

1 **The Genetic Architecture of Biological Age in Nine Human Organ** 2 **Systems**

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24 **Abstract**

25 Understanding the genetic basis of biological aging in multi-organ systems is vital for
26 elucidating age-related disease mechanisms and identifying therapeutic interventions. This study
27 characterized the genetic architecture of the biological age gap (BAG) across nine human organ
28 systems in 377,028 individuals of European ancestry from the UK Biobank. We discovered 393
29 genomic loci-BAG pairs ($P\text{-value} < 5 \times 10^{-8}$) linked to the brain, eye, cardiovascular, hepatic,
30 immune, metabolic, musculoskeletal, pulmonary, and renal systems. We observed BAG-organ
31 specificity and inter-organ connections. Genetic variants associated with the nine BAGs are
32 predominantly specific to the respective organ system while exerting pleiotropic effects on traits
33 linked to multiple organ systems. A gene-drug-disease network confirmed the involvement of the
34 metabolic BAG-associated genes in drugs targeting various metabolic disorders. Genetic
35 correlation analyses supported Cheverud's Conjecture¹ – the genetic correlation between BAGs
36 mirrors their phenotypic correlation. A causal network revealed potential causal effects linking
37 chronic diseases (e.g., Alzheimer's disease), body weight, and sleep duration to the BAG of
38 multiple organ systems. Our findings shed light on promising therapeutic interventions to
39 enhance human organ health within a complex multi-organ network, including lifestyle
40 modifications and potential drug repositioning strategies for treating chronic diseases. All results
41 are publicly available at <https://labs-laboratory.com/medicine>.

42 Main

43 Biological aging is complex and influenced by many factors, including genetics², environmental
44 exposures³, and modifiable lifestyle factors⁴ across multiple organ systems. A comprehensive
45 understanding of the phenotypic landscape and genetic architecture underlying biological aging
46 in multiple human organ systems is paramount in forging the path toward precision medicine⁵,
47 including identifying vulnerability (e.g., smoking) and resilience factors (e.g., physical
48 activities). This knowledge can improve our understanding of the underlying mechanisms
49 driving age-related diseases, identify novel therapeutic targets, and develop personalized
50 interventions for maintaining health and functional independence in the aging population.

51 Previous research efforts have made progress in studying the interconnectedness of multi-
52 organ systems in human health^{3,6-13}. In a recent study by McCracken et al., a heart-brain-liver
53 axis was studied, highlighting direct and indirect associations among the three organs and their
54 interconnectivity and shared biological pathways¹¹. A recent review highlighted the role of inter-
55 organ signals in metabolic control, including the secretion of peptides, small molecules, and lipid
56 mediators by metabolic tissues and the involvement of the central nervous system in
57 coordinating peripheral metabolic functions⁹. Riding the crest of the wave of artificial
58 intelligence (AI), the biomedical community has increasingly adopted the biological age gap
59 (BAG) as a comprehensive biomarker of human aging in multiple human organ systems.
60 Specifically, BAG serves as a quantitative phenotype to capture the disparity between an
61 individual's AI-derived age and chronological age, which can be used to model aging-related
62 normative trajectory at the individual level and holds potential for application in disease
63 populations to capture pertinent pathological processes. For instance, Nie et al. derived the
64 biological age in nine organ systems to predict the possibility of becoming centenarian¹³. In our
65 previous study, Tian et al. derived eight BAGs in eight organ systems, correlating them with
66 cognition, chronic disease, lifestyle factors, and mortality³. We employed a support vector
67 machine in cross-validation to predict BAGs for multiple organ systems (**Method 1** for details).

68 However, genetic determinants and biological pathways that underlie the observed
69 heterogeneity of organ-specific BAGs remain elusive. Furthermore, whether chronic diseases
70 and lifestyle factors causally impact the divergence between predicted age and chronological age
71 in these organ systems remains to be established, manifesting as either a younger or older
72 biological age. Our previous genome-wide association study (GWAS) uncovered the genetic
73 heterogeneity of the multimodal brain BAGs using magnetic resonance imaging (MRI) data¹⁴.
74 Expanding on prior research, the current study sought to comprehensively depict the genetic
75 architecture underlying biological aging across nine human organ systems, including the brain,
76 cardiovascular, eye, hepatic, immune, metabolic, musculoskeletal, pulmonary, and renal BAGs.
77 Our overarching hypothesis postulates that the genetic determinants associated with the nine
78 BAGs are not only specific to individual organ systems (i.e., BAG-organ specificity) but also
79 directly or indirectly interconnected with other organ systems (i.e., inter-organ connection).

80 In the current study, we analyzed multimodal data from 377,028 individuals of European
81 ancestry in the UK Biobank study¹⁵ (UKBB) to comprehensively capture the genetic architecture
82 of the nine organ systems (**Method 2**). First, we used data from 154,774 participants to perform
83 GWAS, gene-level, partitioned heritability, and genetic correlation analyses (**Method 3**). In our
84 Mendelian randomization analyses, we used 222,254 UKBB participants that did not overlap
85 with the individuals used to compute BAG to avoid potential bias¹⁶. We *i*) identified both
86 previously reported and newly identified genomic loci, *ii*) demonstrated a greater genetic
87 heritability estimate for the brain BAG compared to other organ systems, *iii*) constructed a

88 network linking genes, drugs, and diseases for potential drug repurposing, *iv*) confirmed that
89 BAG-associated variants and genes exhibit BAG-organ specificity and inter-organ connection,
90 and *v*) established both genetic correlations and causal networks among the nine BAGs, chronic
91 diseases, and lifestyle factors. All results, including the GWAS summary statistics, are publicly
92 accessible through the MEDICINE (Multi-organ biomEDical sCIeNcE) knowledge portal:
93 <https://labs-laboratory.com/medicine>.

94

95 Results

96 Genome-wide associations identify 393 genomic loci associated with the nine biological age 97 gaps

98 In the European populations, GWAS (Method 3a) identified 11, 44, 17, 41, 61, 76, 24, 67, and
99 52 genomic loci ($P\text{-value} < 5 \times 10^{-8}$) significantly associated with the brain, cardiovascular, eye,
100 hepatic, immune, metabolic, musculoskeletal, pulmonary, and renal BAGs, respectively (Fig. 1).
101 All details of the identified loci are presented in Supplementary eFile 1. Manhattan and QQ
102 plots are presented in Supplementary eFigures 1-9 and available in the MEDICINE knowledge
103 portal (<https://labs-laboratory.com/medicine>).

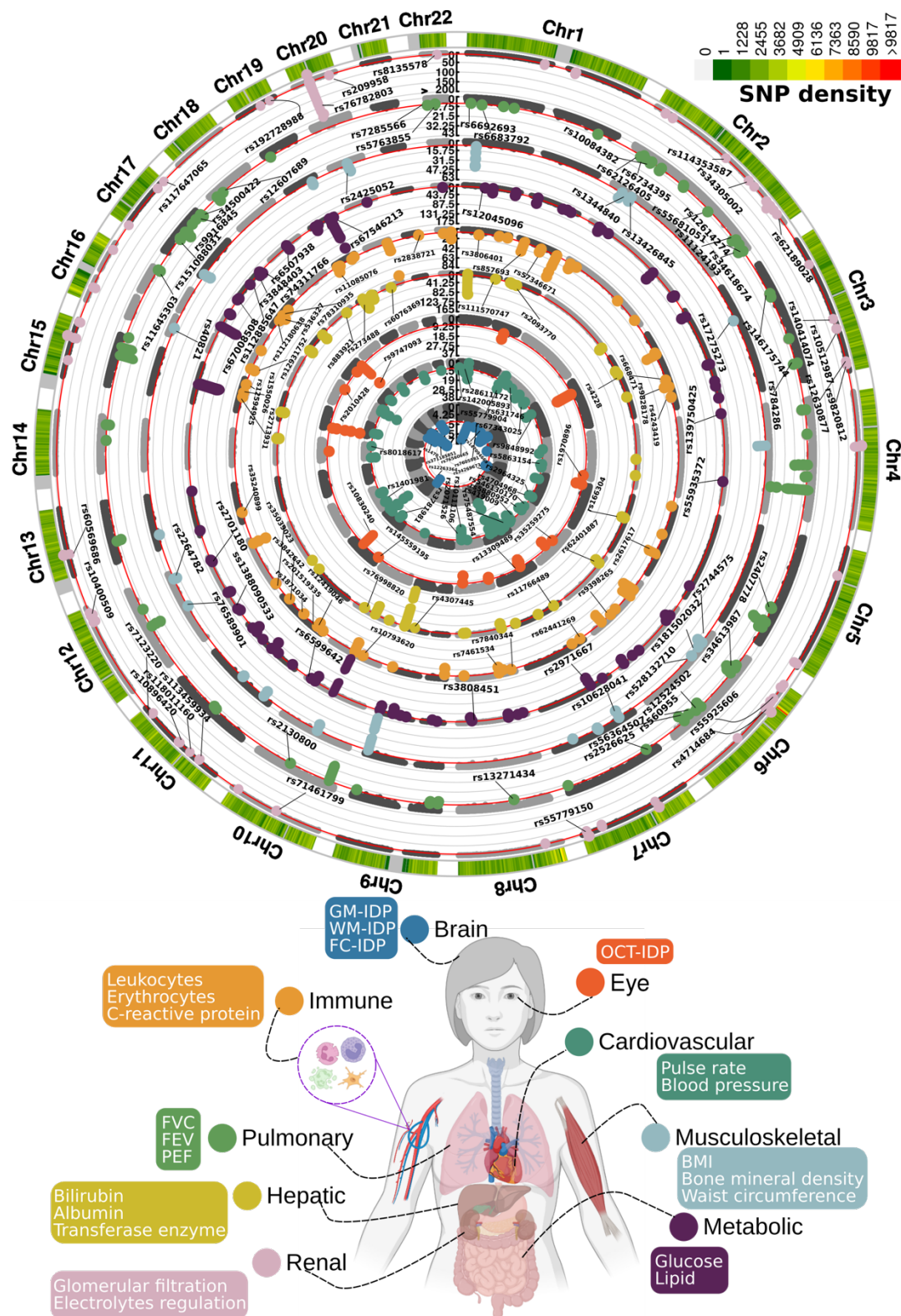
104 We estimated the intercept of linkage disequilibrium score regression (LDSC)¹⁷ for the
105 nine main GWAS and obtained intercepts of 0.9989 ± 0.009 , 1.0185 ± 0.0099 , 0.9926 ± 0.0106 ,
106 1.0416 ± 0.0113 , 1.0293 ± 0.0107 , 1.0308 ± 0.0124 , 1.0282 ± 0.0099 , 1.0442 ± 0.0104 , and
107 1.0257 ± 0.0112 for the nine BAGs. All the intercepts were close to 1, indicating no substantial
108 genomic inflation in the primary GWAS. Furthermore, we conducted four sensitivity analyses
109 (Method 3a) to assess the robustness of the primary nine GWASs on individuals of European
110 ancestry (Supplementary eText 1). Our GWASs demonstrated robustness in split-sample
111 GWAS, with a perfect concordance rate for the sign (+/-) of β values ($C\text{-}\beta=1$) between the split1
112 and split2 GWASs. The two sets of β values were highly correlated ($0.90 < r\text{-}\beta < 0.99$ for Pearson's
113 r) and did not significantly differ ($P\text{-}\beta > 0.48$ for two-sample t-test). We compared the GWAS
114 results with linear models in PLINK and linear mixed-effect models in fastGWA¹⁸, resulting in a
115 perfect concordance for the two sets of β values, as well as very similar LDSC intercept values.
116 These findings further support the absence of cryptic population stratification in our primary
117 GWASs. Sex-stratified GWASs unveiled distinctive genetic patterns specific to each sex, with
118 noteworthy disparities observed in the genetic architecture of the immune BAG ($r\text{-}\beta=0.29$; $P\text{-}\beta=0.01$; $C\text{-}\beta=0.55$). Immune responses exhibit sex differences that vary across the lifespan and
119 are influenced by age and reproductive status¹⁹. Detailed quantitative information regarding these
120 observations can be found in Supplementary eText 1, while visual representations of these
121 patterns are available in Supplementary eFigures 5 and 7. Finally, the genetic signals identified
122 within non-European populations were less prominent compared to the European GWAS due to
123 the limited sample size, but we found a high concordance between the two sets of β values using
124 the three proposed metrics ($0.85 < r\text{-}\beta < 0.95$; $0.89 < C\text{-}\beta < 1$; $P\text{-}\beta > 0.12$). This underscores the
125 necessity of expanding sample sizes within underrepresented ethnic groups in future GWAS
126 studies. Detailed statistics can be found in Supplementary eFiles 2-5.

127
128 Certain genomic loci exhibited unique associations with individual organs, whereas
129 others displayed connections to multiple organ BAGs in close genomic proximity based on their
130 cytogenetic position. For instance, the locus on chromosome 6 associated with the hepatic
131 (rs62401887, position: 24416482 at 6p22.3), immune (rs80215559, position: 25918225 at

132 6p22.3), metabolic (rs79220007, position: 26098474 at 6p22.2), musculoskeletal (rs2744575,
133 position: 24494975 at 6p22.3), pulmonary (rs411535, position: 22061040 at 6p22.3), and renal
134 BAGs (rs55925606, position: 25878848 at 6p22.2) was close with each other on the human
135 genome. Bayesian colocalization²⁰ analyses (**Method 3h**) supported two distinct causal SNP
136 within this locus with the liver and musculoskeletal BAGs. Our results showed a posterior
137 possibility (PP) of two distinct causal variants (PP.H3.ABF=0.744) or one shared causal variant
138 (PP.H4.ABF=0.256) associated with both traits in the *GPLD1* gene, although the PP.H4.ABF
139 hypothesis did not achieve the suggested threshold (>0.8)²⁰. Detailed results are presented in
140 **Supplementary eFigure 10**. However, note that these loci on chromosome 6 are near the major
141 histocompatibility complex (MHC) region; further dedicated analyses are needed to understand
142 the underlying genetics across different BAGs (e.g., pleiotropy).

143 Many of these loci were mapped to protein-encoding genes and provided functional
144 insights. For example, the top lead SNP (rs62401887 at 6p22.3) within the locus of the hepatic
145 BAG was mapped to the *MRS2* gene by position (with a deleterious score of 14.89) and
146 expression quantitative trait loci (eQTL, P-value=1.09x10⁻¹⁰) (**Method 3c**), which enables
147 magnesium ion transmembrane transporter activity. We illustrate the regional Manhattan plot for
148 the genomic locus with the highest significance for each organ BAG in **Supplementary eFigure**
149 **11**. For instance, the brain BAG exhibited a highly significant locus (top lead SNP: rs371185851
150 at 17q21.31) with multiple protein-encoding genes, including the widely recognized *MAPT* gene
151 encoding tau protein associated with neurodegenerative diseases, such as Alzheimer's disease
152 (AD)²¹. Moreover, the SNPs within this locus included enhancers and transcription start sites
153 specific to brain tissue chromatin states, highlighting their functional relevance in brain-related
154 processes (**Supplementary eFigure11a**).

155 **Figure 1: Genomic loci associated with the nine biological age gaps**



156
 157 Organ-specific biological age gap (BAG) was derived from a large cohort of 30,108 to 111,543
 158 European ancestry participants from the UK Biobank cohort. The nine organ systems include the

159 brain ($N=30,108$), cardiovascular ($N=111,543$), eye ($N=36,004$), hepatic ($N=111,543$), immune
160 ($N=111,543$), metabolic ($N=111,543$), musculoskeletal ($N=111,543$), pulmonary ($N=111,543$),
161 and renal ($N=111,543$) BAGs. 393 genomic loci-BAG pairs were identified using a genome-wide
162 P-value threshold [$-\log_{10}(\text{P-value}) > 7.30$]. For visualization purposes, we denoted the genomic
163 loci using their top lead SNPs that are not associated with any clinical traits in the EMBL-EBI
164 GWAS Catalog. The anatomical illustration of the human body was created using
165 [BioRender.com](https://www.biorender.com). All analyses used the Genome Reference Consortium Human Build 37
166 (GRCh37). We present representative features employed in the calculation of each organ organ's
167 BAG. BMI: body mass index; IDP: imaging-derived phenotype; GM: gray matter; WM: white
168 matter; FC: functional connectivity; OCT: optical coherence tomography; FVC: forced vital
169 capacity; FEV: forced expiratory volume; PEF: peak expiratory flow.

170

171 **Phenome-wide associations demonstrate organ system specificity and inter-organ**

172 **connection**

173 We aimed to investigate the agreement of the identified genomic loci in existing GWAS
174 literature. To this end, we performed a phenome-wide association query in the EMBL-EBI
175 GWAS Catalog²² for independent significant SNPs within each locus, considering linkage
176 disequilibrium and redundant associations (**Method 3d**).

177 This pheno-wide associations query identified 11,709 significant associations between
178 the identified loci in our GWAS and clinical traits in the literature linked to each organ system
179 (i.e., BAG-organ specificity) (**Fig. 2a**). The genomic loci associated with the brain BAG
180 exhibited the highest proportion of associations (74 out of 173) with traits related to the brain,
181 including imaging-derived phenotypes such as brain volume metrics and white matter
182 microstructure, demonstrated in the keyword cloud presented in **Fig. 2a**. The brain BAG loci
183 were also largely linked to many other traits related to other organ systems and chronic diseases,
184 evidencing inter-organ connections, including metabolic ($N=43/173$, e.g., cholesterol levels),
185 lifestyle factor ($N=1/173$, i.e., alcohol consumption), neurodegenerative traits ($N=16/173$, e.g.,
186 AD), and immune ($N=7/173$, e.g., lymphocyte count). For the eye BAG loci, most associations
187 were found in the eye ($N=31/128$, e.g., retinal nerve fiber layer thickness) and brain traits
188 ($N=6/128$, e.g., brain morphology), among others.

189 For the seven body organ systems, among the loci associated with the cardiovascular
190 BAG, most associations were observed with cardiovascular traits (319 out of 439), such as
191 systolic/diastolic blood pressure and coronary artery disease. Other associations were found with
192 musculoskeletal ($N=30/439$), metabolic ($N=14/439$), immune ($N=6/439$), renal ($N=18/1890$), and
193 brain ($N=9/439$) traits. 376 out of 1853 associations were related to hepatic traits (e.g., blood
194 protein, cirrhosis, and bilirubin) for the hepatic BAG loci. Among the loci associated with the
195 immune BAG, abundant associations were found in metabolic (929 out of 1773), immune
196 ($N=244/1773$), hepatic ($N=149/1853$), musculoskeletal ($N=57/1853$), and cardiovascular traits
197 ($N=72/1853$). For the metabolic BAG loci, most associations were observed in metabolic traits
198 (3841 out of 4907). We found a significant intertwining of metabolic systems with other organ
199 systems, highlighting inter-organ connections in human metabolic activities. Details of the
200 phenome-wide associations are presented in **Supplementary eFile 6**. Furthermore, we reported
201 the complementary results of this phenome-wide association query using the GWAS Atalas²³
202 platform (**Supplementary eText 2** and **Supplementary eFile 7**).

203

204 The SNP-based heritability estimates of the nine biological age gaps

205 We estimated the SNP-based heritability (h^2) across the nine organ systems using the full sample
206 sizes (**Fig. 2b**) of the nine BAGs. Additionally, the distributions of the magnitude of the β
207 coefficient in GWAS and the allele frequency of the alternative allele (effect allele) are shown in
208 **Fig. 2c** and **d**. Notably, the sample sizes of the brain and eye BAGs were much smaller than that
209 of the seven body organ BAGs; the body organ BAGs had the same populations.

210 Upon analyzing the full sample sizes, the estimated h^2 for the brain BAG (0.47 ± 0.02)
211 outperformed all other organ systems, followed by the eye (0.38 ± 0.02), pulmonary (0.36 ± 0.006),
212 renal (0.31 ± 0.006), metabolic (0.29 ± 0.006), cardiovascular (0.27 ± 0.006), musculoskeletal
213 (0.24 ± 0.006), hepatic (0.23 ± 0.006), and immune BAGs (0.21 ± 0.006) (**Fig. 2b**). All heritability
214 estimates were statistically significant after controlling for multiple comparisons using the
215 Bonferroni correction. This trend persisted when subsampling the population of other BAGs to
216 match that of the brain BAG, with comparable distributions in sex and age (**Supplementary**
217 **eFigure 12a**). Detailed results of the h^2 estimate are presented in **Supplementary eTable 1a-b**.
218 Of note, we employed the GCTA²⁴ software to estimate h^2 , acknowledging that previous
219 research^{25,26} has demonstrated variations in the magnitude of h^2 estimates based on the choice of
220 methods.

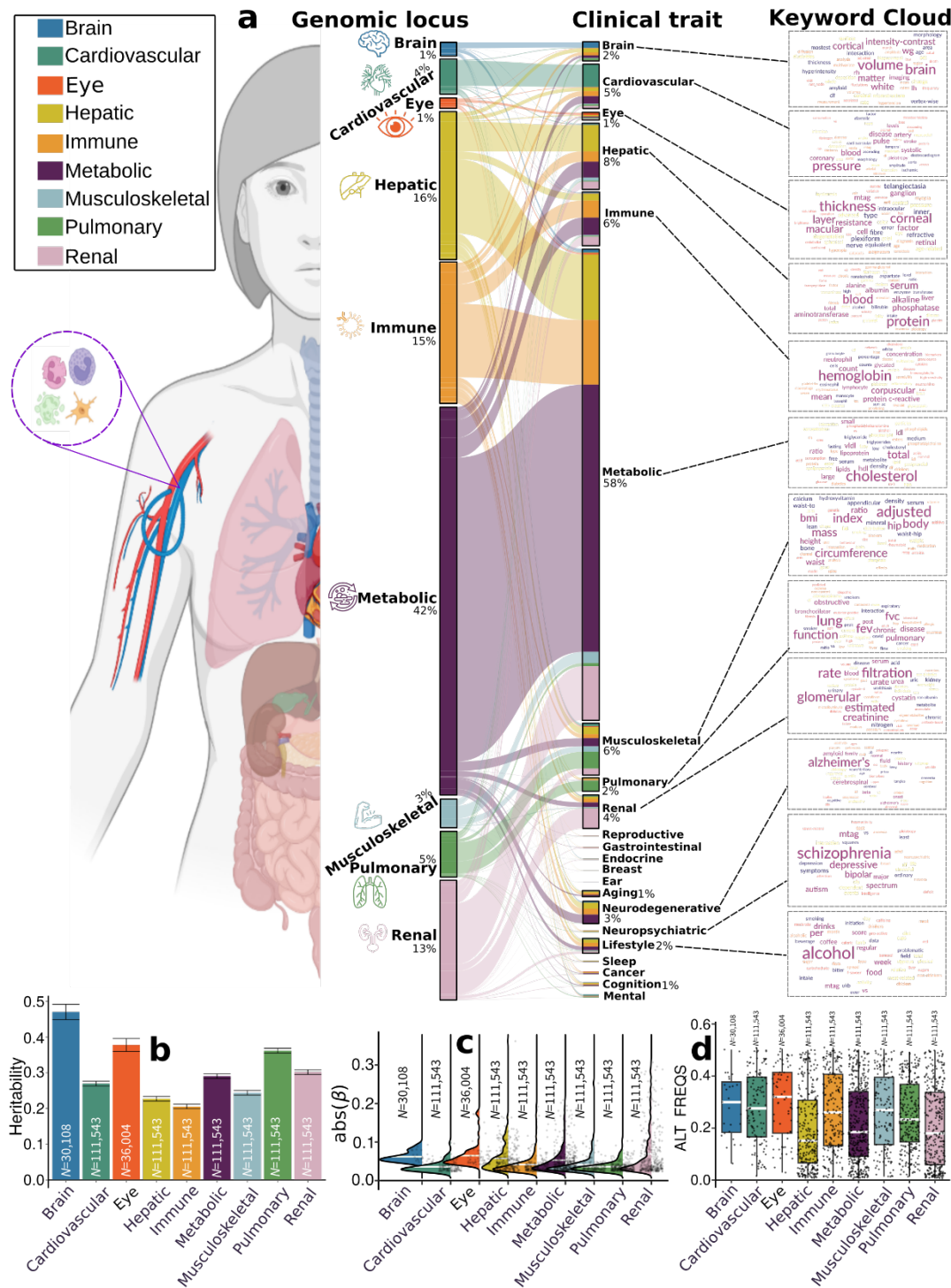
221 To gain deeper insights into the significant genetic signals in the brain and eye, we
222 conducted a detailed examination of the effect sizes (β coefficient) in the GWAS of the nine
223 BAGs, as the effect size is independent of the sample size. The independent significant SNPs of
224 the brain ($|\beta|=0.062\pm 0.013$; [0.0470, 0.093]) and eye ($|\beta|=0.0645\pm 0.030$) BAG showed larger
225 mean magnitudes than the seven body organ systems (**Fig. 2c**). Among the body organ BAGs
226 with the same sample size, the renal BAG showed the largest effect size ($0.023<|\beta|<0.306$). This
227 pattern persisted with the results using the subsampled populations to the brain BAGs, presented
228 in **Supplementary eFigure 12b**. The full set of statistics (e.g., β coefficient) of the independent
229 significant SNPs is detailed in **Supplementary eFile 5** for the European ancestry GWAS.

230 It is widely recognized that the effect size of common genetic variants tends to increase
231 as the allele frequency decreases^{27,28}. This “inverse relationship” was evidenced by our data
232 using independent significant SNPs from the 9 BAGs (**Supplementary eFigure 13**); the SNP
233 with a lower allele frequency requires a larger sample size to achieve statistical significance. We
234 then hypothesized that the smaller sample sizes of the brain and eye BAGs enabled us to detect
235 significant variants with a relatively higher allele frequency but could not identify the SNPs with
236 a relatively lower allele frequency associated with the body organ BAGs. As shown in **Fig. 2d**,
237 we observed that the alternative (effect) allele frequency of the independent significant SNPs
238 associated with the brain and eye BAGs was relatively higher than that of the body organ BAGs.
239 This indicates that larger samples are required for the brain and eye to detect SNP effects with a
240 relatively lower allele frequency. This relationship persisted by subsampling the population of
241 other BAGs to that of the brain BAGs, which is presented in **Supplementary eFigure 12c**. As
242 expected, the β coefficients derived from the whole samples ($N>10k$ for body organ BAGs) were
243 not significantly different from the results using the brain-BAG comparable down-sampled
244 samples ($N=30,108$) (**Supplementary eTable 2**).

245 Another hypothesis is that the features used to compute the brain and eye BAGs – *in vivo*
246 imaging features – are more heritable than those of the body-organ systems. We compared the
247 genetic structure of the nine BAGs and the individual features used to compute the BAGs. This
248 comparison is crucial for gaining insights into how the choice of predictors impacts the results of
249 BAG GWAS, which, in turn, is fundamental for subsequent analyses related to pleiotropy and

250 trait associations. We first estimated the SNP-based heritability for four pulmonary features and
251 compared these with a set of multimodal brain imaging-derived phenotypes from our previous
252 studies^{14,29–32} using the same GCTA software. We hypothesized that the brain imaging features
253 would exhibit a higher degree of heritability than the 4 pulmonary features of the pulmonary
254 BAG (i.e., forced vital capacity, forced expiratory volume, peak expiratory flow, and the ratio of
255 forced expiratory volume to forced vital capacity), supported by the results in **Supplementary**
256 **eTable 1c**. We then performed GWAS for the four pulmonary features within the European
257 ancestry populations. The Manhattan and QQ plots are presented in **Supplementary eFigure 14**.
258 The pulmonary BAG showed high genetic correlations using LDSC with the four pulmonary
259 features ($-0.79 < g_c < 0.83$, **Supplementary eTable 3**). Using Bayesian colocalization analysis
260 (**Method 3h**), we identified 99 potential causal variants ($PP.H4.ABF > 0.80$) between the
261 pulmonary BAG and the four underlying features (**Supplementary eFile 8**). We showcased one
262 causal variant evidenced at one locus (4q24) between the pulmonary BAG and the FEV/FCV
263 feature (**Supplementary eFigure 15**). The $PP.H4.ABF$ (0.99) denotes the posterior probability
264 of hypothesis H4, which suggests that both traits share the same causal SNP (rs7664805, mapped
265 gene: *NPNT*). SNPs in linkage disequilibrium with the causal SNP were previously linked to
266 chronic obstructive pulmonary disease in the GWAS Catalog. To elucidate the genetic overlap at
267 the individual SNP level, we showed the β coefficient of the 48 potential causal variants that
268 passed the genome-wide significance for the pulmonary BAG and at least one pulmonary feature
269 in **Supplementary eFigure 16**.

270 **Figure 2: Phenome-wide associations of the identified genomic loci and SNP-wide**
 271 **heritability estimates of the nine biological age gap**
 272



273 **a)** Phenome-wide association query of the identified genomic loci in the EMBL-EBI GWAS
 274 Catalog (query date: 24th April 2023, via FUMA version: v1.5.4) showed an organ-specific and
 275 inter-organ landscape. By examining the independent significant SNPs considering linkage
 276 disequilibrium (**Method 3d**) within each genomic locus, we linked them to various clinical traits.
 277

278 These traits were categorized into high-level groups encompassing different organ systems,
279 neurodegenerative and neuropsychiatric disorders, and lifestyle factors. To visually represent the
280 findings, we generated keyword cloud plots based on the frequency of these clinical traits within
281 each BAG. The length of each rectangle block indicates the number of associations concerning
282 the genomic loci in our analysis and clinical traits in the literature. The individual disease traits
283 were categorized within their respective organ systems. However, this categorization doesn't
284 imply that the sum of these diseases exclusively represents the entirety of the organ system or
285 that these diseases are solely associated with one specific organ system. Additional searches on
286 alternative public GWAS platforms, such as the GWAS Atlas, are provided in **Supplementary**
287 **eText 2. b)** Brain BAG is more heritable than other organ systems using GCTA²⁴. **c)** Brain BAG
288 showed larger effect sizes of the independent significant SNPs than other organ systems. The
289 kernel density estimate plot shows the distribution of the effect sizes (i.e., the magnitude of the
290 linear regression β coefficients) in the nine GWAS. The white horizontal lines represent the
291 mean effect sizes. **d)** The distribution of the alternative allele frequency (effect allele) for the
292 nine BAGs. Of note, only independent significant SNPs were shown for each BAG in Figures **c-**
293 **d**. All results in Figures **b-d** used the original full sample sizes of the nine BAGs; the brain, eye,
294 and other body organ BAGs have different sample sizes. Error bars represent the standard error
295 of the estimated parameters. Results for Figure **b-d** using the down-sampled sample sizes
296 ($N=30,108$ of the brain BAG) are shown in **Supplementary eFigure 12**. ALT FREQS: allele
297 frequency of the alternative (effective) allele.
298

299 **Genes linked to the nine biological age gaps are implicated in organ system-specific** 300 **biological pathways**

301 To biologically validate our GWAS findings at the gene level, we performed gene-based
302 associations using the MAGMA³³ software based on the full P-value distribution from the
303 GWAS of the nine BAGs. The significantly associated genes (**Supplementary eFile 9**) were
304 used for the gene set enrichment analysis (GSEA, **Method 3e**) to annotate relevant biological
305 pathways underlying each organ system (**Fig. 3a**).

306 Genes associated with the cardiovascular BAG were implicated in the insulin-like growth
307 factor II binding (IGF-II) pathway ($P\text{-value}=7.08\times 10^{-7}$). Genes associated with the eye BAG
308 were enriched in the pathway of forebrain dorsal-ventral pattern (FDVP) formation ($P\text{-}$
309 $\text{value}=6.46\times 10^{-7}$). Among others, the most significant enrichment result shown in the hepatic
310 BAG was the flavonoid glucuronidation pathway ($P\text{-value}=1.71\times 10^{-8}$). Genes linked to the
311 metabolic BAG displayed enrichment in several pathways, including the flavonoid
312 glucuronidation pathway ($P\text{-value}=2.46\times 10^{-15}$) and triglyceride-rich lipoprotein particle clearance
313 pathway ($P\text{-value}=3.72\times 10^{-15}$), both of which are implicated in liver function. In addition, the
314 neutral lipid metabolic process, regulated by complex pathways featuring lipid metabolism
315 enzymes and structural proteins, was also identified. Genes associated with the musculoskeletal
316 BAG exhibited enrichment in the gene set in an amplicon at 20q11 ($P\text{-value}=1.54\times 10^{-15}$), defined
317 by a study of copy number alterations conducted on 191 patients with breast tumors³⁴. Genes
318 associated with the pulmonary BAG displayed significant enrichment in the pathways of the
319 negative regulation biosynthetic process ($P\text{-value}=3.72\times 10^{-10}$), consistent with a previous DNA
320 methylation analysis of pulmonary function using old-aged Chinese monozygotic twins³⁵. Genes
321 associated with the renal BAG were implicated in the xenobiotic glucuronidation pathway ($P\text{-}$

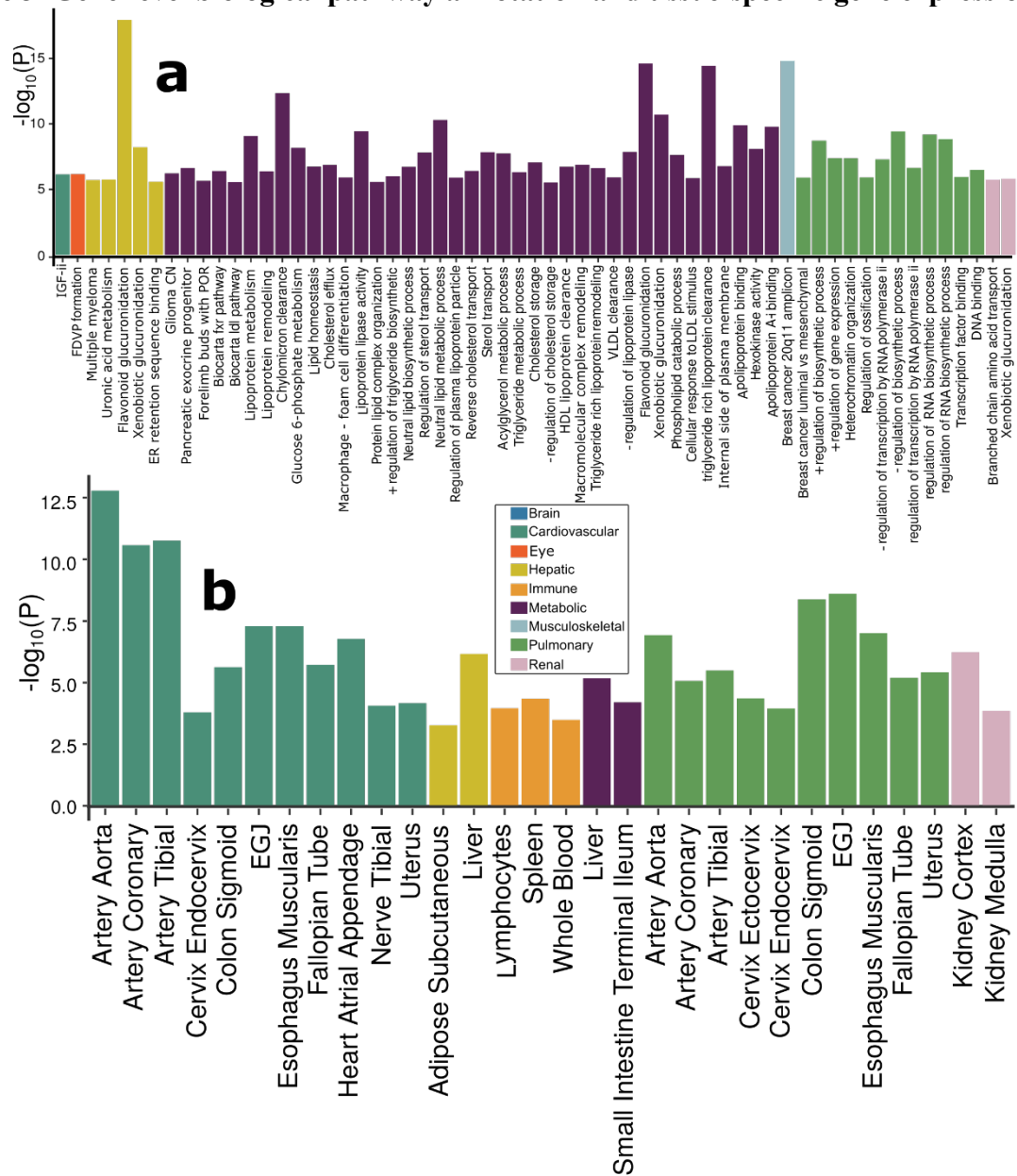
322 value= 1.56×10^{-6}). Given that the kidney contains most enzymes metabolizing foreign substances
323 (i.e., xenobiotics), it plays a crucial role in the overall metabolism of drugs and other foreign
324 compounds within the body (**Fig. 3a**). Detailed results of GSEA are presented in
325 **Supplementary eFile 10**. Sex-stratified results are presented in **Supplementary eFigure 17**.
326

327 **Genes linked to the nine biological age gaps display organ system-specific gene expression** 328 **patterns**

329 To investigate the gene expression patterns of the significant genes associated with the nine
330 BAGs, we performed a tissue-specific gene expression analysis³³ using MAGMA and the GTEx
331 RNA-seq dataset³⁶ (**Method 3f**).

332 Across 54 human organ tissues (**Fig. 3b**), genes associated with the cardiovascular BAG
333 exhibited significant overexpression in various heart-related tissues (e.g., the aorta and tibial
334 artery) and other organs (e.g., the uterus and colon sigmoid). Genes associated with the hepatic
335 BAG were overexpressed in the liver and adipose subcutaneous. Several immune system-related
336 tissues showed a high average expression of the genes related to the immune BAG, including the
337 spleen, blood, and lymphocytes. Likewise, the genes associated with the metabolic BAG showed
338 a high expression level in the liver and intestine – critical organs in the metabolic system. The
339 genes related to the pulmonary BAG displayed significant overexpression in the esophagus
340 gastroesophageal junction, artery, and others. The genes associated with the renal BAG were
341 overexpressed in the kidney. Detailed results are presented in **Supplementary eFile 11**. Sex-
342 stratified results are presented in **Supplementary eFigure 18**.

343 **Figure 3: Gene-level biological pathway annotation and tissue-specific gene expression**



344 **a)** Validation of the nine BAGs in gene set enrichment analyses. Gene set enrichment analyses
 345 were performed using curated gene sets and GO terms from the MsigDB database. **b)** Validation
 346 of the nine BAGs in gene-property analyses. Gene-property analyses evaluate tissue-specific
 347 gene expressions for the nine BAG-related genes using the full SNP P-values distribution. Only
 348 significant gene sets are presented after adjusting for multiple comparisons using the Bonferroni
 349 correction. Abbreviation: EGJ: esophagus gastroesophageal junction.
 350
 351
 352

353 **Gene-drug-disease network substantiates potentially repositionable drugs for aging-related**
354 **diseases**

355 We performed a drug target enrichment analysis³⁷ for the genes linked to the nine BAGs in the
356 targeted gene sets of drug categories using the DrugBank database³⁸, thereby constructing a
357 gene-drug-disease network of potentially repositionable drugs (**Method 3g**).

358 The constructed gene-drug-disease network (**Fig. 4**) identified significant interactions
359 between 12 metabolic BAG-linked genes, 46 drugs, and many metabolic disorders encoded in
360 the ICD10 code (E70-E90). For instance, the *PPARD* gene was the target gene of the PPAR- δ
361 agonist (SAR 351034, denoted in **Fig. 4**), which aimed to improve insulin sensitivity and lipid-
362 related activities and battle against inflammation and oxidative stress, serving as actionable drugs
363 for metabolic disorders, diabetes, and kidney and liver injury-related diseases³⁹. Our results
364 showed that genes associated with the metabolic BAG were used to develop drugs treating
365 various other diseases – beyond metabolic disorders – related to multiple organ systems (**Fig. 4**).
366 These included heart-related diseases (e.g., chronic rheumatic heart diseases for I05-I09) and
367 cerebrovascular disease (I60-I69), although the enrichment did not survive correction for
368 multiple comparisons (**Fig. 4**). For instance, the drug MPSK3169A (clinical trial number:
369 NCT01609140; metabolic BAG linked gene: *PCSK9*) is used to treat cerebrovascular disease and
370 coronary heart disease; T3D-959 (clinical trial number: NCT04251182; pulmonary BAG linked
371 gene: *PPARD*), was a candidate drug targeting AD. Detailed results are presented in
372 **Supplementary eFile 12**.

373 The drug-gene-disease network reveals the association between genes related to the
374 metabolic BAG and drugs targeting various chronic diseases. It highlights the importance of the
375 metabolic system in the overall functioning of the human body and the potentials of
376 repositioning existing drugs to tackle biological aging.

377
378

379 **Figure 4: Gene-drug-disease network of the nine biological age gaps**



380
 381 The gene-drug-disease network reveals a broad spectrum of gene, drug, and disease interactions
 382 across the nine BAGs, highlighting the metabolic-related genes. The ICD-10 code icons
 383 symbolize disease categories linked to the primary organ systems (e.g., G30 for Alzheimer's
 384 disease in the CNS). All presented genes passed the nominal P-value threshold (<0.05) and were
 385 pharmaco-genetically associated with drug categories in the DrugBank database; the symbol *
 386 indicates gene-drug-disease interactions that survived the Bonferroni correction. Abbreviation:
 387 ICD: International Classification of Diseases; EGJ: esophagus gastroesophageal junction.

388
389 **Heritability enrichment in different cell types, functional categories, tissue-specific gene**
390 **expression, and chromatin states**

391 To further biologically validate our GWAS findings at the SNP level, we performed partitioned
392 heritability analyses⁴⁰ (**Method 3i**) to estimate the heritability enrichment of genetic variants
393 related to the nine BAGs concerning three different cell types⁴¹ (i.e., neurons, oligodendrocytes,
394 and astrocytes, **Fig. 5a**), 53 non-tissue-specific functional categories⁴⁰ (**Fig. 5b**), 205 tissue-
395 specific gene expression data³⁶ (**Fig. 5c**) and 489 tissue-specific chromatin states^{42,43} (**Fig. 5d**).

396 We found significant heritability enrichment in oligodendrocytes (P-value=0.03), a
397 specific type of neuroglial cells, for the brain BAG. The cardiovascular BAG also exhibited
398 significant heritability enrichment in neurons (P-value=0.01) (**Fig. 5a, Supplementary eFile**
399 **13**). Concerning the heritability enrichment in non-tissue-specific functional categories, we
400 exemplified the four highest significant partitioned heritability estimates for each BAG in **Fig.**
401 **5b**. For the brain BAG, the super-enhancer regions employed 17.16% of SNPs to explain
402 0.47 ± 0.04 of SNP heritability (P-value= 1.80×10^{-11}), and the histone H3 at lysine 9
403 (H3K9ac) regions used 12.61% of SNPs to explain 0.61 ± 0.12 of SNP heritability (P-
404 value= 2.96×10^{-4}). For the eye BAG, the super-enhancer regions explained 0.39 ± 0.05 of SNP
405 heritability (P-value= 2.12×10^{-6}) using 16.84% of SNPs. For the hepatic BAG, the H3K9ac
406 regions explained 0.69 ± 0.13 of SNP heritability (P-value= 3.60×10^{-5}) using 12.61% of SNPs. For
407 the immune BAG, the TSS regions (i.e., core promoters) explained 0.37 ± 0.08 of SNP heritability
408 (P-value= 1.48×10^{-6}) using 1.82% of SNPs. The 3.11% of SNPs annotated by the promoter
409 regions explained 0.30 ± 0.08 of SNP heritability (P-value= 7.64×10^{-4}) for the metabolic BAG. For
410 the cardiovascular (enrichment= 16.39 ± 2.23 ; P-value= 4.70×10^{-11}), musculoskeletal
411 (enrichment= 17.34 ± 4.08 ; P-value= 1.65×10^{-6}), pulmonary (enrichment= 16.82 ± 2.51 ; P-
412 value= 7.58×10^{-9}), and renal (enrichment= 13.96 ± 1.88 ; P-value= 7.25×10^{-9}) BAGs, the highest
413 heritability enrichment was found in the regions conserved across mammals (**Fig. 5b,**
414 **Supplementary eFile 14**). These results suggested disproportionate genomic contributions to the
415 heritability of BAGs from multiple functional categories.

416 In addition, the nine BAGs showed high heritability enrichment in specific tissues
417 corresponding to their organ systems. For example, the cardiovascular BAG showed significant
418 heritability enrichment in multiple tissue types, including the artery (e.g., the aorta: P-
419 value= 1.03×10^{-7}), myometrium (P-value= 1.35×10^{-4}), and uterus (P-value= 2.43×10^{-4}). Significant
420 heritability enrichment was found in the liver for the hepatic (P-value= 5.60×10^{-9}) and metabolic
421 BAGs (P-value= 6.24×10^{-9}). For the immune BAG, significant heritability enrichment was found
422 in fetal blood tissues (P-value= 7.36×10^{-9}) (**Fig. 5c, Supplementary eFile 15**). These findings
423 were aligned with the tissue-specific gene expression patterns observed at the gene level (**Fig.**
424 **3b**).

425 The results from multi-tissue chromatin states-specific data further provide the proof-of-
426 concept for the organ-specific heritability enrichment among these nine BAGs. For the brain
427 BAG, significant heritability enrichment was found in multiple brain tissues in the H3K4me3
428 (e.g., P-value= 9.06×10^{-5} for the hippocampus), H3K4me1 (e.g., P-value= 6.94×10^{-5} for the
429 hippocampus), and H3K27ac (e.g., P-value= 1.15×10^{-5} for the anterior caudate) regions. For the
430 cardiovascular BAG, significant heritability enrichment was shown in the right ventricle in the
431 H3K4me3 region (P-value= 6.36×10^{-5}) and the artery aorta in the H3K27ac region (P-
432 value= 5.81×10^{-7}). Significant heritability enrichment was found in primary hematopoietic stem

433 cells in the H3K4me1 region for the immune BAG for both females (P -value= 5.61×10^{-5}) and
434 males (P -value= 9.50×10^{-5}). The fetal leg muscle tissue in the DNase regions (P -value= 6.54×10^{-5})
435 for the musculoskeletal BAG showed significant heritability enrichment. For the pulmonary
436 BAG, significant heritability enrichment was found in the fetal lung in the H3K4me1 (P -
437 value= 1.33×10^{-9}) and DNase regions (P -value= 3.80×10^{-8}), among other tissues from the
438 stomach, artery, and muscle. For the renal BAG, significant enrichment was shown in the liver in
439 the H3K9ac region (P -value= 2.46×10^{-5}) and the gastric tissues in the H3K27ac region (P -
440 value= 6.24×10^{-5}) (**Fig. 5d, Supplementary eFile 16**).

441
442
443 **Cheverud's Conjecture: genetic correlations between the nine biological age gaps mirror**
444 **their phenotypic correlations**

445 We estimated the genetic correlation (g_c) (**Method 3h**) and the phenotypic correlation (p_c for
446 Pearson's correlation coefficient) between each pair of the nine BAGs. Our results supported the
447 long-standing Cheverud's Conjecture¹ – the genetic correlation between two clinical traits
448 reflects their phenotypic correlation (**Fig. 5e**).

449 The musculoskeletal and hepatic BAGs showed the highest genetic correlation ($g_c=0.40$)
450 and phenotypic correlation ($p_c=0.38$). Similarly, the hepatic and renal BAGs showed a high
451 genetic correlation ($g_c=0.39$) and phenotypic correlation ($p_c=0.37$). The musculoskeletal BAG
452 also showed significant genetic and phenotypic correlations with pulmonary ($g_c=0.35$, $p_c=0.19$)
453 and renal BAGs ($g_c=0.13$, $p_c=0.21$). In addition, the eye BAG showed small genetic and
454 phenotypic correlations with the brain BAG ($g_c=0.15$, $p_c=0.11$). The correlations between the
455 brain and eye BAGs and other organ BAGs were relatively weaker than those observed among
456 other organ pairs. These findings indicate the presence of shared genetic underpinnings that
457 collectively contribute to the biological aging processes captured by these organ BAGs. Most of
458 the genetic correlations showed consistency between females and males, albeit sex differences
459 were evident in certain BAGs, particularly in the cardiovascular BAG results. Specifically, males
460 exhibited dominant correlations between cardiovascular BAGs and hepatic and renal BAGs,
461 while females demonstrated unique correlations with musculoskeletal and pulmonary BAGs
462 (**Supplementary eFigure 19**). Sex differences in cardiovascular diseases have been explored in
463 prior literature⁴⁴, highlighting the divergent effects of factors associated with both sex and gender
464 on the clinical presentations and outcomes of cardiovascular disease. Detailed results are
465 presented in **Supplementary eFile 17**.

466
467 **Genetic correlations between the nine biological age gaps and 41 clinical traits of chronic**
468 **diseases, cognition, and lifestyle factors**

469 We also estimated g_c between the nine BAGs and 41 clinical traits to examine their genetic
470 correlations. The 41 clinical traits encompassed many common chronic diseases and conditions
471 and their disease subtypes^{7,45–48}, cognition (e.g., general intelligence and reaction time, and
472 lifestyle factors (e.g., computer use) (**Fig. 5f and Supplementary eTable 4**).

473 The brain BAG was genetically associated with several brain diseases of the central
474 nervous system (CNS) and their subtypes, including AD ($g_c=0.37 \pm 0.14$) and late-life depression
475 (LLD, $g_c=0.25 \pm 0.07$). Furthermore, we observed significant genetic correlations between the

476 brain BAG and years of education ($g_c = -0.14 \pm 0.05$) and intelligence ($g_c = -0.15 \pm 0.05$). The
477 cardiovascular BAG was positively correlated with stroke ($g_c = 0.20 \pm 0.05$), a significant
478 cardiovascular disease, and was negatively correlated with years of education ($g_c = -0.17 \pm 0.05$).
479 The musculoskeletal BAG was positively correlated with hyperlipidemia ($g_c = 0.18 \pm 0.06$),
480 rheumatoid arthritis ($g_c = 0.13 \pm 0.03$), and Crohn's disease ($g_c = 0.19 \pm 0.06$) and was negatively
481 correlated with atrial fibrillation ($g_c = -0.11 \pm 0.04$), years of education ($g_c = -0.21 \pm 0.04$), and
482 intelligence ($g_c = -0.18 \pm 0.03$). The pulmonary BAG was positively associated with
483 hyperlipidemia ($g_c = 0.12 \pm 0.04$), stroke ($g_c = 0.15 \pm 0.05$), liver fat ($g_c = 0.12 \pm 0.04$), and lung
484 carcinoma ($g_c = 0.17 \pm 0.05$). Finally, the renal BAG was positively correlated with chronic kidney
485 disease ($g_c = 0.39 \pm 0.06$) and atrial fibrillation ($g_c = 0.09 \pm 0.03$). Notably, type 2 diabetes showed
486 abundant positive genetic correlations with multiple BAGs, including the brain, cardiovascular,
487 metabolic, pulmonary, and renal. Detailed results are presented in **Supplementary eFile 18**.
488 Furthermore, we calculated the genetic correlation between the nine BAGs and longevity⁴⁹ and
489 household income⁵⁰. Our findings indicated that the cardiovascular ($g_c = -0.16 \pm 0.09$) and
490 pulmonary BAG ($g_c = -0.12 \pm 0.07$) exhibited negative associations with longevity, defined as
491 cases surviving at or beyond the age corresponding to the 90th survival percentile; the brain
492 BAG ($g_c = -0.21 \pm 0.04$), musculoskeletal ($g_c = -0.29 \pm 0.03$), and pulmonary BAG ($g_c = -0.16 \pm 0.03$)
493 were negatively genetically correlated with household income. We used GWAS summary
494 statistics from a prior study⁵¹ to detect a significant genetic correlation between the immune
495 BAG ($g_c = -0.13 \pm 0.03$), pulmonary BAG ($g_c = -0.09 \pm 0.03$), and telomere length (**Supplementary**
496 **eTable 5**).

497 These genetic correlations yield insights into potential shared mechanisms underlying the
498 nine BAGs, their relationships with chronic diseases, particularly AD and type 2 diabetes, and
499 cognition. These compelling results prompted us to explore the potential causal effects of these
500 traits on the nine BAGs. In the subsequent section, we unbiasedly selected 17 clinical traits
501 encompassing chronic diseases, cognition, and lifestyle factors to perform Mendelian
502 randomization (**Method 3g**).

510 annotations in the full baseline model, which prevents a biased estimate inflated by heritability in
511 flanking regions⁵². **c)** Tissue-specific partitioned heritability estimates using gene sets from
512 multi-tissue gene expression data. **d)** Tissue and chromatin-specific partitioned heritability
513 estimates using multi-tissue chromatin data. **e)** Cheverud's Conjecture: the genetic correlation
514 between two BAGs (g_c , lower triangle) mirrors their phenotypic correlation (p_c , upper triangle).
515 **f)** Genetic correlations between the nine BAGs and 41 clinical traits, including chronic diseases
516 and their subtypes involving multiple human organ systems, education, intelligence, and reaction
517 time. The symbol * denotes Bonferroni-corrected significance; the absence of * indicates all
518 results remain significant after correction. The standard error of the estimated parameters is
519 presented using error bars. Abbreviation: AD: Alzheimer's disease; ASD: autism spectrum
520 disorder; LLD: late-life depression; SCZ: schizophrenia; DB: type 2 diabetes; WMH: white
521 matter hyperintensity; HPLD: hyperlipidemia; AF: atrial fibrillation; RA: rheumatoid arthritis;
522 CD: Crohn's disease; CKD: chronic kidney disease.
523

524 **Hepatic and musculoskeletal biological age gaps are causally associated with each other**

525 We performed two-sample bi-directional Mendelian randomization for each pair of BAGs by
526 excluding overlapping populations to avoid bias¹⁶ (**Method 3j**). We found that the hepatic and
527 musculoskeletal BAGs showed a bi-directional causal relationship [from the hepatic BAG to the
528 musculoskeletal BAG: P-value= 9.85×10^{-7} , OR (95% CI) = 1.47 (1.26, 1.71); from the
529 musculoskeletal BAG to the hepatic BAG: P-value= 1.54×10^{-8} , OR (95% CI) = 2.78 (1.95, 3.97)]
530 (**Fig. 6**). This causal relationship echoes our genetic correlation results: the musculoskeletal and
531 hepatic BAGs showed the highest genetic correlation compared to other organ systems (**Fig. 5e**).
532 Detailed results and sensitivity check results are presented in **Supplementary eFile 19** and
533 **Supplementary eFigure 20** and **21**.

534 We performed three additional sensitivity check analyses for this bi-directional causal
535 relationship. First, we reperformed the GWAS for hepatic BAG and musculoskeletal BAG,
536 incorporating weight as a covariate due to its established causal associations with several organ
537 systems (**Fig. 6**). This analysis reaffirmed this bi-directional causal relationship (**Supplementary**
538 **eText 3A**). Furthermore, we performed Mendelian randomization by excluding the common
539 SNP within the *APOE* gene (rs429358) due to its pleiotropic effects. This analysis underscored
540 the robustness of the potential causal relationship from the hepatic BAG to the musculoskeletal
541 BAG, both with and without including this SNP as an instrumental variable, as elaborated in
542 **Supplementary eText 3B**. Finally, the latent causal variable (LCV⁵³, **Method 3j**) model
543 confirmed a partially genetically causal effect from the hepatic BAG to the musculoskeletal
544 BAG [genetic causality proportion = 0.75 ± 0.14 , $-\log_{10}(\text{P-value}) = 11.0$, $g_c = 0.41 \pm 0.06$]
545 (**Supplementary eTable 6**).
546
547

548 **Biological age gaps are causally associated with several chronic diseases, body weight, and** 549 **sleep duration**

550 We investigated the bi-directional causal effects between chronic diseases (e.g., AD) and
551 lifestyle factors (e.g., sleep duration) and the nine BAGs. We unbiasedly and systematically
552 included 17 clinical traits (**Method 3j**) guided by our genetic correlation results (**Fig. 5f**). The 17

553 clinical traits included chronic diseases linked to the brain, cardiovascular, metabolic, digestive,
554 renal, and musculoskeletal systems, cognition, and lifestyle factors (**Supplementary eTable 7**).

555 In the forward Mendelian randomization, we found potential causal effects of AD on the
556 brain [P-value= 3.99×10^{-8} , OR (95% CI) = 1.05 (1.03, 1.06), number of SNPs=10], hepatic [P-
557 value= 7.53×10^{-7} , OR (95% CI) = 1.03 (1.02, 1.04), number of SNPs=10], musculoskeletal [P-
558 value= 1.73×10^{-5} , OR (95% CI) = 0.98 (0.97, 0.99), number of SNPs=10], and renal [P-
559 value= 5.71×10^{-4} , OR (95% CI) = 0.98 (0.97, 0.99), number of SNPs=10] BAGs. Body weight
560 showed causal effects on multiple organ systems, including the immune [P-value= 8.96×10^{-5} , OR
561 (95% CI) = 1.08 (1.04, 1.11), number of SNPs=160], musculoskeletal [P-value= 4.32×10^{-15} , OR
562 (95% CI) = 0.83 (0.79, 0.86), number of SNPs=160], pulmonary [P-value= 3.50×10^{-7} , OR (95%
563 CI) = 0.84 (0.79, 0.90), number of SNPs=160], and renal BAGs [P-value= 4.53×10^{-13} , OR (95%
564 CI) = 1.18 (1.13, 1.23), number of SNPs=160]. In addition, we also found that Crohn's disease
565 had causal effects on the hepatic BAG [P-value= 3.00×10^{-3} , OR (95% CI) = 1.02 (1.00, 1.03),
566 number of SNPs=77], type 2 diabetes on the metabolic BAG [P-value= 9.92×10^{-12} , OR (95% CI)
567 = 1.16 (1.09, 1.24), number of SNPs=8], inflammatory bowel disease [P-value= 1.42×10^{-3} , OR
568 (95% CI) = 1.02 (1.00, 1.03), number of SNPs=80] and primary biliary cholangitis [P-
569 value= 7.41×10^{-4} , OR (95% CI) = 1.02 (1.00, 1.03), number of SNPs=16] on the musculoskeletal
570 BAG (**Fig. 6**).

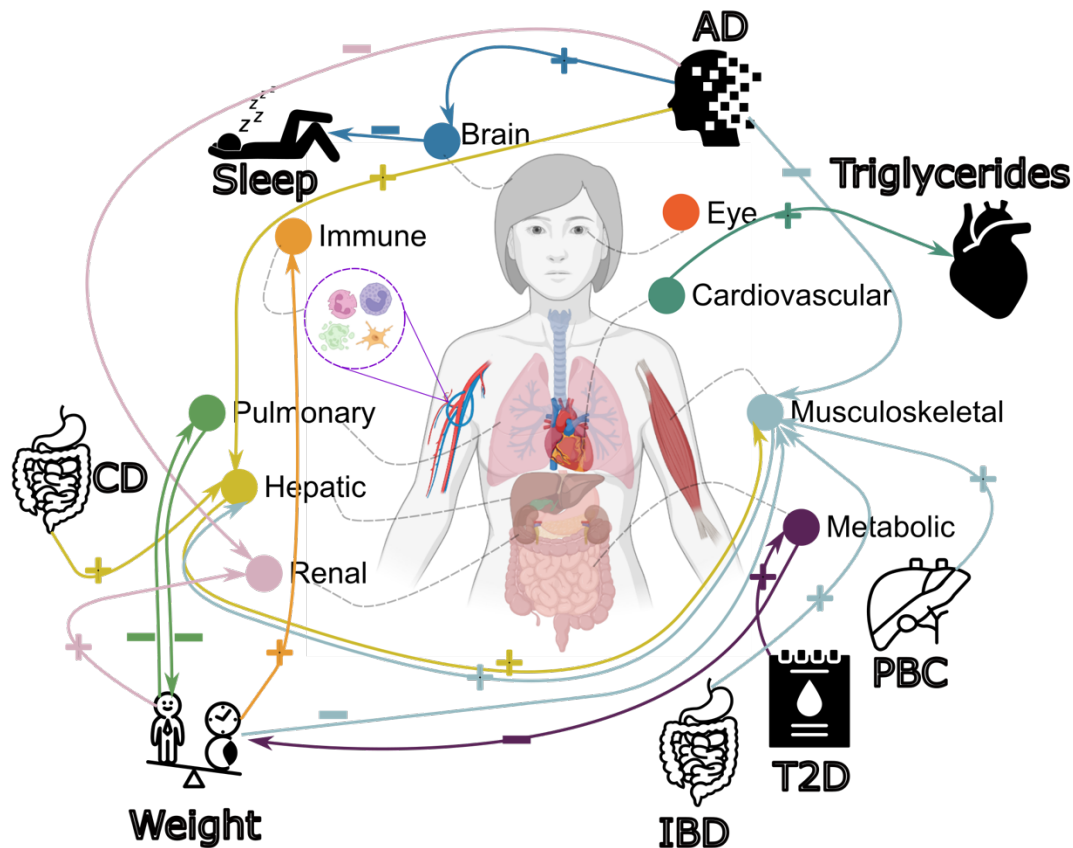
571 For the inverse Mendelian randomization, we found potential causal effects of the
572 metabolic [P-value= 6.85×10^{-4} , OR (95% CI) = 0.94 (0.91, 0.97), number of SNPs=71] and
573 pulmonary [P-value= 3.79×10^{-5} , OR (95% CI) = 0.84 (0.79, 0.91), number of SNPs=62] BAGs on
574 body weight, the cardiovascular BAG on triglycerides versus lipid ratio in very large very-low-
575 density lipoprotein (VLDL) [P-value= 2.14×10^{-4} , OR (95% CI) = 1.09 (1.04, 1.14), number of
576 SNPs=39], and the brain BAG on sleep duration [P-value= 2.61×10^{-3} , OR (95% CI) = 1.09 (1.04,
577 1.14), number of SNPs=10] (**Fig. 6**). Detailed results are presented in **Supplementary eFile 20**.

578 We performed several sensitivity analyses (**Method 3j**) to test the robustness of our
579 findings. Based on these sensitivity checks, we identified potential outlier instrumental variables
580 (IVs, i.e., SNPs) for four Mendelian randomization tests (AD and body weight on
581 musculoskeletal BAG, Crohn's disease on hepatic BAG, and type 2 diabetes on metabolic BAG)
582 in the forward Mendelian randomization and one Mendelian randomization test (metabolic BAG
583 on body weight) in the inverse Mendelian randomization. Detailed results of the sensitivity check
584 are presented in **Supplementary eFigure 22-37** for all significant results. We showcased a
585 detailed analysis of the sensitivity results for the metabolic BAG on body weight in
586 **Supplementary eText 3C**. In summary, the potential causal link from the metabolic BAG to
587 body weight remained robust across several sensitivity checks despite the identification of two
588 potential outlier instrumental variables, namely, rs117233107 and rs33959228.

589 In addition, we used the LCV method and found a partially genetically causal effect from
590 longevity (99th survival percentile) to the brain BAG (genetic causality proportion = 0.45 ± 0.20 ,
591 P-value=0.04). Importantly, we selected the LCV method over Mendelian randomization
592 because of the partial population overlap between the longevity GWAS summary statistics and
593 our BAG GWAS summary statistics. The LCV analysis also detected a partially genetically
594 causal effect from telomere length to the immune BAG (genetic causality proportion = 0.33 ± 0.12 ,
595 P-value=0.0002) and the pulmonary BAG (genetic causality proportion = 0.67 ± 0.20 , P-
596 value= 3.57×10^{-16}) (**Supplementary eTable 6**).

597

598 **Figure 6: Causal multi-organ network between the 9 biological age gaps and 17 clinical**
 599 **traits of chronic diseases, lifestyle factors, and cognition**
 600



601 We conducted two sets of Mendelian randomization analyses. Firstly, we examined the causal
 602 relationships between each pair of BAGs, excluding overlapping populations. Secondly, we
 603 investigated the causal associations between the 9 BAGs and the 17 unbiasedly selected clinical
 604 traits. Bi-directional analyses, including forward and inverse analyses on the exposure and
 605 outcome variables, were performed in all experiments. Significant tests were adjusted for
 606 multiple comparisons using the Bonferroni correction. Each colored arrow represents a potential
 607 causal effect connecting the exposure variable to the outcome variable. The symbol "+" denotes
 608 an OR larger than 1, while "-" represents an OR smaller than 1. Detailed OR and 95%CI
 609 information can be found in **Supplementary eFigure 38** and **eFile 19-20**. It's crucial to approach
 610 the interpretation of these potential causal relationships with caution despite our thorough efforts
 611 in conducting multiple sensitivity checks to assess any potential violations of underlying
 612 assumptions. Abbreviation: AD: Alzheimer's disease; T2D: type 2 diabetes; PBC: primary
 613 biliary cholangitis; CD: Crohn's disease; IBD: inflammatory bowel disease; CI: confidence
 614 interval; OR: odds ratio.
 615
 616

617 **Discussion**

618 The current study comprehensively depicts the genetic architecture of common genetic variants
619 on biological aging of nine human organ systems using multimodal data from 377,028 European
620 ancestry participants. We identified many genomic loci for the BAGs of nine human organ
621 systems, which exhibited significant associations with a wide range of clinical traits documented
622 in the GWAS Catalog. These associations were observed within a phenotypic landscape
623 characterized by BAG-organ specificity and inter-organ connections. The brain BAG showed the
624 highest SNP-based heritability estimate among all nine organ systems. GSEA, tissue-specific
625 gene expression patterns, and heritability enrichment results provided additional evidence
626 supporting biological validation for BAG-organ specificity and inter-organ connections. The
627 phenotypic correlation between BAGs was a proxy for their genetic correlation, thereby
628 supporting the long-standing Cheverud's Conjecture. Mendelian randomization demonstrated
629 potential causal relationships between chronic diseases, particularly AD and type 2 diabetes,
630 body weight, sleep duration, and the nine BAGs.

631 Our large-scale multi-organ GWAS significantly expands the current catalog of genetic
632 variants associated with health-related traits. The discovery of these identified genomic loci has
633 significant clinical implications. These findings provide an invaluable foundation to validate
634 genes or regulatory elements, molecular pathways, and biological processes related to the clinical
635 traits and diseases of interest in the current study and future GWAS analyses. Previous GWAS
636 mainly focused on the BAG in one organ system, such as the brain BAG⁵⁴⁻⁵⁷ from imaging-
637 derived phenotypes. These investigations have largely overlooked the inherent
638 interconnectedness of human organ systems, which are intricately intertwined with distinct axes.
639 Recent studies have identified notable axes, such as the heart-brain-liver¹¹, brain-eye⁵⁸, and
640 brain-heart⁵⁹ axes, highlighting the importance of comprehending these intricate relationships to
641 understand human physiology and health.

642 Our phenome-wide associations validate the pleiotropic effects of the identified genomic
643 loci, influencing various health-related clinical traits in the GWAS Catalog. Our findings also
644 highlight BAG-organ specificity and inter-organ connections, further supporting that biological
645 aging is a complex, multifaceted phenomenon. The human brain regulates various physiological
646 processes and maintains homeostasis throughout the body. Consequently, it is unsurprising that
647 the brain exhibits interconnectedness with clinical traits associated with multiple organ systems.
648 The remarkable enrichment of metabolic traits across various organ systems is unsurprising. As a
649 vital metabolic organ, the liver substantially overlaps genetic variants and loci with both the
650 hepatic and metabolic BAGs. Biologically, the liver's metabolic functions are intricately
651 regulated by hormones like insulin and other metabolic regulators¹². Similarly, the interplay
652 between immune and metabolic processes is essential for maintaining overall health and is
653 crucial for the body's ability to respond to pathogens and regulate metabolic homeostasis⁶.

654 We highlighted that the brain BAG is the most heritable among the nine organ systems.
655 Determining the genetic heritability of specific organ systems can be complex as no organ
656 system functions independently, and many diseases or traits involve complex interactions
657 between multiple organ systems, as well as genetic and environmental factors. The brain plays a
658 crucial role in developing and functioning various physiological processes across the body. Its
659 intricate structure and diverse cell types render it vulnerable to genetic influences⁶⁰. Therefore,
660 the brain may exhibit higher genetic stability and less environmental variability⁶¹ than other
661 organs. The human brain's extensive functional connectivity and intricate networks may also
662 contribute to its higher heritability. These networks facilitate the transmission of genetic

663 information and the propagation of genetic effects across different brain regions³⁰. Lastly,
664 genetic variations shaping the human brain are pleiotropic and influence cognitive abilities,
665 behavior, and susceptibility to neurological and psychiatric disorders. Collectively, these factors
666 may contribute to the marked genetic heritability observed in the human brain compared to other
667 organ systems.

668 Our gene-level and partitioned heritability analyses further validate our GWAS findings,
669 supporting BAG-organ specificity and inter-organ connections. In GSEA, the genes associated
670 with the cardiovascular BAG were implicated in the IGF-II pathway. IGF-II activates two
671 receptors (IGF-1R and IR-A) to promote cell growth and survival. The IGF signaling pathway is
672 essential for cardiac development in the human heart - the first functional organ to develop⁶². In
673 particular, IGF-II promotes fetal cardiomyocyte proliferation through the tyrosine kinase
674 receptors IGF1R and INSR. Previous research provided appealing evidence on IGF signaling in
675 cardiac regeneration in animal models and induced pluripotent stem cells⁶³. The flavonoid
676 glucuronidation pathway was the most significant enrichment result shown in the hepatic BAG.
677 A previous study demonstrated that procyanidin C1, a flavonoid in grape seed extract, extended
678 the lifespan of mice⁶⁴. Furthermore, ample evidence indicated that natural flavonoids could be
679 potential therapeutic approaches for non-alcoholic fatty liver disease⁶⁵. The metabolites formed
680 through this pathway can also exert effects beyond the liver and impact other organ systems. Our
681 tissue-specific gene expression analyses provided additional support for the biological relevance
682 of our GWAS findings, as the identified genes exhibited specific expression patterns within
683 tissues from the corresponding organ systems.

684 The heritability enrichment analysis further validates the BAG-organ specificity and
685 inter-organ connections by highlighting the disproportional heritability enrichment of genetic
686 variants in different functional categories, cell types, tissues, and chromatin states. The cell type-
687 specific enrichment results in the brain (i.e., oligodendrocytes) and cardiovascular (i.e., neurons)
688 BAGs align with previous research. Specifically, Zhao et al. conducted a large-scale GWAS on
689 brain white matter microstructure and found significant heritability enrichment in glial cells,
690 particularly oligodendrocytes³¹, which aligns with our current findings. Our previous multimodal
691 brain BAG GWAS⁵⁴ also confirmed this enrichment in the brain BAG derived from the white
692 matter microstructural features. Similarly, research has revealed the presence of an "intrinsic
693 cardiac nervous system" within the heart, often called the "heart brain." This system consists of
694 around 40,000 neurons similar to those found in the brain, indicating that the heart possesses a
695 distinct nervous system⁶⁶.

696 Our genetic correlation results confirmed that the genetic correlation generally mirrors
697 phenotypic correlations in multi-organ biological age. This suggests that environmental factors
698 likely affect the aging of multiple organ systems in the same direction. Providing evidence for
699 Cheverud's Conjecture can have clinical implications by providing valuable insights into the
700 genetic basis of complex age-related diseases. For instance, by identifying the shared genetic
701 factors underlying multiple age-related diseases, we can target these common pathways to
702 develop novel treatments or repurpose existing drugs⁶⁷ that have proven efficacy in one disease
703 or condition for treating others. Moreover, the validation of Cheverud's Conjecture emphasizes
704 the importance of considering the genetic covariance of age-related diseases in clinical practice.
705 It underscores the need for comprehensive genetic assessments and genomic analyses to
706 understand disease risk and progression⁶⁸.

707 We found a bi-directional causal relationship between the hepatic and musculoskeletal
708 BAGs. Abundant research has suggested that liver function and metabolic health, particularly

709 related to glucose and lipid metabolism, can significantly impact musculoskeletal health⁶⁹. This
710 inter-organ connection can cause dysregulation of liver metabolism (e.g., non-alcoholic fatty
711 liver disease) linked to musculoskeletal disorders, including osteoporosis, sarcopenia, and
712 muscle wasting. The musculoskeletal system can also exert an inverse influence on liver
713 function. Regular physical activity and muscle strength have been linked to enhanced liver health
714 and decreased susceptibility to liver diseases. To further support this, causal effects of primary
715 biliary cholangitis, a chronic liver disease, on elevated musculoskeletal BAG were confirmed in
716 our Mendelian randomization results (**Fig. 6**). The absence of direct causal relationships between
717 the remaining BAGs can be attributed to various factors with potential explanations and
718 implications. One possible explanation is that the brain BAG, having the smallest sample size in
719 our GWAS (after removing overlapping participants), may be limited in statistical power. In
720 addition, this may suggest that various factors, including chronic diseases, environmental
721 exposures, and lifestyle choices, influence biological aging in alternative pathways or mediate
722 such changes. Thus, understanding the collective contribution of chronic diseases, environmental
723 factors, and lifestyle choices is crucial for comprehending the overall aging process and its
724 impact on organ health.

725 We found that several clinical traits collectively cause organ systems to appear older or
726 younger than their chronological age. For instance, body weight was causally associated with the
727 immune, musculoskeletal, metabolic, and pulmonary BAGs. For several reasons, body weight
728 can causally influence multiple organ systems. Excessive body weight (e.g., obesity) has
729 metabolic consequences, including increased inflammation, insulin resistance, and dysregulation
730 of metabolic pathways in adipose tissue⁷⁰. It also leads to mechanical stress on the body,
731 contributing to musculoskeletal strain⁷¹ and cardiovascular workload⁷². Hormonal imbalances⁷³
732 and lifestyle factors linked to body weight also influence multi-organ function and the
733 development of chronic diseases. Being overweight is also a risk factor for type 2 diabetes,
734 which was positively causally associated with metabolic BAG (**Fig. 6**). AD was causally linked
735 to the brain, hepatic, musculoskeletal, and renal BAGs. AD, a neurodegenerative disorder
736 primarily affecting the brain, can have causal influences on multiple organ systems. For example,
737 it has broader systemic involvement beyond the brain, mediated by mechanisms including
738 protein aggregation (e.g., amyloid- β and tau⁷⁴), vascular dysfunction⁷⁵, inflammation⁷⁶, and other
739 secondary factors. Protein aggregates can spread to other organs; vascular abnormalities can
740 impact blood flow; inflammation can affect distant organ systems; secondary factors, such as
741 medication use and lifestyle changes, also contribute.

742 743 **Limitations**

744 This study has several limitations. First, the generalizability of genetic findings from European to
745 non-European ancestry populations is limited. Future studies can extend their scope to
746 encompass a more diverse array of underrepresented ethnicities, a wider range of disease
747 cohorts, and individuals of varying ages throughout their entire lifespan. Secondly, it is essential
748 to approach the causality results cautiously, considering the assumptions underlying Mendelian
749 randomization. In future studies, more advanced multi-response Mendelian randomization
750 methods⁷⁷ should be utilized. Thirdly, despite our efforts of quality check analyses to scrutinize
751 our primary GWAS, it's essential to acknowledge that potential ascertainment bias⁷⁸ and
752 confounding related to demographic and socioeconomic factors could potentially introduce
753 cryptic population stratification, which may not be entirely resolved in the current study. Finally,
754 the large number of genomic loci identified in our GWAS may have connections to BAGs due to

755 various factors, such as biological processes, potential confounding due to demographics, or
756 specific study design and phenotyping aspects. It's important to note that the effects at these loci
757 might not be inherently biological but could be influenced by other unmeasured confounding
758 factors.

759 760 **Outlook**

761 In conclusion, our study presents compelling genetic evidence to support that *no organ system is*
762 *an island*¹ – the collective influence of various chronic diseases on these multi-organ systems
763 and the interconnectedness among these human organ systems. These findings highlight the
764 importance of comprehensively understanding the underlying causes of chronic diseases within
765 the multi-organ network. By shedding light on its comprehensive genetic architecture, our study
766 paves the way for future research to unravel complex disease mechanisms and develop holistic
767 approaches to ameliorate overall organ health.
768

¹ We adapt the concept of "No Man Is An Island" from the poem by John Donne, highlighting the interconnectedness of human organ systems.

769 **Methods**

770 **Method 1: Support vector machines to predict the chronological age of nine organ systems**

771 Our prior study³ used support vector machines to predict the chronological age of healthy
772 individuals – defined as no self-reported and healthcare-documented lifetime chronic medical
773 conditions – based on phenotypes from the nine organ systems. Support vector machine
774 regression was preferred over linear regression for its enhanced robustness to outliers and
775 overfitting. We performed a 20-fold cross-validation procedure and developed predictive models
776 for each organ system.

777 In each of the 20-fold cross-validation iterations, a linear support vector machine was
778 employed to predict chronological age. The training set consisted of 19 folds of individuals, and
779 the fitted regression coefficients (feature weights) were then applied iteratively to the remaining
780 held-out set (test set) to predict the chronological age of each healthy individual. This approach
781 ensured that the prediction model was not trained using the same individuals for which it made
782 predictions, minimizing the risk of overfitting. Before each iteration of model training, all
783 measures (excluding categorical variables) were standardized using the weighted column mean
784 and standard deviation computed within the training set. The SVM box constraint and kernel
785 scale were set to unity, while the half-width of the epsilon-insensitive band was set to a tenth of
786 the standard deviation of the interquartile range of the predicted variable (chronological age).
787 The SVM was solved using sequential minimal optimization with a gap tolerance of 0.001. The
788 mathematical principles of support vector machines are well-established in the field and have
789 been widely recognized⁷⁹. Further details on this topic can be found in our previous study³.

790 The concept of biological age gap derived from artificial intelligence has been widely
791 investigated, especially the brain age^{80,81}. The calculation of the nine BAGs were established in
792 our previous works^{3,14}. We previously showed that the prediction accuracy of biological age was
793 not influenced by the number of phenotypes, despite variations across different organ systems.
794 While some prior studies⁸² used deep learning for brain BAG and obtained a lower mean
795 absolute error, we have previously demonstrated that lower mean absolute error might
796 compromise sensitivity to disease-related information⁸³. In our previous GWAS¹⁴, which
797 separately examined three multimodal brain BAGs derived from T1-weighted, diffusion, and
798 resting-state fMRI data, we extensively investigated the influence of various brain imaging
799 feature types and study designs on the genetic signals. Our results unveiled both the consistency
800 and distinctions in the genetic foundations across these diverse contexts. Finally, we recognize
801 that ascertainment bias may be present in our GWAS due to variations in sequencing techniques,
802 differences between populations (e.g., disease populations vs. healthy controls), and
803 socioeconomic factors that have not been explicitly modeled in our study.

804

805 **Method 2: Study populations**

806 UKBB is a population-based study of approximately 500,000 people recruited between 2006 and
807 2010 from the United Kingdom. The UKBB study has ethical approval, and the ethics committee
808 is detailed here: [https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/governance/ethics-
809 advisory-committee](https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/governance/ethics-advisory-committee).

810 The current study analyzed multimodal data, including imaging-derived phenotypes
811 (IDP) and physical and physiological measures in nine human organ systems from 154,774
812 UKBB participants. In our previous study, we constructed BAGs for eight organ systems using
813 machine learning, including MRI data for brain BAG from 30,108 participants (European

814 ancestry), pulse rate and blood pressure data for cardiovascular BAG, liver-related blood
815 biomarkers for hepatic BAG, C-reactive protein and blood hematology variables for immune
816 BAG, blood biomarkers for metabolic BAG, physical measurements and vitamin D for
817 musculoskeletal BAG, lung functioning measurements for pulmonary BAG, and glomerular
818 filtration and electrolyte regulation biomarkers for renal BAG from 111,543 participants.
819 Furthermore, the current study also used 60 optical coherence tomography (OCT)-derived
820 measures from 36,004 participants to derive the BAG of the ninth organ system – the eye BAG.
821 The inclusion criteria for the features used to predict the eight BAGs, the machine learning
822 methods, and cross-validation procedures are detailed in our previous study³. We initially used
823 the 88 OCT-derived measures (category ID: 10079) for the additional eye BAG in 67,549
824 participants. Of these measures, 28 were excluded due to a high missing rate (>20% of
825 participants). Additionally, 4172 participants were excluded due to missing data, and 1798
826 participants identified as outliers (outside mean +/- 6SD) for the 60 remaining measures were
827 discarded. This finally resulted in 41,966 participants (36,004 European ancestry participants).
828 The included 2444 features to derive the BAG of the nine organ systems are presented in
829 **Supplementary eFile 21**.

830 In addition, we also performed GWAS for seven variables from 222,254 UKBB
831 participants by excluding the 154,774 participants from the BAG populations to avoid bias due
832 to overlapping samples. These variables included six lifestyle factors and one cognitive variable:
833 $N=219,661$ (European ancestry) for coffee intake (Field ID:1498), $N=221,393$ for fresh fruit
834 intake (Field ID:1309), $N=221,739$ for tea intake (Field ID:1488), $N=220,765$ for sleep duration
835 (Field ID:1160), $N=209,012$ for time spent outdoors in summer (Field ID:1050), $N=221,337$ for
836 body weight (Field ID:21002), and $N=220,624$ for reaction time (Field ID:20023).

837 The current work was jointly performed under application numbers 35148 (i.e., genetic
838 data) and 60698 (i.e., the generation of the nine BAGs). In total, we analyzed data from 377,028
839 individuals of European ancestry in the current study.

840

841 **Method 3: Genetic analyses**

842 We used the imputed genotype data for all genetic analyses, and our quality check pipeline
843 resulted in 487,409 participants and 6,477,810 SNPs. After merging with the population for each
844 BAG, we included 30,108-111,543 European ancestry participants for the nine BAGs (**Fig. 1**).
845 To avoid bias due to overlapping populations¹⁶, we also used the rest of the UKBB participants
846 of European ancestry (non-overlapping) to derive the GWAS summary statistics for several
847 lifestyle factors (**Method 3j**). We summarize the genetic QC pipeline. First, we excluded related
848 individuals (up to 2nd-degree) from the complete UKBB sample using the KING software for
849 family relationship inference.⁸⁴ We then removed duplicated variants from all 22 autosomal
850 chromosomes. Individuals whose genetically identified sex did not match their self-
851 acknowledged sex were removed. Other excluding criteria were: i) individuals with more than
852 3% of missing genotypes; ii) variants with minor allele frequency (MAF) of less than 1%
853 (dosage mode⁸⁵); iii) variants with larger than 3% missing genotyping rate; iv) variants that
854 failed the Hardy-Weinberg test at 1×10^{-10} . To adjust for population stratification,⁸⁶ we derived
855 the first 40 genetic principle components (PC) using the FlashPCA software⁸⁷. Details of the
856 genetic quality check protocol are described elsewhere^{14,46,88}. Details of the genetic quality check
857 protocol are described elsewhere^{29,46}.

858

859 **(a): Genome-wide association analysis:** For GWAS, we ran a linear regression using Plink⁸⁹ for
860 each BAG, controlling for confounders of age, dataset status (training/validation/test or
861 independent test dataset), age x squared, sex, age x sex interaction, age-squared x sex interaction,
862 and the first 40 genetic principal components; additional covariates for total intracranial volume
863 and the brain position in the scanner were included for brain BAG GWAS. We adopted the
864 genome-wide P-value threshold (5×10^{-8}) and annotated independent genetic signals considering
865 linkage disequilibrium (see below).

866 To check the robustness of our GWAS results, we performed several sensitivity check
867 analyses, including *i*) sex-stratified GWAS for males and females, *ii*) split-sample GWAS by
868 randomly dividing the entire population into two splits (sex and age-matched), *iii*) non-European
869 ancestries GWAS, and *iv*) fastGWA for linear mixed effect GWAS, hypothesizing that the main
870 GWASs with European ancestry did not show substantial genomic inflation due to cryptic
871 population stratification. In all our sensitivity check analyses, we considered linkage
872 disequilibrium. We only evaluated the independent significant SNPs of the two sets of β
873 coefficients between splits, genders, ancestry groups, and GWAS methods. The definition of the
874 independent significant SNPs used the same parameters as in FUMA (**Supplementary eMethod**
875 **1**). We used the raw genotype data and the Plink *clump* command (250 kb) and defined a set of
876 SNPs in linkage disequilibrium with the independent significant SNPs – analogous to the
877 candidate SNPs in FUMA.

878
879 **(b): SNP-based heritability:** We estimated the SNP-based heritability (h^2) using GCTA²⁴ with
880 the same covariates in GWAS. We reported results from two experiments for each BAG using *i*)
881 the full sample sizes and *ii*) randomly down-sampled sample sizes to that ($N=30,108$) of the brain
882 BAG with comparable distributions regarding sex and age – the sample size of brain BAGs was
883 smaller than the other BAGs.

884
885 **(c): Annotation of genomic loci:** The annotation of genomic loci and mapped genes was
886 performed via FUMA⁹⁰. For the annotation of genomic loci, FUMA first defined lead SNPs
887 (correlation $r^2 \leq 0.1$, distance < 250 kb) and assigned them to a genomic locus (non-
888 overlapping); the lead SNP with the lowest P-value (i.e., the top lead SNP) was used to represent
889 the genomic locus in **Fig. 1**. For gene mappings, three different strategies were considered. First,
890 positional mapping assigns the SNP to its physically nearby genes (a 10 kb window by default).
891 Second, eQTL mapping annotates SNPs to genes based on eQTL associations using the GTEx v8
892 data. Finally, chromatin interaction mapping annotates SNPs to genes when there is a significant
893 chromatin interaction between the disease-associated regions and nearby or distant genes⁹⁰. The
894 definition of top lead SNP, lead SNP, independent significant SNP, and candidate SNP can be
895 found in **Supplementary eMethod 1**.

896 For the top lead SNP of each identified genomic locus, we showcased whether it was
897 previously associated with any clinical traits considering linkage disequilibrium (5000kb around
898 the top lead SNP) in the EMBL-EBI GWAS Catalog platform
899 (<https://www.ebi.ac.uk/gwas/home>). For instance, we aimed to query the locus with the top lead
900 SNP (rs60569686) associated with the renal BAG. First, we looked up the chromosomal position
901 (i.e., chromosome 13) and found that the location is chr13:49170160 (GRCh38). We then search
902 the GWAS Catalog for a 5000kb region around this top lead SNP: “chr13:49167660-49172660”
903 (<https://www.ebi.ac.uk/gwas/regions/chr13:49167660-49172660>; query date: 12th October
904 2023). In this region, we discovered no prior associations. It's important to note that this search is

905 not comprehensive, as new GWAS studies continually emerge on various open platforms, such
906 as IEU OpenGWAS⁹¹ (<https://gwas.mrcieu.ac.uk/>) and GWAS ATLAS²³
907 (<https://atlas.ctglab.nl/PheWAS>).

908
909 **(d): Phenome-wide association look-up queries:** We first queried the significant independent
910 SNPs within each locus in the EMBL-EBI GWAS Catalog (query date: 24th April 2023, via
911 FUMA version: v1.5.4) to determine their previously identified associations with any other traits
912 (P-value < 1x10⁻⁵ by default in the EMBL-EBI GWAS Catalog). For visualization purposes, we
913 further mapped the associated traits into organ-specific groups and other chronic disease traits
914 and cognition. We performed the following procedure to fully consider LD and remove
915 redundant associations among the independent significant SNPs. If the top lead SNP showed any
916 clinical associations, this would present the current locus; if not, we queried the independent
917 significant SNPs (in high correlation with the top lead SNP), starting with the most significant
918 SNPs, until we identified established associations. In this way, only one genetic variant within
919 each genomic locus was considered. We also conducted a complementary phenome-wide
920 association query on the GWAS Atlas platform. We applied the same P-value threshold search
921 criteria as those used in the EMBL-EBI GWAS Catalog. The same procedure, considering
922 linkage disequilibrium and redundant associations, was applied. These exemplary findings are
923 presented as a supplementary search to complement the results shown in **Fig. 2a**, and are
924 available in **Supplementary eText 2**.

925
926 **(e): Gene set enrichment analysis:** We first performed gene-level association analysis using
927 MAGMA³³. First, gene annotation was performed to map the SNPs (reference variant location
928 from Phase 3 of 1,000 Genomes for European ancestry) to genes according to their physical
929 positions. Of note, other advanced annotation methods exist that integrate functional insights,
930 such as brain chromatin interaction⁹² and cell-type-specific gene expression⁹³. We then
931 performed gene-level associations based on the SNP GWAS summary statistics to obtain gene-
932 level p-values between the nine BAGs and the curated protein-encoding genes containing valid
933 SNPs. We performed GSEA using the gene-level association p-values. Gene sets were obtained
934 from the Molecular Signatures Database (MsigDB, v7.5.1)⁹⁴, including 6366 curated and 10,402
935 ontology gene sets. All other parameters were set by default for MAGMA. The Bonferroni
936 method was used to correct multiple comparisons for all tested gene sets.

937
938 **(f): Tissue-specific gene expression analysis:** MAGMA performed gene-property analyses to
939 identify tissue-specific gene expression of the nine BAGs. The gene-property analysis converts
940 the gene-level association P-values (above) to Z scores and tests a specific tissue's gene
941 expression value versus the average expression value across all tissues in a regression model.
942 Bonferroni correction was performed for all tested gene sets. We reported the results from the 54
943 tissue types using the GTEx V8 data.

944
945 **(g): Gene-drug-disease network:** We tested the enrichment of the nine BAG-linked genes in the
946 targeted gene sets for different drug categories from the DrugBank database³⁸. The gene-drug-
947 disease network was constructed to prioritize potentially repositionable drugs. The GREP
948 software³⁷ performs Fisher's exact tests to examine whether the prioritized genes are enriched in
949 gene sets targeted by drugs in a clinical indication category for a certain disease or condition.
950 Bonferroni correction was performed for all tested drugs.

951
952 **(h): Genetic correlation:** We used the LDSC¹⁷ software to estimate the pairwise genetic
953 correlation (g_c) between each pair of BAGs, as well as between the nine BAG and 41 other
954 clinical traits, including chronic diseases involving multiple organ systems, such as AD for brain
955 and chronic kidney disease for kidney, cognition, and lifestyle factors. We used the precomputed
956 LD scores from the 1000 Genomes of European ancestry. To ensure the suitability of the GWAS
957 summary statistics, we first checked that the selected study's population was European ancestry;
958 we then guaranteed a moderate SNP-based heritability h^2 estimate. Notably, LDSC corrects for
959 sample overlap and provides an unbiased estimate of genetic correlation⁶⁸. The inclusion criteria
960 and finally included traits are detailed in **Supplementary eTable 3**. Bonferroni correction was
961 performed for the 41 clinical traits.

962
963 **(i): Partitioned heritability estimate:** Our objective is to comprehend how distinct functional
964 genome categories play varying roles in contributing to the heritability of the nine BAGs.
965 Therefore, the partitioned heritability analysis via stratified LD score regression calculates the
966 extent to which heritability enrichment can be attributed to predefined and annotated genome
967 regions and categories⁴⁰. Three sets of functional categories and cell and tissue-specific types
968 were considered. First, the partitioned heritability was calculated for 53 general functional
969 categories (one including the entire set of SNPs). The 53 functional categories are not specific to
970 any cell type and include coding, UTR, promoter and intronic regions, etc. The details of the 53
971 categories are described elsewhere⁴⁰. Subsequently, cell and tissue type-specific partitioned
972 heritability was estimated using gene sets from Cahoy et al.⁴¹ for three main cell types (i.e.,
973 astrocyte, neuron, and oligodendrocyte), multi-tissue chromatin states-specific data
974 (ROADMAP⁴² and ENTEX⁴³), and multi-tissue gene expression data (GTEx V8³⁶). Bonferroni
975 correction was performed for all tested annotations and categories. The detailed methodologies
976 for the stratified LD score regression are presented in the original work⁴⁰. The LD scores and
977 allele frequencies for the European ancestry were obtained from a predefined version based on
978 data from the 1000 Genomes project.

979
980 **(j): Two-sample bi-directional Mendelian randomization:** We investigated whether one BAG
981 was causally associated with another BAG and whether the 41 clinical traits were causally
982 associated with the nine BAGs (**Fig. 5**). To this end, we employed a bidirectional, two-sample
983 Mendelian randomization using the TwoSampleMR package⁹⁵. Both the forward and inverse
984 Mendelian randomization were performed between each pair of traits by switching the exposure
985 and outcome variables. We applied five different Mendelian randomization methods and
986 reported the results of inverse variance weighted (IVW) in the main text and the four others (i.e.,
987 Egger, weighted median, simple mode, and weighted mode estimators) in the supplement.

988 Mendelian randomization needs to fulfill several instrumental variable assumptions⁹⁶,
989 including:

- 990
- 991 • the genotype is associated with the exposure
 - 992 • the genotype is associated with the outcome through the studied exposure only (exclusion
993 restriction assumption)
 - 994 • the genotype is independent of other factors that affect the outcome (independence
995 assumption⁹⁷)

996 We followed a systematic procedure guided by the STROBE-MR Statement⁹⁸ in all steps
of our causality analyses, including selecting exposure and outcome variables, reporting

997 comprehensive statistics, performing sensitivity checks for potential violations of underlying
998 assumptions, and performing the analyses using alternative methods and software^{53,77}. For the
999 causal inference of each pair of BAGs, all GWAS summary statistics were derived from our
1000 analyses by excluding overlapping populations of the two BAGs. For example, to test the causal
1001 relationship between the brain BAG and cardiovascular BAG, we reran GWAS for the
1002 cardiovascular BAG by excluding the partially overlapping population from the brain BAG. For
1003 all the seven body organ systems that had entirely overlapping populations, we used the GWAS
1004 data from the split-sample analyses (**Method 3a**). For instance, the GWAS for the cardiovascular
1005 BAG was from the first-split data, and the pulmonary BAG was from the second-split data.
1006 Bonferroni correction was performed for the tested BAGs.

1007 One key challenge in our hypothesis-driven Mendelian randomization is to select these
1008 exposure variables unbiasedly. Clinical traits sharing common genetic covariance with nine
1009 BAGs are more likely to be causally associated with them. We performed a systematic inclusion
1010 procedure using the following criteria to overcome this. We manually queried the 41 clinical
1011 traits – used in our genetic correlation analyses – in the IEU GWAS database, specifically
1012 curated for Mendelian randomization analyses. We ranked all available studies for a certain trait
1013 (e.g., AD) based on the sample sizes. We then chose the study whose populations were of
1014 European ancestry and did not include UKBB participants to avoid bias due to overlapping
1015 populations¹⁶. For the traits whose GWAS data were available in the IEU GWAS database, we
1016 used the TwoSampleMR package to perform the Mendelian randomization analysis. For the
1017 traits whose data were not appropriate in the IEU GWAS database, we then performed another
1018 manual query in the EMBL-EBI GWAS Catalog database to download the available GWAS
1019 summary statistics with the same filter criteria. For the traits whose GWAS data were dominated
1020 by studies using UKBB participants in both databases, we ran GWAS using our own UKBB data
1021 by excluding overlapping populations. Finally, after harmonizing their GWAS summary
1022 statistics (using the function *harmonise_data* from 2SampleMR), this resulted in 17 clinical traits
1023 with at least eight valid IVs (i.e., SNPs). The 17 clinical traits included chronic diseases affecting
1024 multiple organ systems, cognition, and lifestyle factors (**Supplementary eTable 7**). Bonferroni
1025 correction was performed for all tested clinical traits.

1026 We performed several sensitivity analyses. First, a heterogeneity test was performed to
1027 check for violating the IV assumptions. Horizontal pleiotropy was estimated to navigate the
1028 violation of the IV's exclusivity assumption⁹⁹ using a funnel plot, single-SNP Mendelian
1029 randomization approaches, and Mendelian randomization Egger estimator¹⁰⁰. Moreover, the
1030 leave-one-out analysis excluded one instrument (SNP) at a time and assessed the sensitivity of
1031 the results to individual SNP.

1032 Following these analyses, we performed three supplementary sensitivity checks for some
1033 specific significant causal signals: *i*) The exclusion of two common SNPs/IVs (rs429358 and
1034 rs7412) in the *APOE* gene, considering their potential pleiotropic effects for the hepatic BAG on
1035 musculoskeletal BAG; *ii*) Incorporating body weight as a covariate in the GWAS for the bi-
1036 directional causality between the hepatic BAG and musculoskeletal BAG, as body weight
1037 displayed causal associations with BAGs in multiple organ systems; *iii*) Re-executing the
1038 Mendelian randomization analysis using alternative software. Specifically, we scrutinized the
1039 causal relationship between the hepatic BAG and musculoskeletal BAG using the latent causal
1040 variance (LCV) model⁵³. Employing different modeling assumptions and instrumental variables
1041 in contrast to Mendelian randomization, it examined the causal relationship between two
1042 interchangeable traits without distinction between the direct and inverse directions. A latent

1043 causal variable (L) acted as a mediator for the genetic correlation between the two traits,
1044 allowing us to quantify the genetic causality proportion (GCP). A positive GCP value between 0
1045 and 1 indicates that trait 1 is partially genetically causal; a negative GCP value means trait 2 is
1046 partially genetically causal.

1047
1048 **(h): Bayesian colocalization:** The R package (*coloc*) was employed to investigate the genetic
1049 colocalization signals between two traits at each genomic locus defined by the pulmonary BAG
1050 GWAS. We employed the Fully Bayesian colocalization analysis using Bayes Factors
1051 (*coloc.abf*). The method tests five hypotheses, denoted by their posterior probabilities: H0 (no
1052 association with either trait), H1 (association with trait 1 but not trait 2), H2 (association with
1053 trait 2 but not trait 1), H3 (association with both traits but with separate causal variants), and H4
1054 (association with both traits with a shared causal variant). It examines the posterior probability
1055 (PP.H4.ABF: Approximate Bayes Factor) to evaluate hypothesis *H4*, which suggests the
1056 presence of a single shared causal variant associated with both traits within a specific genomic
1057 locus. To determine the significance of the *H4* hypothesis, we set a threshold of
1058 $PP.H4.ABF > 0.8^{20}$ and at least 100 SNPs were included within the genomic locus. All other
1059 parameters (e.g., the prior probability of p_{12}) were set as default.

1060

1061 **Data Availability**

1062 The GWAS summary statistics corresponding to this study are publicly available on the
1063 MEDICINE knowledge portal (<https://labs-laboratory.com/medicine>).

1064 **Code Availability**

1065 The software and resources used in this study are all publicly available:

- 1066 • MEDICINE: <https://labs-laboratory.com/medicine>, knowledge portal for dissemination
- 1067 • BioAge: <https://github.com/yetianmed/BioAge>, biological age prediction
- 1068 • PLINK: <https://www.cog-genomics.org/plink/>, linear model GWAS
- 1069 • FUMA: <https://fuma.ctglab.nl/>, gene mapping, genomic locus annotation
- 1070 • GCTA: <https://yanglab.westlake.edu.cn/software/gcta/#Overview>, heritability estimates,
1071 mixed effect GWAS
- 1072 • LDSC: <https://github.com/bulik/ldsc>, genetic correlation, and partitioned heritability
- 1073 • TwoSampleMR: <https://mrcieu.github.io/TwoSampleMR/index.html>, Mendelian
1074 randomization
- 1075 • Coloc: <https://github.com/chr1swallace/coloc>, Bayesian colocalization
- 1076 • LCV: <https://github.com/lukejconnor/LCV>, Latent causal variable for causal inference

1077 **Competing Interests**

1078 None

1079

1080 **Authors' contributions**

1081 Dr. Wen has full access to all the data in the study and takes responsibility for the integrity of the
1082 data and the accuracy of the data analysis.

1083 *Study concept and design:* Wen

1084 *Acquisition, analysis, or interpretation of data:* Wen, Tian, Zalesky, Davatzikos

1085 *Drafting of the manuscript:* Wen, Tian, Zalesky, Davatzikos

1086 *Critical revision of the manuscript for important intellectual content:* all authors

1087 *Statistical analysis:* Wen

1088 *BAG index generation:* Tian

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