatric (1%) diseases. For example, AD2 genomic loci were largely associated with
308 traits related to the brain (565 out of 781, e.g., brain IDPs), musculoskeletal (133/781, e.g.,
309 standing height), immune (17/781, e.g., reticulocyte count), cognition (15/781, e.g., cognitive
310 performance), lifestyle factors (13/781, e.g., smoking), and neurodegenerative traits (1/781, i.e.,
311 neurofibrillary tangles).

312 The findings closely align with the phenotypic associations observed in **Fig. 2c**,
313 reinforcing that the DNEs share genetic determinants linked to organs beyond the brain, lifestyle
314 factors, and cognition.

315 **Figure 3: Genome-wide associations of the nine DNEs**



316
 317 **a)** Genome-wide associations identified 66 (10, 8, 5, 21, 9, 1, 3, 3, 6 for the nine DNEs) genomic
 318 loci ($P\text{-value} < 5 \times 10^{-8}$) associated with the nine DNEs. Using the top lead SNP, we denoted each
 319 genomic loci linked to the 9 DNEs. Red * symbols indicate that the locus (considering the top

320 lead SNP and SNPs in high LD with it) have not been previously associated with any trait in the
321 EMBL-EBI GWAS catalog. The left legend indicates the significant SNP-based heritability (h^2)
322 for the nine DNEs; the right legend represents the SNP density of our genetic data throughout the
323 human genome. GWAS was performed using the Genome Reference Consortium Human Build
324 37 (GRCh37). **b)** Phenome-wide association query of the previously identified genomic loci (left
325 panel) in the EMBL-EBI GWAS Catalog (via FUMA 1.4.2) shows a brain-dominant genetic
326 architecture. We categorized all clinical traits (middle panel) into several high-level categories
327 linked to multiple organ systems, neurodegenerative and neuropsychiatric disorders, lifestyle
328 factors, etc. We then show the keyword cloud plots for each category (right panel).

329

330 **The genetic correlation of the nine DNEs**

331 To understand the shared genetic underpinnings, we estimated the genetic correlation³⁷ (g_c)
332 (**Method 4e**) between the nine DNEs, the BAG of nine human organ systems¹⁷, and six brain
333 diseases (AD, attention-deficit/hyperactivity disorder, autism spectrum disorder, bipolar,
334 obsessive-compulsive disorder, schizophrenia; **Supplementary eTable 3a**) from PGC and four
335 lifestyle factors and cognitive scores (**Supplementary eTable 3b**).

336 We first estimated the g_c between each pair of DNEs (**Fig. 4a**). Numerous DNEs
337 exhibited strong genetic correlations among each other. The highest positive genetic correlation
338 was obtained between ASD2 and SCZ1 ($g_c=0.57\pm 0.04$); the highest negative genetic correlations
339 were obtained between ASD2 and ASD1 ($g_c=-0.55\pm 0.04$), and between ASD3 and SCZ1 ($g_c=-$
340 0.51 ± 0.05). We also observed a substantial alignment between the phenotypic correlation (p_c)
341 and the genetic correlation of pairwise DNEs, supporting the long-standing Cheverud's
342 Conjecture⁴⁸. However, we identified two exceptions where the observed phenotypic and genetic
343 correlations exhibited opposite directions. ASD1 and ASD3 showed a negative phenotypic ($p_c=-$
344 0.39 ± 0.08) but a positive genetic correlation ($g_c=0.21\pm 0.05$); ASD1 and LLD1 showed a
345 negative phenotypic ($p_c=-0.34\pm 0.09$) but a positive genetic correlation ($g_c=0.16\pm 0.07$)
346 (**Supplementary eTable 4**). This implies that non-genetic factors, such as lifestyle and
347 environmental factors, may exert opposite influences on the two DNEs. We performed additional
348 MAGMA gene-set analysis⁴⁹ to test the genetic similarity between ASD2 and SCZ1. The most
349 significant biological pathway underlying ASD2 is the negative regulation of locomotion (GO
350 0040013, P-value= 2.27×10^{-5} , $\beta=0.22\pm 0.02$), implicated in biological processes that stop, prevent,
351 or reduce the frequency, rate, or extent of locomotion of a cell or organism. The most significant
352 biological pathway for SCZ1 is the negative regulation of neurotransmitter transport (GO
353 0051589, P-value= 1.41×10^{-5} , $\beta=0.22\pm 0.02$), involved in biological processes that downregulate
354 the directed movement of a neurotransmitter into, out of, or within a cell. In particular, the latter
355 supports the involvement of dopamine and glutamate, two major neurotransmitters in the central
356 nervous system, in schizophrenia⁵⁰.

357 Between the nine DNEs and the BAGs across nine human organ systems, we found
358 significant genetic correlations between AD1 ($g_c=0.23\pm 0.05$), ASD1 ($g_c=0.44\pm 0.05$), LLD2
359 ($g_c=0.24\pm 0.07$), SCZ1 ($g_c=0.26\pm 0.06$), and the brain BAG, and between ASD1 and the eye BAG
360 ($g_c=0.19\pm 0.07$) (**Fig. 4b** and **Supplementary eTable 5**).

361 Finally, we also found a marginally significant genetic correlation between AD2 and AD
362 ($g_c=0.22\pm 0.12$), AD1 and bipolar disorder (BIP, $g_c=-0.08\pm 0.04$), and ASD3 and BIP
363 ($g_c=0.09\pm 0.04$) using GWAS summary statistics from PGC (**Fig. 4c** and **Supplementary eTable**
364 **6a**). We observed a nominal genetic correlation signal between ASD1 and reaction time
365 ($g_c=0.35\pm 0.15$; **Fig. 4d** and **Supplementary eTable 6b**).

366 In summary, the nine DNEs demonstrate substantial genetic correlations among
367 themselves and with organ systems beyond the brain. These findings highlight the
368 interconnectedness of the neuroanatomical patterns and genetic determinants across multiple
369 body systems and diseases, suggesting shared underlying disease mechanisms and potential
370 pleiotropic effects.

371

372 **The genetic colocalization of the nine DNEs**

373 To seek the shared causal variants between two clinical traits (e.g., AD1 vs. LLD2), we
374 performed Approximate Bayes Factor colocalization⁵¹ analyses (**Method 4f**) between the nine
375 DNEs (**Fig. 4e**), with the nine BAGs (**Fig. 4f**), and the six brain disorders from PGC⁴⁷ (**Fig. 4g**).

376 Among the nine DNEs, we detected 44 causal variants (SNPs) exhibiting significant
377 colocalization signals. We showcased the shared causal variant (rs2790099 at 6p21.1) between
378 ASD2 and SCZ2 with a PP.H4.ABF (Approximate Bayes Factor)=0.92 (**Fig. 4e**), which
379 examines the posterior probability (PP) to evaluate the hypothesis, the presence of a single
380 shared causal variant associated with both traits within a specific genomic locus. This causal
381 SNP was mapped to the *RUNX2* gene. The loss of function in *RUNX2* causes a rare autosomal
382 dominant skeletal disorder – cleidocranial dysplasia⁵², but it was implicated in ASD or SCZ in
383 previous literature.

384 Between the nine DNEs and nine BAGs, we identified 13 causal variants (SNPs)
385 exhibiting significant colocalization signals. We showcased the shared causal variant (rs5848503
386 at 3p22.1) between ASD2 and the brain BAG with a PP.H4.ABF=0.95 (**Fig. 4f**). One mapped
387 gene in this locus is the *MOPB* gene, which encodes the myelin-associated oligodendrocytes
388 basic protein and is actively involved in the structural constituent of the myelin sheath and
389 nervous system development. This gene was previously implicated in ASD using single-cell
390 genomics⁵³, SCZ⁵⁴, amyotrophic lateral sclerosis, and Parkinson's disease⁵⁵.

391 Between the nine DNEs and six brain diseases from PGC, we identified 6 causal variants
392 (SNPs) exhibiting significant colocalization signals. We showcased the shared causal variant
393 (rs9257566 at 6p22.1) between ASD3 and SCZ with a PP.H4.ABF=0.82 (**Fig. 4g**). In this locus,
394 multiple olfactory receptor (OR) genes and the dysfunction of the olfactory system were
395 implicated in SCZ^{56,57} and ASD^{58,59}. For instance, the *OR2J2* and *OR2J3* genes are two protein-
396 coding genes in copy number variants associated with SCZ using microRNA data⁶⁰. The causal
397 SNP (rs9257566) was associated with SCZ and brain IDP, such as white matter microstructural
398 measures (**Supplementary eFigure 11**). Besides those two conditions, AD has also been widely
399 associated with early olfactory dysfunction^{61,62}. The sensitivity checks on the prior probability
400 (*p*12) for the three illustrations are shown in **Supplementary eFigure 12a-c**. The causal variant,
401 cytogenetic region, and their colocalization signal direction (based on β coefficients) are presented in
402 **Supplementary eFigure 13a-c**. Detailed results are shown in **Supplementary eFile 15-17**.

403 The genetic colocalization of the nine DNEs revealed causal genetic variants, indicating
404 that the same genomic regions may causally influence the expression of these AI-derived
405 endophenotypes.

406

407 **The causal relationship of the nine DNEs**

408 We applied bidirectional two-sample Mendelian randomization analyses⁶³ (**Method 4g**) to depict
409 a causal network between the nine DNEs, the eight BAGs (excluding the brain BAG), and eleven
410 chronic diseases spanning the whole-body system.

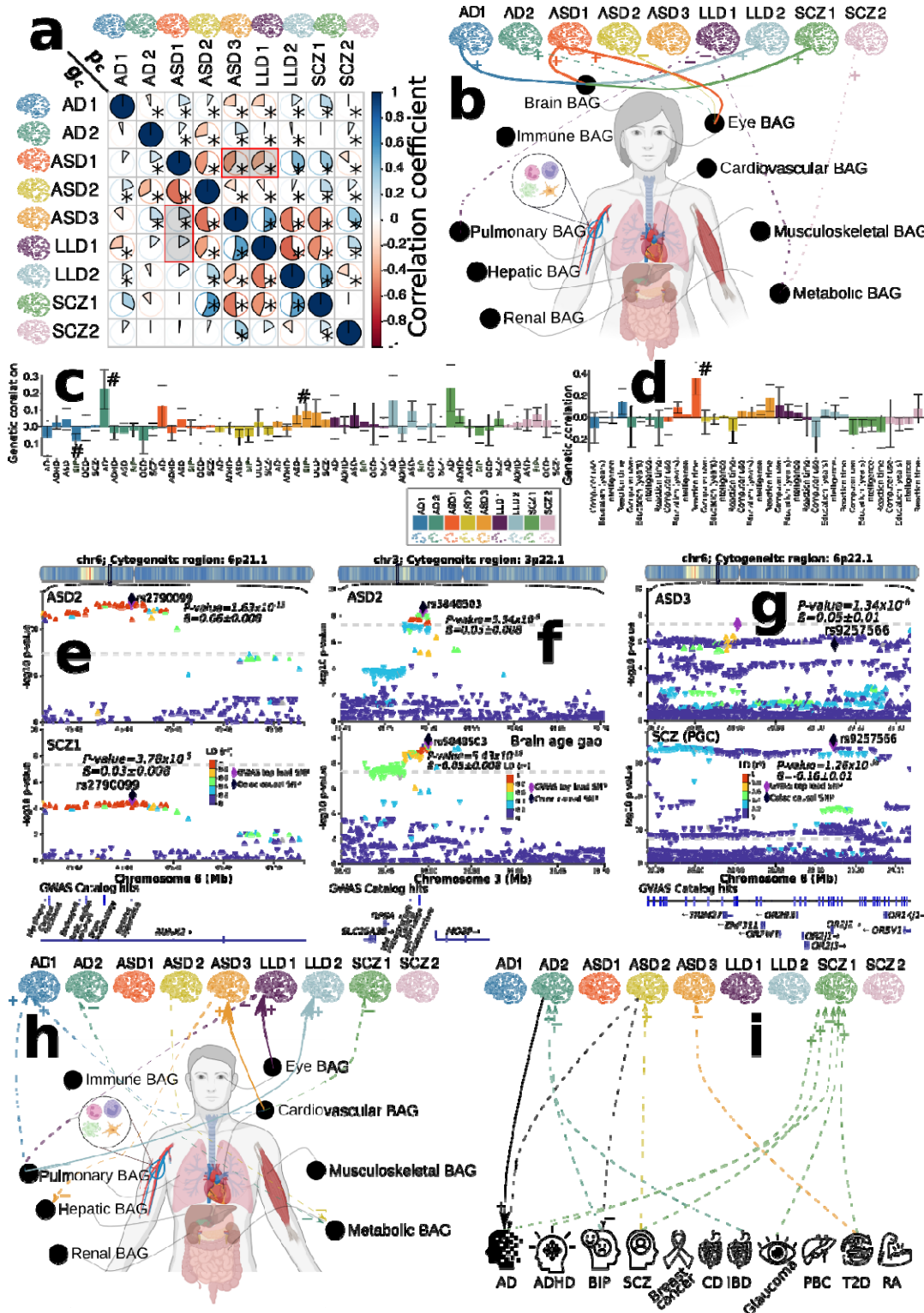
411 For each pair of DNEs, as the GWAS populations completely overlapped, conducting
412 two-sample Mendelian randomization was not feasible⁶⁴. Alternatively, the split-sample GWAS
413 did not yield sufficient statistical power due to the limited number of instrumental variables (VI)
414 available (< 6 SNPs).

415 Among the nine DNEs and eight BAGs, we found potential causal effects of the eye
416 BAG on LLD1 [P-value= 4.57×10^{-3} , OR (95% CI) = 1.14 (1.04, 1.24), number of SNPs=16], the
417 cardiovascular BAG on ASD3 [P-value= 6.04×10^{-3} , OR (95% CI) = 1.16 (1.04, 1.29), number of
418 SNPs=34], and the pulmonary BAG on LLD2 [P-value= 1.98×10^{-3} , OR (95% CI) = 1.14 (1.04,
419 1.25), number of SNPs=49]. No significant causal signals persisted after the Benjamini-
420 Hochberg correction in the inverse analyses (**Fig. 4h**). Details of the results, including all five
421 different Mendelian randomization estimators, are shown in **Supplementary eFile 18**.

422 Between the nine DNEs and eleven chronic diseases, encompassing brain-related
423 conditions and diseases affecting other organs, we identified a potential causal effect from AD2
424 to AD using the GWAS summary statistics from PGC – the largest sample size ($N=1,126,536$
425 individuals) in the AD case-control study [P-value= 1.74×10^{-4} , OR (95% CI) = 1.25 (1.11, 1.40),
426 number of SNPs=7] (**Fig. 4i**). We didn't detect a causal link in the opposite direction from AD to
427 AD2. This aligns with the endophenotype hypothesis, suggesting that DNEs are situated within
428 the causal pathway from genetics to external phenotypes, such as AD diagnosis and cognitive
429 decline. Details of the results, including all five different Mendelian randomization estimators,
430 are shown in **Supplementary eFile 19**. The results of the sensitivity check are presented in
431 **Supplementary eFigure 14-17**.

432 The Mendelian randomization results further emphasize the potential benefits of overall
433 organ health for brain-related conditions. This highlights the interconnectedness between various
434 organ systems and the brain, underscoring the significance of a holistic health and disease
435 prevention approach.

436 **Figure 4: The genetic correlation, colocalization, and causal networks of the nine DNEs**



437
 438 **a)** The genetic correlation between two DNEs (g_c , lower triangle) mirrors their phenotypic
 439 correlation (p_c , upper triangle). Red-shadowed rectangles highlight two exceptions. The symbol
 440 * indicates significant results after the Benjamini-Hochberg correction. The symbol # indicates
 441 nominal significance. **b)** genetic correlations between the nine DNEs and nine biological age

442 gaps (BAG) for nine human organ systems¹⁷. **c)** genetic correlations between the nine DNEs and
443 six neurodegenerative and neuropsychiatric disorders. **d)** genetic correlations between the nine
444 DNEs and four traits related to lifestyle factors and cognition. **e)** genetic colocalization was
445 evidenced at one locus (6p21.1) between ASD2 and SCZ1. The signed PP.H4.ABF (0.92)
446 denotes the posterior probability (PP) of hypothesis H4, which suggests that both traits share the
447 same causal SNP (rs2790099). A positive PP indicates concordant β values for both DNEs, while
448 a negative PP implies opposite β values. **f)** genetic colocalization was evidenced at one locus
449 (3p.22.1) between ASD2 and brain BAG: PP.H4.ABF=0.95 with the cause SNP rs5848503. **g)**
450 genetic colocalization was evidenced at one locus (6p.22.1) between ASD3 and SCZ case-
451 control GWAS⁴⁵ from PGC (European ancestry): PP.H4.ABF=0.82 with the cause SNP
452 rs9257566. **h)** the causal network of the nine DNEs with the eight multi-organ BAGs. Solid
453 arrow lines (from the exposure to the outcome variables) indicate significant causal relationships
454 after the Benjamini-Hochberg correction; dotted arrow lines show nominal significance (P-
455 value<0.05). The symbols + (OR>1 and $g_c>0$) and - (OR<1 and $g_c<0$) represent a positive
456 relationship between the two traits. **i)** the causal network of the nine DNEs with the eleven
457 chronic diseases (e.g., AD, ADHD, BIP, and SCZ from PGC). Abbreviation: AD: Alzheimer's
458 disease; ADHD: Attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; BIP:
459 bipolar disorder; SCZ: schizophrenia; OCD: Obsessive-compulsive disorder; RA: rheumatoid
460 arthritis; CD: Crohn's disease; T2D: type 2 diabetes; IBD: inflammatory bowel disease; PBC:
461 Primary biliary cirrhosis.

462

463 **The nine DNEs and their PRSs significantly improve prediction for 14 systemic diseases**

464 **and mortality**

465 We investigated the added prediction power of the nine DNEs and their respective PRS (**Method**
466 **4h**) for 14 systemic diseases based on the ICD-10 code (**Supplementary eTable 7-8**), 8
467 cognitive scores(**Supplementary eTable 9**), and mortality outcomes (i.e., the date of death). The
468 definition of the patient and healthy control groups and the mortality outcome are presented in
469 **Method 5**. Of note, we did not perform prediction on the four brain diseases (AD, ASD, LLD,
470 and SCZ) due to the small and highly imbalanced sample sizes in the UKBB general population
471 (**Method 1**). As anticipated, the prediction performance across all tasks was modest, considering
472 that the DNEs were derived from specific disease populations.

473 In addition to commonly available features, such as age and sex, we found that AD1,
474 ASD1, LLD1, SCZ1, and SCZ2 provided additional prediction power (i.e., incremental R^2) for
475 many disease categories (**Method 5a**). Across the 14 disease categories, the DNEs showed
476 higher incremental R^2 in mental and behavioral disorders (ICD-10 code: F group) and diseases
477 linked to the central nervous system (ICD-10 code: G group) than other disease categories,
478 proving that the nine DNEs in the general population capture disease-related effects of the four
479 brain diseases. Combining all nine DNEs further improved the incremental R^2 , especially in
480 mental and behavioral disorders ($R^2=1.01\%$, P-value= 1.74×10^{-5}) and diseases linked to the
481 central nervous system ($R^2=0.63\%$, P-value= 1.33×10^{-5}) (**Fig. 5a**). The incremental R^2 values for
482 all tests are shown in **Supplementary eTable 7**. All metrics, encompassing sample sizes and
483 incremental R^2 for both the null and alternative models, are outlined in **Supplementary eFile**
484 **20**. Results using only the PRS target population are presented in **Supplementary eFigure 18**.

485 Compared to the nine DNEs, the nine PRSs provided smaller additional prediction power.
486 For example, the PRS for ASD3 explained an additional 0.05% of the variance (incremental R^2)

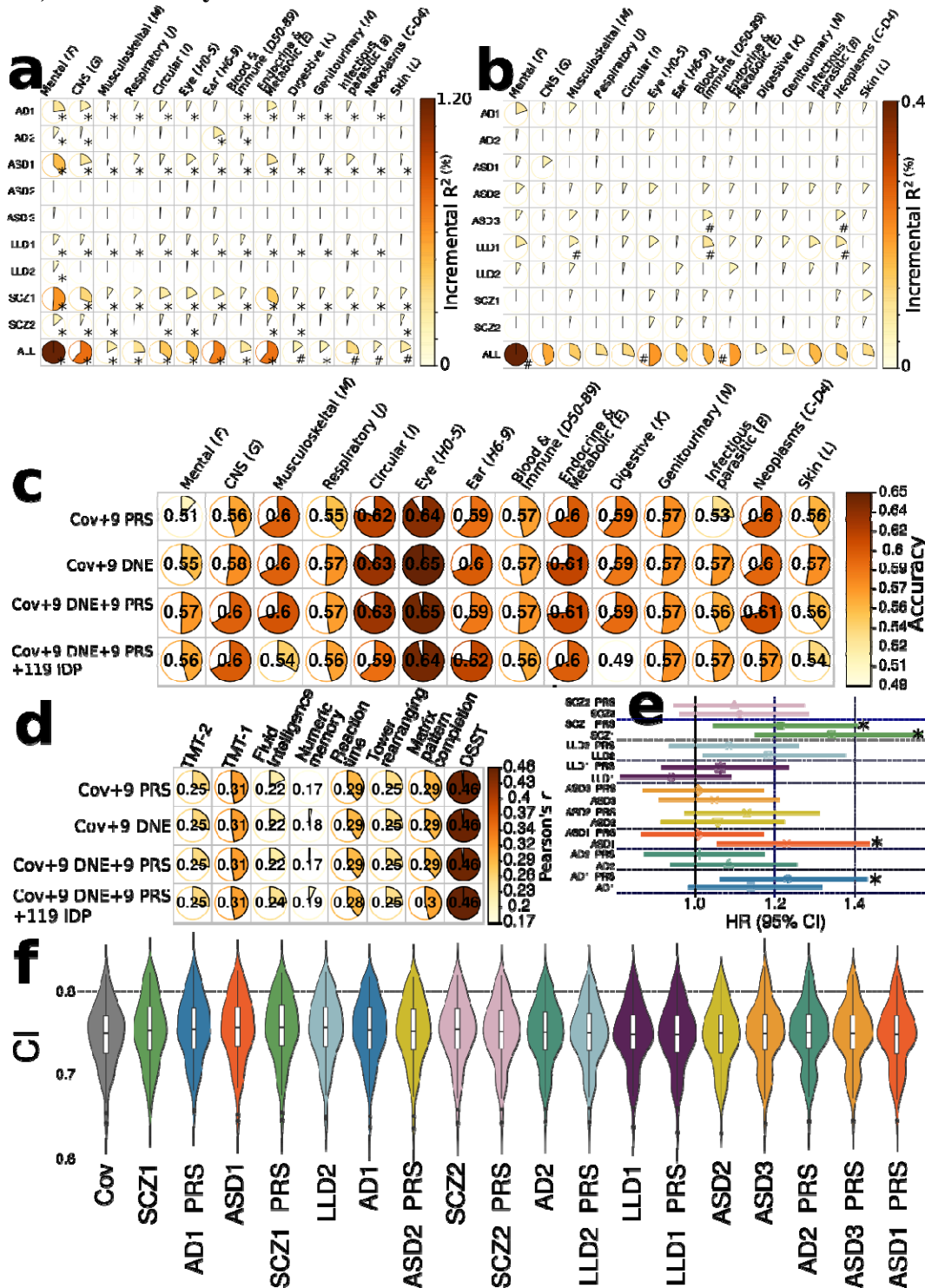
487 in diseases associated with the blood and immune systems (P-value=0.03), as well as neoplasms
488 (P-value=0.04). Combining all nine PRSs improves the incremental R^2 , particularly in mental
489 and behavioral disorders ($R^2=0.3\%$, P-value=0.047). No results survived multiple comparisons
490 using the Benjamini-Hochberg method (**Fig. 5b**). Detailed results are shown in **Supplementary**
491 **eTable 8** and **eFile 21**.

492 We assessed the prediction ability of support vector machines (SVM) at the individual
493 level to classify the 14 disease categories (**Method 5b**). The highest performance was observed
494 for eye diseases (ICD-codes: H0-5). Age and sex significantly enhanced the classification
495 accuracy. Including age and sex alongside the 9 DNEs and 9 PRSs boosted the classification
496 accuracy from 0.55 to 0.65. The inclusion of PRSs, DNEs, and the combination of both, along
497 with age and sex as features, resulted in improved classification accuracy for mental and
498 behavioral disorders. For example, the accuracy increased from 0.51 to 0.55 and 0.57 for features
499 of age and sex, 9 DNEs, and 9 PRSs, incrementally (**Fig. 5c**). These findings highlight the added
500 value of incorporating the nine DNEs and PRSs in predicting these disease categories. Detailed
501 results are shown in **Supplementary eTable 9a**. The full evaluation metrics of the cross-
502 validated and independent test results are presented in **Supplementary eFile 22**.

503 We examined the predictive capability of these feature sets in estimating 8 cognitive
504 scores (**Method 5c**). The digit symbol substitution test (DSST) demonstrated the highest
505 performance, reaching a Pearson's r of 0.46 (e.g., P-value= 3.9×10^{-189} and MAE=3.75 for the
506 feature set of 9 DNE plus covariates) in the independent test dataset using all different sets of
507 features (**Fig. 5d**). The combination of DNEs and PRSs did not notably enhance prediction
508 accuracy. However, contrary to the 14 systemic disease classifications, incorporating the 119
509 GM imaging-derived phenotypes alongside DNEs and PRSs resulted in a 2% increase in the
510 prediction accuracy for fluid intelligence, measured by Pearson's r (**Supplementary eTable 9b**).
511 The full evaluation metrics of the cross-validated and independent test results are presented in
512 **Supplementary eFile 23**.

513 Finally, we evaluated the prediction power of the nine DNEs and PRSs for mortality risk
514 prediction using the Cox regression (**Method 5d**). Among these, SCZ1, SCZ1-PRS, ASD1, and
515 AD1-PRS were significantly associated with the risk of mortality (**Fig. 5e** and **Supplementary**
516 **eTable 10a**). Adding SCZ1, AD1-PRS, ASD1, and SCZ1-PRS to age and sex further improved
517 the prediction, but the performance decreased afterward (**Fig. 5f**). Lastly, incorporating the nine
518 DNEs from the second scan of 1348 participants into the model slightly increased the statistical
519 significance and the HR (**Supplementary eTable 10b** and **c**).

520 **Figure 5: Additional prediction power of the nine DNEs and PRSs for 14 systemic diseases,**
 521 **cognition, and mortality outcomes**



522 a) The incremental R-squared (R^2) values of the nine DNEs for predicting 14 systemic disease
 523 categories were assessed using the entire UKBB sample, with $N=39,178$ participants as
 524 independent test data. The results focusing only on the PRS target population ($N=15,891$) can be
 525 found in **Supplementary eFigure 18**. "ALL" indicates the incremental R^2 contributed by
 526

527 combining the nine DNEs. **b)** The incremental R^2 of the PRS of the nine DNEs to predict 14
528 systemic diseases based on the ICD-10 code using only the PRS target sample. **c)** In the PRS
529 target sample, disease classification accuracy from the independently hold-out test data ($N=5581$)
530 was assessed using nested cross-validated support vector machines in the training/validation/test
531 data ($N=10,000$) by fitting various sets of features (Cov indicates age and sex). **d)** In the PRS
532 target sample, cognitive score prediction accuracy (Pearson's r) from the independently hold-out
533 test data ($3632 < N < 5570$) was assessed using nested cross-validated support vector regression
534 models. **e)** The SCZ1, SCZ1-PRS, AD1-PRS, and ASD1 show significant associations with the
535 risk of mortality in the PRS target sample. Age and sex were included as covariates in the Cox
536 proportional hazard model. **f)** The nine DNEs and PRSs were cumulatively included as features
537 in cross-validation for mortality risk prediction. The symbol * indicates significant results that
538 survived the Benjamini-Hochberg correction. The symbol # indicates nominal significance. HR:
539 hazard ratio; CI: concordance index; DSST: digit symbol substitution test; TMT: trail-making
540 test.

541 **Discussion**

542 This study investigated the manifestation of nine disease-related brain endophenotypes – derived
543 from four case-control studies via semi-supervised AI methods – in the general population of
544 39,178 participants in UKBB. We assessed commonalities and differences among the nine
545 DNEs, their genetic correlates in the general population, their relationships with the multiple
546 human organ systems, and their predictive capacity for 14 systemic disease categories and
547 mortality. Our findings demonstrate the potential of the nine AI-derived DNEs in identifying
548 high-risk individuals within the general population prone to developing the four major brain
549 disorders.

550

551 **Shared neuroanatomical patterns and genetic determinants across the four brain diseases** 552 **in the general population**

553 Understanding the shared disease mechanism of neurodegenerative and neuropsychiatric
554 diseases is a complex and ongoing challenge in medical research^{15,16,41,43–46,65}. Our results
555 suggest that shared underlying mechanisms and genetic factors may contribute to the
556 development and progression of these disorders. This notion of shared disease mechanisms
557 across the four major neurodegenerative and neuropsychiatric diseases, namely ASD, SCZ, LLD,
558 and AD, has garnered considerable attention and reshaped our understanding of these
559 conditions^{15,16}.

560 Despite the inherent heterogeneity among neuroanatomical patterns observed in different
561 brain diseases (**Fig. 2a**), a notable commonality exists regarding their manifestations, which
562 might emanate from underlying mechanisms sharing neuropathologic characteristics and
563 pathways. As an illustration, AD1, LLD2, and SCZ1 exhibited a negative correlation (brain
564 atrophy) with widespread cortical volumes, such as the bilateral insula and middle frontal gyrus.
565 This aligns with expectations, considering that the UKBB population includes individuals
566 primarily from mid to late life (above 45 years). From an etiological standpoint, various factors
567 can contribute to the global cortical volume reduction within the general population, with late-
568 onset neurodegenerative and neuropsychiatric disorders and aging exerting a significant impact.
569 Likewise, ASD2 and SCZ2 exhibited a positive association with the basal ganglia, including the
570 globus pallidum. This could imply the existence of potential protective genetic or environmental
571 factors that collectively contribute to the concept of "brain reserve", which might mitigate
572 volume loss in a portion of the general population. Notably, we previously revealed that
573 individuals predominantly expressing SCZ2 exhibited higher levels of education⁴ and higher
574 remission rates than those primarily influenced by SCZ1. Alternatively, these volume increases
575 might reflect neuropathologic mechanisms, such as disrupted connectivity, which are not
576 necessarily associated with neurodegenerative and neurodevelopmental components related to
577 relatively lower brain volumes. Ultimately, another significant aspect to consider involves the
578 impact of medications prescribed by clinicians, affecting both disease-specific and general
579 populations. Research indicates that antipsychotic medications, commonly prescribed for most
580 individuals with schizophrenia and some with ASD and AD, have been shown to delay brain
581 volume loss in the basal ganglia⁶⁶ and pallidum⁶⁷.

582 The commonalities in neuroanatomical patterns across brain diseases can be attributed to
583 several factors. First, shared genetic factors may influence brain structure and function^{28,30},
584 contributing to similar neuroanatomical alterations across different diseases. Genetically, this
585 was largely evidenced by our genetic correlation (**Fig. 4a**) and colocalization results (**Fig. 4e**).

586 For instance, ASD2 showed prominent positive genetic overlap with SCZ1. Historically, there
587 has been a long-standing association between ASD and SCZ, leading to the notion that autism
588 could be a form of "childhood schizophrenia"⁶⁸. This conceptual link between the two conditions
589 has been debated and discussed. Previous case-control neuroimaging studies demonstrated
590 divergent structural and functional brain patterns in individuals with ASD compared to those
591 with SCZ^{69,70}, largely ignoring the neuroanatomical heterogeneity within each condition. Genetic
592 variants that impact key signaling pathways, synaptic function, and neuronal connectivity^{71,72}
593 could influence multiple disease phenotypes, leading to overlapping neuroanatomical patterns.

594 AD1 also shared genetic similarities with LLD1, both characterized by spatially extensive
595 brain atrophy and increased brain age. Previous studies found a higher prevalence of depressive
596 symptoms and LLD in individuals with AD compared to the general population⁷³⁻⁷⁵. The
597 relationship between AD and LLD likely involves multiple factors and may be bidirectional. On
598 the one hand, LLD may increase the risk of developing AD or accelerate the progression of
599 cognitive decline in individuals already affected by AD. On the other hand, AD-related changes
600 in the brain, such as neuroinflammation and neurochemical imbalances, may worsen depressive
601 symptoms in individuals with LLD.

602 Recognizing the shared disease mechanisms across the four brain diseases underscores
603 the importance of a broader perspective on clinical presentations and underlying biological
604 mechanisms. This understanding is important for developing targeted and personalized
605 approaches to patient care, leading to more effective treatments and interventions. Future
606 research may explore disease heterogeneity to transcend traditional classification boundaries and
607 identify data-driven subtypes or dimensions within a transdiagnostic framework⁷⁶.

608

609 **Beyond the brain**

610 Our findings strongly concur with a paradigm shift in treating brain diseases. While the
611 conventional approach has predominantly concentrated on interventions targeting the brain,
612 emerging evidence highlights the critical importance of considering the broader systemic and
613 environmental factors that influence disease onset and progression.

614 Unraveling the intricate interconnections between the brain and other organ systems is
615 crucial in broadening our understanding of brain diseases, as demonstrated by our findings and
616 other findings. The brain does not function in isolation but interacts with and is influenced by
617 various physiological systems throughout the body. Our results showed a close genetic
618 association and causality between the DNEs and the eye, cardiovascular, and pulmonary systems
619 (**Fig. 4b, f, and h**). These findings parallel previous literature. For instance, eye-related
620 pathological changes have been revealed to mirror early signs of neurological and
621 neuropsychiatric conditions⁷⁷. The nervous and cardiovascular systems – the heart-brain axis –
622 are intricately linked, with brain regions controlling heart function via sympathetic and
623 parasympathetic pathways⁷⁸. Dysfunctions in one system can affect the other's function, resulting
624 in brain and cardiovascular diseases. The immune system plays a crucial role in modulating
625 inflammation and neuroinflammation, which are implicated in many brain disorders, such as
626 AD⁷⁹, SCZ⁸⁰, and depression⁸¹. Similarly, the gut-brain axis highlights the bidirectional
627 communication between the gut microbiota and the brain, with emerging evidence linking
628 alterations in the gut microbiome to brain diseases such as Parkinson's disease⁸² and
629 depression⁸³. Understanding and targeting these systemic interactions can modulate disease
630 processes and improve treatment outcomes.

631 Furthermore, considering environmental and lifestyle factors is essential in treating brain
632 diseases⁸⁴. Our previous work¹⁷ has shown that the BAGs of nine human organ systems comply
633 with Cheverud's Conjecture: the phenotypic correlation of two BAGs mirrors their genetic
634 correlations. However, herein we showed that the phenotypic correlation between two DNEs
635 (e.g., ASD1 vs. LLD1) did not reflect their underlying genetic correlation (**Fig. 4a**), indicating
636 potentially strong environmental and lifestyle factors that exert opposite effects on the two
637 DNEs. Furthermore, an interesting observation from our study was that the heritability estimate
638 (h^2) of early-onset diseases, such as ASD, was higher than that of late-onset diseases, such as
639 LLD, within the three neuropsychiatric disorders. This finding suggests that genetic factors play
640 a more prominent role in developing ASD at a younger age. In contrast, other factors, such as
641 environmental influences, socioeconomic factors, and lifestyle choices, may have a stronger
642 impact on developing LLD later in life. These differential heritability patterns shed light on the
643 complex interplay between genetic and non-genetic factors in the underlying disease mechanism
644 of neurodegenerative and neuropsychiatric disorders across different stages of life. These
645 heritability patterns aligned with a previous study that examined multiple GWAS drawn from
646 more than 200,000 patients for 25 brain-associated disorders and 17 phenotypes¹⁶.

647 In conclusion, going beyond the brain is crucial for understanding and treating brain
648 diseases. By considering the connections between the brain and other organ systems,
649 understanding the impact of environmental and lifestyle factors, and harnessing the power of
650 advanced AI technologies, we can develop more effective and personalized approaches to
651 prevent, diagnose, and treat brain diseases.

652

653 **AI-derived DNEs for precision diagnostics in the general population**

654 The present study leverages cutting-edge, semi-supervised AI methods²² and open science
655 advancements to enhance our understanding of disease heterogeneity in neurodegenerative and
656 neuropsychiatric disorders^{1-3,6,9}. In this context, implementing these AI-derived DNEs at early
657 disease or preclinical stages – in the general population – may facilitate the identification of
658 individuals at risk, and the initiation of proactive interventions before the onset of noticeable
659 symptoms, likely leading to more effective treatments and interventions and better outcomes.

660 The proposed AI-derived DNEs capture intricate brain structure and function variations,
661 often subtle and spatially complex, which traditional diagnostic methods and case-control studies
662 may overlook. By quantifying the neuroanatomical patterns associated with specific brain
663 disorders, DNEs may offer a personalized disease vulnerability assessment, inform interventions
664 at early preclinical stages, and potentially prevent or delay the onset of symptoms. At the
665 individual level, integrating genetic information (i.e., PRSs) with DNEs significantly improves
666 prediction performance for 14 systemic diseases and mortality outcomes (**Fig. 5**). In addition, our
667 Mendelian randomization analyses supported the well-established endophenotype hypothesis in
668 genetic psychiatry²³ – endophenotype in psychiatric disorders resides inside the causal pathway
669 from underlying genetics to their exo-phenotypes (i.e., the disease syndrome itself), thereby
670 being closer to its disease mechanisms. We found that AD2, characterized by focal medial
671 temporal lobe atrophy, exerted a causal relationship with AD. However, we did not find evidence
672 of a reverse causal relationship, suggesting that the underlying genetics may influence the
673 development of AD through the DNE, although it may not be the exclusive pathway contributing
674 to the disease. This highlights the role of genetics in influencing the disease process, particularly
675 through the identified DNE, shedding light on potential pathways and mechanisms involved in
676 AD development.

677

678 **Limitation**

679 The present study has several limitations. Firstly, the genetic analysis focused exclusively on
680 common genetic variants. Future investigations should explore the contribution of rare variants
681 to these brain diseases. Secondly, it is important to recognize that our GWAS analyses
682 predominantly involved participants of European ancestry, limiting the generalizability of the
683 genetic findings to other populations with different ancestral backgrounds. Further research
684 efforts are necessary to collect more diverse genetic data and include underrepresented racial and
685 ethnic groups to enhance the generalizability of the findings. Additionally, the validation of the
686 nine DNEs would benefit from additional longitudinal analyses. Fortunately, ongoing efforts to
687 collect longitudinal brain MRI data in UKBB⁸⁵ hold promise for providing valuable insights to
688 the scientific community and advancing the field of precision medicine. Furthermore, more
689 advanced methodological developments will be developed and integrated within our semi-
690 supervised clustering learning framework to alleviate potential domain shifts⁸⁶. Finally, our
691 future research will incorporate multimodal imaging to generate DNEs sensitive to a broader
692 range of brain alterations, including macrostructural volumetric changes, functional disruptions,
693 and structural network abnormalities.

694

695 **Outlook**

696 Together, our AI-derived DNEs have emerged as novel instruments for precision medicine. By
697 capturing the complexity and heterogeneity of brain disorders, DNEs provide a better
698 understanding of disease pathology, facilitate personalized risk assessment, and hold promise for
699 targeted interventions and population selection.

700 **Methods**

701 **Method 1: Study populations**

702 Our previous studies used semi-supervised AI models to define the nine DNEs from four disease
703 case-control populations. These populations consisted of 865 healthy controls (CN), 1096
704 individuals with mild cognitive impairment (MCI), and 414 AD patients from ADNI²⁰ for AD1
705 and AD2, 362 typically developing controls, and 307 patients with autism spectrum disorder
706 (ASD) from ABIDE²¹ for ASD1-3, 495 healthy controls and 501 LLD patients from the LLD
707 study³ for LLD1-2, and 364 healthy controls and 307 SCZ patients from PHENOM⁴ for SCZ1-2.
708 For more detailed information about the characteristics of the study populations, please refer to
709 the original papers.

710 The trained AI models were then applied to the UKBB general population as independent
711 data. UKBB is a population-based study of approximately 500,000 people recruited from the
712 United Kingdom between 2006 and 2010. The UKBB study has ethical approval, and the ethics
713 committee is detailed here: [https://www.ukbiobank.ac.uk/learn-more-about-uk-](https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/governance/ethics-advisory-committee)
714 [biobank/governance/ethics-advisory-committee](https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/governance/ethics-advisory-committee). The current study analyzed 39,178 multimodal
715 brain MRI data from UKBB. T1-weighted MRI data were locally processed at the University of
716 Pennsylvania; imaging-derived phenotypes (IDP) from diffusion and resting-state functional
717 MRI were downloaded from UKBB. In addition, we processed the imputed genotype data²⁶ from
718 UKBB for GWAS analyses. Last, other clinical traits were also analyzed, including phenotypes
719 related to nine human organ systems. The current work was performed under application
720 numbers 35148 and 60698. To unbiasedly evaluate the PRS and machine learning models, we
721 defined the following populations:

- 722 • *Disease case-control populations*: The four datasets used to train the AI models and
723 define the nine DNEs from four brain diseases.
- 724 • *Independent UKBB general population (N=39,178)*: The UKBB population in which the
725 trained AI models were applied to derive the nine DNEs.
- 726 • *PRS base/target population (split1/split2) (N=15,968)*: the UKBB population was
727 divided into two splits (split1 vs. split2) in the split-sample GWAS. To derive the PRS,
728 we used the GWAS from split1 as the base data and split2 as the target data. All disease
729 and mortality prediction tasks involving PRS used only the PRS target population
730 (N=15,968).

731 Within the UKBB general population, individuals with various diseases are classified
732 under the ICD-10 code (Data field: 41270), though often in smaller numbers. Among the 39,178
733 participants from the UK Biobank included in our study, we outline the sample sizes and criteria
734 for the healthy control group, as well as those with AD, ASD, LLD (encompassing a broad
735 spectrum of depression), and SCZ, all categorized according to the ICD-10 code:

- 736 • *Healthy control*: 6390 participants without any ICD-10-based disease diagnoses from the
737 data field: 41270 from the training/validation/test dataset in **Method 5**.
- 738 • *AD*: 23 AD patients based on the ICD-10 code (G30).
- 739 • *ASD*: 6 ASD patients based on the ICD-10 code (F84.0).
- 740 • *LLD*: 1329 patients based on the ICD-10 code (F32).
- 741 • *SCZ*: 23 SCZ patients based on the ICD-10 code (F20).
- 742 • *The 14 systemic disease categories*: we used the ICD-10 code to define the disease
743 groups. The exact ICD-10 code for each category is detailed in **Fig. 5a**.

744

745

746

747 **Method 2: Semi-supervised AI methods to derive the nine DNEs**

748 The methodologies used in the current study to derive the nine DNEs belong to the semi-
749 supervised learning algorithms (**Fig. 1a**) pioneered by our group. Refer to a review for details of
750 this type of modeling. In particular, the current study employed the HYDRA²⁹ and Surreal-
751 GAN¹⁴ models.

752

753 **(a): Surreal-GAN:** Surreal-GAN¹⁴ dissects underlying disease-related heterogeneity via a deep
754 representation learning approach, instead of the discriminative SVM, under the principle of semi-
755 supervised clustering – the "*I-to-k*" mapping. The methodological advance of this method is that
756 Surreal-GAN models disease heterogeneity as a continuous dimensional representation, enforces
757 monotone disease severity in each dimension, and allows the non-exclusive manifestation of all
758 dimensions in the same participant (**Supplementary eMethod 1a**).

759 We encapsulated the characteristics of the AD1 and AD2 derived by Surreal-GAN from
760 the disease-specific population. AD1 represents a "diffuse-AD" dimension characterized by
761 widespread brain atrophy, whereas AD2, described as a "medial temporal lobe-AD" dimension,
762 exhibits focal atrophy in the medial temporal lobe (MTL)¹.

763

764 **(b): HYDRA:** HYDRA leverages a widely used discriminative method, i.e., support vector
765 machines (SVM), to seek the "*I-to-k*" mapping. The novelty is that HYDRA extends multiple
766 linear SVMs to the non-linear case piecewise, thereby simultaneously serving for classification
767 and clustering. Specifically, it constructs a convex polytope by combining the hyperplane from *k*
768 linear SVMs, separating the CN group from the *k* subpopulation of the PT (patient) group.
769 Intuitively, each face of the convex polytope can be regarded to encode each subtype, capturing a
770 distinct disease effect (**Supplementary eMethod 1b**).

771 We summarized the main characteristics of the ASD1-3, LLD1-2, and SCZ1-2 derived by
772 HYDRA in the disease-specific populations. ASD1 showed correlations with reduced brain
773 volume, decreased cognitive function, and genetic variants related to aging. ASD2 exhibited
774 enlarged subcortical volumes and was linked to the use of antipsychotic medication. ASD3 was
775 identified by expanded cortical volumes and higher performance in nonverbal cognitive tasks².
776 LLD1 displayed relatively maintained brain structure without disruptions in white matter
777 compared to healthy control individuals, whereas LLD2 exhibited extensive brain atrophy,
778 disruptions in white matter integrity, cognitive decline, and increased severity of depression³.
779 SCZ1 exhibited widespread reduction in grey matter volumes, particularly notable in the
780 thalamus, nucleus accumbens, medial temporal, medial prefrontal/frontal, and insular cortices.
781 SCZ2 displayed increased volume in the basal ganglia and internal capsule, while other brain
782 volumes remained relatively normal⁴.

783

784

785 **Method 3: Imaging analyses**

786 **(a): T1-weighted MRI processing:** All images were first corrected for magnetic field intensity
787 inhomogeneity.⁸⁷ A deep learning-based skull stripping algorithm was applied to remove extra-
788 cranial material. In total, 145 IDPs were generated in gray matter (GM, 119 ROIs), white matter

789 (WM, 20 ROIs), and ventricles (6 ROIs) using a multi-atlas label fusion method from the
790 MUSE atlas.⁸⁸ The ROIs were fit to the four machine learning models to derive the nine DNEs.
791 The imaging quality check is detailed in **Supplementary eMethod 2**. The other IDPs derived
792 from other MRI modalities [i.e., diffusion (category code: 135) and resting-state MRI (data-field
793 code: 25750)] were downloaded from UKBB.

794

795 **(b): Neuroanatomical pattern of the nine DNEs:** We assessed the neuroanatomical patterns
796 exhibited by the nine DNEs within the general population. Since the DNEs were defined based
797 on the 119 GM ROIs obtained from T1-weighted MRI scans, we aimed to test whether these
798 patterns observed in the disease populations were manifested in the general population. To this
799 end, we used a linear regression model in which each DNE was treated as the dependent
800 variable, while the ROI, age, age-squared, sex, age x sex interaction, age-squared x sex
801 interaction, intracranial volume, brain positions in the scanner (lateral, transverse, and
802 longitudinal; Field ID: 25756-25758), and head motion were considered independent variables
803 and covariates. We employed the Bonferroni method for multiple comparisons and reported
804 significant results accordingly.

805

806 **(c): PWAS for the nine DNEs:** We performed PWAS to associate the nine DNEs to each of the
807 611 additional phenotypes. PWAS excluded the 119 GM ROIs utilized to derive the nine DNEs
808 to prevent any potential circular effects. Instead, the analysis incorporated IDPs from other
809 modalities, such as diffusion and resting-state functional MRI. The same linear regression
810 models and multiple comparison corrections were employed as in **Method 3b**.

811 To check the robustness of our PWAS results, we also performed two sensitivity checks:
812 *i)* sex-stratified PWAS for males and females, and *ii)* split-sample PWAS by randomly dividing
813 the entire population into two splits (sex and age did not significantly differ).

814

815 **Method 4: Genetic analyses**

816 We used the imputed genotype data for all genetic analyses, and our quality check pipeline
817 resulted in 31,929 participants with European ancestry and 6,477,810 SNPs. First, we excluded
818 36,394 related individuals (up to 2nd-degree) from the full UKBB sample ($N \sim 500k$) using the
819 KING software for family relationship inference⁸⁹. We then removed duplicated variants from all
820 22 autosomal chromosomes. Individuals whose genetically identified sex did not match their
821 self-acknowledged sex were removed. Other excluding criteria were: *i)* individuals with more
822 than 3% of missing genotypes; *ii)* variants with minor allele frequency (MAF) of less than 1%;
823 *iii)* variants with larger than 3% missing genotyping rate; *iv)* variants that failed the Hardy-
824 Weinberg test at 1×10^{-10} . The Hardy-Weinberg test removes the SNPs that deviate from the
825 expected HWE frequency, ensures the integrity of the genetic data, reduces false-positive
826 findings, and improves the overall robustness of the GWAS results. To adjust for population
827 stratification,⁹⁰ we derived the first 40 genetic principle components (PC) using the FlashPCA
828 software⁹¹. Details of the genetic quality check protocol are described elsewhere.

829

830 **(a): GWAS:** For GWAS, we ran a linear regression using Plink⁹² for each DNE, controlling for
831 confounders of age, age-squared, sex, age x sex interaction, age-squared x sex interaction, the
832 first 40 genetic principal components, total intracranial volume, three brain position parameters
833 in the scanner, and head motion were included, as suggested by a previous study²⁸. We adopted

834 the genome-wide P-value threshold (5×10^{-8}) and annotated independent genetic signals
835 considering linkage disequilibrium (see below).

836 To check the robustness of our GWAS results, we also performed several sensitivity
837 checks: *i*) fastGWA^{39,40} for a generalized mix effect model, *ii*) sex-stratified GWAS for males
838 and females, *iii*) split-sample GWAS by randomly dividing the entire population into two splits
839 (sex and age did not significantly differ), *iv*) comparison of the GWAS results using the 1348
840 participants (i.e., 1116 European ancestry) that were collected for baseline and longitudinal scans
841 from UKBB, *v*) non-European GWAS ($N=4783$), *vi*) independent GWAS on ADNI whole-
842 genome sequencing data ($N=1555$) on AD1 and AD2, *vii*) concordance with six European
843 ancestry GWAS from PGC, including AD, ADHD, ASD, BIP, OCD, and SCZ (**Supplementary**
844 **eTable 3a**).

845
846 **(b): SNP-based heritability:** We estimated the SNP-based heritability (h^2) using GCTA³⁸ with
847 the same covariates as in GWAS. GCTA estimates the SNP-based heritability using a method
848 called restricted maximum likelihood (REML) to quantify the proportion of phenotypic variance
849 in a trait that the additive effects of all common SNPs can explain, which was claimed to address
850 the “missing heritability”. The main steps involved in GCTA include constructing the genetic
851 relationship matrix, modeling phenotypic variance, and using REML to estimate the h^2 .

852
853 **(c): Annotation of genomic loci:** The annotation of genomic loci and mapped genes was
854 performed via FUMA⁹³. For the annotation of genomic loci, FUMA first defined lead SNPs
855 (correlation $r^2 \leq 0.1$, distance < 250 kilobases) and assigned them to a genomic locus (non-
856 overlapping); the lead SNP with the lowest P-value (i.e., the top lead SNP) was used to represent
857 the genomic locus. For gene mappings, three different strategies were considered. First,
858 positional mapping assigns the SNP to its physically nearby genes (a 10 kb window by default).
859 Second, eQTL mapping annotates SNPs to genes based on eQTL associations using the GTEx v8
860 data⁹⁴. Finally, chromatin interaction mapping annotates SNPs to genes when there is a
861 significant chromatin interaction between the disease-associated regions and nearby or distant
862 genes⁹³. The definition of top lead SNP, lead SNP, independent significant SNP, and candidate
863 SNP can be found in **Supplementary eMethod 3**.

864 To determine if a genomic locus is new (i.e., newly discovered in our study), we queried
865 the candidate SNPs, independent significant SNPs, and top lead SNP in the EMBL-EBI GWAS
866 Catalog, taking LD into account. A locus is considered new if no previous GWAS has identified
867 associations with any of these SNPs.

868
869 **(d): Phenome-wide association queries for the identified loci in the GWAS Catalog:** We
870 queried the candidate and significant independent SNPs, fully considering LD (**Supplementary**
871 **eMethod 3**), within each locus in the EMBL-EBI GWAS Catalog (query date: 2nd June 2023,
872 via FUMA version: v1.5.4) to determine their previously identified associations with any other
873 traits. For these associated traits, we further mapped them into several high-level categories for
874 visualization purposes. We categorized these traits based on their primary affected organ
875 systems, with examples including blood pressure under cardiovascular, brain MRI-derived
876 measures under brain, and AD under neurodegenerative disorders. Other platforms, such as the
877 GWAS Atlas (<https://atlas.ctglab.nl/PheWAS>), used a similar categorization approach.

878

879 **(e): Genetic correlation:** We used the LDSC³⁷ software to estimate the pairwise genetic
880 correlation (g_c) between each pair of DNEs, as well as between the nine DNEs and 9 BAGs of
881 multiple organ systems from our previous work¹⁷ and 6 neurodegenerative and neuropsychiatric
882 disorders from PGC (**Supplementary eTable 3a**). We used the precomputed LD scores from the
883 1000 Genomes of European ancestry. To ensure the suitability of the GWAS summary statistics,
884 we first checked that the selected study's population was European ancestry; we then guaranteed
885 a moderate SNP-based heritability h^2 estimate. Notably, LDSC corrects for sample overlap and
886 provides an unbiased estimate of genetic correlation⁹⁵. Benjamini-Hochberg procedure was
887 performed to account for multiple comparisons.

888
889 **(f): Bayesian colocalization:** We used the R package (*coloc*) to investigate the genetic
890 colocalization signals between two traits at each genomic locus. We employed the Fully
891 Bayesian colocalization analysis using Bayes Factors (*coloc.abf*). This method examines the
892 posterior probability (PP.H4.ABF: Approximate Bayes Factor) to evaluate hypothesis $H4$, which
893 suggests the presence of a single shared causal variant associated with both traits within a
894 specific genomic locus. To determine the significance of the $H4$ hypothesis, we set a threshold of
895 $PP.H4.ABF > 0.8^{51}$. All other parameters (e.g., the prior probability of p_{12}) were set as default. We
896 also performed relevant sensitivity analyses to check the robustness of our findings. For each
897 pair of traits, the genomic locus ($N > 100$ SNPs) was defined by default from FUMA on the nine
898 DNEs, and then the *coloc* package extracted and harmonized the GWAS summary statistics
899 within this locus for the other trait.

900
901 **(g): Two-sample bidirectional Mendelian randomization:** We did not perform causal
902 inference between each pair of DNEs due to the overlapped populations and low sample sizes in
903 split-sample analyses.

904 We employed a bidirectional, two-sample Mendelian randomization using the
905 TwoSampleMR package⁶³ to infer the causal relationships between the nine DNEs and the eight
906 BAGs across nine human organ systems¹⁷ (excluding the brain). The forward and inverse
907 Mendelian randomization was performed between each trait pair by switching the exposure and
908 outcome variables. We applied five different Mendelian randomization methods and reported the
909 results of inverse variance weighted (IVW) in the main text and the four others (i.e., Egger,
910 weighted median, simple mode, and weighted mode estimators) in the supplement.

911 We then performed Mendelian randomization between the nine DNEs and eleven chronic
912 diseases spanning the whole-body system. These diseases include four diseases from PGC (the
913 ASD and OCD GWAS summary statistics did not provide the allele frequency information) and
914 seven diseases unbiasedly curated in our previous work¹⁷, which detailed a systematic procedure
915 to choose the appropriate traits. After harmonizing their GWAS summary statistics (using the
916 function *harmonise_data* from 2SampleMR), this resulted in 11 clinical traits with at least six
917 valid IVs (i.e., SNPs). The clinical traits included in our Mendelian randomization are presented
918 in **Supplementary eTable 11**. Benjamini-Hochberg correction was performed for all tested
919 traits.

920 We performed several sensitivity analyses. First, a heterogeneity test was performed to
921 check for violating the IV assumptions. Horizontal pleiotropy was estimated to navigate the
922 violation of the IV's exclusivity assumption⁹⁶ using a funnel plot, single-SNP Mendelian
923 randomization approaches, and Mendelian randomization Egger estimator⁹⁷. Moreover, the

924 leave-one-out analysis excluded one instrument (SNP) at a time and assessed the sensitivity of
925 the results to individual SNP.

926

927 **(h): PRS calculation for the nine DNEs:** We calculated the PRS using the GWAS results from
928 the split-sample analyses. The weights of the PRS were defined based on split1 data (base data),
929 and the split2 GWAS summary statistics were used as the target data for PRS calculation. The
930 QC steps for the base data are as follows: *i*) removal of duplicated and ambiguous SNPs for the
931 base data; *ii*) clumping the base GWAS data; *iii*) pruning to remove highly correlated SNPs in
932 the target data; *iv*) removal of high heterozygosity samples in the target data; *v*) removal of
933 duplicated, mismatching and ambiguous SNPs in the target data. After rigorous QC, we used
934 PLINK to generate PRS for the split2 population by adopting the classic C+T method (clumping
935 + thresholding). To determine the "best-fit" PRS, we performed a linear regression using the PRS
936 calculated at different P-value thresholds (0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5), controlling for age,
937 sex, intracellular volume, and the first forty genetic PCs. For each DNE-PRS, we chose the P-
938 value threshold with the highest incremental R^2 (**Supplementary eFigure 19**).

939 We also tested the PRS-CS⁹⁸ method to derive the nine PRS, which infers posterior SNP
940 effect sizes under continuous shrinkage priors using GWAS summary statistics and an LD
941 reference panel (i.e., UKBB reference). Compared to the PLINK method, PRS-CS obtained
942 higher incremental R^2 to explain the 9 DNEs in the split2 data (1.99% vs. 0.52%, P-value=0.003
943 for two-sample t-test, **Supplementary eFigure 20**). Second, the 9 PRSs from PLINK and PRS-
944 CS were highly concordant and correlated with each other (Pearson's r correlation=0.98, P-
945 value=0.000007, **Supplementary eFigure 21**). Last but not least, the 9 PRSs from PRS-CS did
946 not predict well for mental and behavioral disorders (ICD-10 code: F group) and diseases linked
947 to the central nervous system (ICD-10 code: G group). That is, the highest incremental R^2 was
948 obtained for ear diseases (H6-H9) using all combined 9 PRSs (**Supplementary eFigure 22**).
949 Therefore, we chose to use the 9 PRSs derived from PLINK for all results presented in **Fig. 5**.

950

951 **Method 5: Disease, cognition, and mortality outcome prediction.**

952 We employed logistic regression to calculate the incremental R-squared (R^2) statistics of the nine
953 DNEs and PRSs to predict 14 disease categories (a), support vector machines to classify the
954 healthy control participants from the disease groups (b), and Cox proportional hazard model to
955 predict mortality outcomes (c). The patients for the 14 disease categories were defined based on
956 the ICD-10 code from the UKBB website (Data field: 41270). The healthy control group
957 included participants without any ICD-10-based disease diagnoses. The cognitive function data
958 included 8 cognitive scores (Category: 100026), which were detailed in **Supplementary eFile 23**.
959 The mortality outcome refers to the date of death:
960 <https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=40000>.

961

962 **(a): Pseudo R-squared (R^2) statistics of the logistic regression:** We built a null model by
963 including age, sex, and intracranial volume as predictors and the disease as the outcome variable.
964 The alternative model took the disease-specific DNE or PRS as one additional predictor. The
965 incremental R^2 was calculated as the difference between the pseudo R^2 of the alternative model
966 and that of the null model, implemented by the *PseudoR2* function from the *DescTools* R
967 package (v 0.99.38). For the nine PRSs, we used the PRS target sample ($N=15,891$). For the nine
968 DNEs, we calculated the incremental R^2 using the entire UKBB sample ($N=39,178$) and the PRS

969 target sample ($N=15,891$). We reported the incremental R^2 of the DNE/PRS in the main
970 manuscript (**Fig. 5a** and **b**). Other metrics, including R^2 of the null and the alternative model,
971 sample sizes, and the β values of other covariates, are presented in **Supplementary eFile 20-21**.
972

973 **(b): Support vector machines to classify patients vs. controls:** Using the PRS target sample
974 ($N=15,891$), we used 10000 participants in a nested cross-validation (CV) procedure (i.e., CV
975 training/validation/test datasets) to select the hyperparameter C in SVM. In addition, we held out
976 5581 participants as an independent test dataset. In **Fig. 5c**, we only presented the classification
977 accuracy from the independent test dataset. The nested cross-validation (CV) procedure⁹⁹
978 involved an outer loop repeated 50 times, where 80% of the data were randomly selected for
979 training/validation and 20% for testing. Within each outer loop iteration, an inner loop used 80%
980 of the training/validation data for a 10-fold training/validation split. Critically, the model trained
981 on the training/validation/test datasets generalized to the independent test dataset (**Fig. 5c**).
982 **Supplementary eFile 22** contains various metrics, including balanced accuracy, sensitivity,
983 specificity, negative predictive value (NPV), positive predictive value (PPV), and sample sizes
984 for the independent dataset (*Ind. accuracy*) and the CV training/validation/test datasets (*CV*
985 *accuracy*). We did not statistically compare the performance between different machine learning
986 models as this is a complex matter without a universal solution. A standard t -test on cross-
987 validation results is too liberal and should not be applied, as shown by Nadeau and Bengio¹⁰⁰.
988 The corrected resampled t -test¹⁰⁰ was proposed, but it depends on the data and the cross-
989 validation setup.

990
991 **(c): Support vector regression to predict cognitive scores:** Using the PRS target sample
992 ($N=15,891$), we used 10000 participants in a nested cross-validation (CV) procedure (i.e., CV
993 training/validation/test datasets) to select the hyperparameter C in SVM. In addition, we held out
994 5581 participants (some had missing values depending on specific cognitive scores) as an
995 independent test dataset (*Ind. r*). In **Fig. 5d**, we only presented Pearson's r from the independent
996 test dataset. The same nested CV procedure was used, as mentioned above. Likewise,
997 **Supplementary eFile 23** encompasses a range of metrics, including mean absolute error, P-
998 values, and sample sizes, pertaining to the independent dataset (*Ind. r*) and the CV
999 training/validation/test datasets (*CV r*).

1000
1001 **(d): Cox proportional hazard model to predict the date of death:** To evaluate the predictive
1002 capacity of individual DNE and PRS for mortality risk, we employed a Cox proportional hazard
1003 model while adjusting for covariates such as age and sex. The hazard ratio (HR) was calculated
1004 and reported as the effect size measure that indicates the influence of each DNE or PRS on
1005 mortality risk. Furthermore, we incrementally added the most predictive DNE or PRS to the Cox
1006 model to determine when the model's performance reached saturation. The concordance index
1007 (CI) was utilized to assess the model's performance using a 5-fold cross-validation procedure.
1008 All survival analyses were conducted using the *lifelines* (v0.25.7) Python package.

1009 **Data Availability**

1010 The GWAS summary statistics corresponding to this study are publicly available on the
1011 MEDICINE knowledge portal (<https://labs-laboratory.com/medicine/>). Genomic loci annotation
1012 used data from FUMA (<https://fuma.ctglab.nl/>). UKBB data can be requested at
1013 <https://www.ukbiobank.ac.uk/>. GWAS summary data from the Psychiatric Genomics
1014 Consortium (PGC) can be accessed at <https://pgc.unc.edu/>.

1015 **Code Availability**

1016 The software and resources used in this study are all publicly available:

- 1017 • *HYDRA*: <https://github.com/anbai106/mlni>, DNEs for ASD1-3, LLD1-2, SCZ1-2
- 1018 • *Surreal-GAN*: <https://github.com/zhijian-yang/SurrealGAN>, DNEs for AD1-2
- 1019 • *MLNI*: <https://github.com/anbai106/mlni>, SVM classification, cognitive regression
- 1020 • *PLINK*: <https://www.cog-genomics.org/plink/>, GWAS, PRS
- 1021 • *FUMA*: <https://fuma.ctglab.nl/>, gene mapping, genomic locus annotation
- 1022 • *GCTA*: <https://yanglab.westlake.edu.cn/software/gcta/#Overview>, heritability estimates,
- 1023 and fastGWA
- 1024 • *LDSC*: <https://github.com/bulik/ldsc>, genetic correlation, partitioned heritability
- 1025 • *TwoSampleMR*: <https://mrcieu.github.io/TwoSampleMR/index.html>, MR
- 1026 • *Coloc*: <https://chr1swallace.github.io/coloc/>, Bayesian colocalization
- 1027 • *PRS-CS*: <https://github.com/getian107/PRSes>, PRS
- 1028 • *Lifelines*: <https://lifelines.readthedocs.io/en/latest/>, Survival analyses
- 1029 • *DescTools*: <https://cran.r-project.org/web/packages/DescTools/index.html>, Incremental
- 1030 R^2 analysis
- 1031

1032 **Competing Interests**

1033 None

1034

1035 **Authors' contributions**

1036 Dr. Wen has full access to all the data in the study and takes responsibility for the integrity of the
1037 data and the accuracy of the data analysis.

1038 *Study concept and design:* Wen, Davatzikos

1039 *Acquisition, analysis, or interpretation of data:* all authors

1040 *Drafting of the manuscript:* Wen

1041 *Critical revision of the manuscript for important intellectual content:* all authors

1042 *Statistical analysis:* Wen

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