

1 **Plasma proteomics in the UK Biobank reveals youthful brains and immune systems**
2 **promote healthspan and longevity**

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19 **ABSTRACT**

20 Organ-derived plasma protein signatures derived from aptamer protein arrays track organ-
21 specific aging, disease, and mortality in humans, but the robustness and clinical utility of these
22 models and their biological underpinnings remain unknown. Here, we estimate biological age of
23 11 organs from 44,526 individuals in the UK Biobank using an antibody-based proteomics
24 platform to model disease and mortality risk. Organ age estimates are associated with future
25 onset of heart failure (heart age HR=1.83), chronic obstructive pulmonary disease (lung age
26 HR=1.39), type II diabetes (kidney age HR=1.58), and Alzheimer's disease (brain age HR=1.81)
27 and sensitive to lifestyle factors such as smoking and exercise, hormone replacement therapy, or
28 supplements. Remarkably, the accrual of aged organs progressively increases mortality risk while
29 a youthful brain and immune system are uniquely associated with disease-free longevity. These
30 findings support the use of plasma proteins for monitoring organ health and the efficacy of drugs
31 targeting organ aging disease.
32

33 MAIN

34 Aging leads to global dysfunction of organ systems, chronic disease, and ultimately death.
35 Interventions including exercise, young plasma treatment, or rapamycin treatment seem to slow
36 aging in model organisms, extending healthspan and lifespan¹, but whether these findings would
37 extrapolate to humans is unclear, as both our molecular understanding of human aging and our
38 ability to efficiently assess the efficacy of aging interventions in humans is limited. Thus, molecular
39 biomarkers of human biological age that are linked with age-related health and disease are
40 needed.

41
42 Recent studies show that human organs age at different rates²⁻⁵ similar to what has been reported
43 in animals⁶⁻⁸, which suggests a need for organ-specific measures of biological age. Previously
44 developed organ age estimates include those developed from clinical metrics of organ function
45 (glomerular filtration rate, blood pressure, etc), clinical blood chemistry, brain MRI scans, immune
46 cell DNA methylation profiles, and the levels of organ-specific proteins in blood plasma²⁻⁵. Many
47 questions regarding the reproducibility and utility of organ age estimates remain. For example, it
48 is unclear the extent to which organ age estimates are stable across cohorts and longitudinal
49 sampling, are sensitive to organ-specific diseases and modifiable lifestyle choices, and whether
50 they predict mortality independent of each other and established aging biomarkers. Furthermore,
51 it is unclear which organs are key to longevity in humans.

52
53 Given that plasma is simple to acquire, the levels of plasma proteins provide molecular
54 information on organ function, and technologies to measure the levels of plasma proteins are
55 rapidly advancing, we sought to further investigate the utility of plasma proteomics in estimating
56 organ-specific biological age and understanding human longevity. In comparison to our previous
57 study where we introduced our organ age estimation approach using SomaScan plasma
58 proteomics data from 5,678 individuals⁴, here we aimed to test our approach in a much larger
59 cohort of 44,526 individuals in the UK Biobank (age 40-70), using an orthogonal proteomics
60 platform (Olink). The dramatically increased sample size and deeper tracking of age-related
61 phenotypes allowed us to address several important questions in the field. Specifically, we
62 assessed whether plasma protein-based age estimates for 11 major organs could identify
63 different subtypes of organ agers in the population, predict risk of age-related organ diseases,
64 track with beneficial/detrimental lifestyle choices, and predict mortality versus longevity (**Fig. 1a**).

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66

67 Plasma protein-derived organ age estimates in the UK Biobank

68 To derive measures of organ-specific physiological state and biological age from the plasma
69 proteome, we 1) identified plasma proteins likely derived from a specific organ (**Supplementary**
70 **Tables 1-2**), 2) trained a machine learning model to predict chronological age based on the levels
71 of identified organ-specific proteins (**Supplementary Tables 3-4**), and 3) calculated the age gap
72 based on each person's predicted age (the relative predicted age compared to individuals of the
73 same chronological age; See methods; **Fig. 1a**). The age gap provides a measure of relative
74 biological age compared to same-aged peers.

75
76 We performed these three steps for each of 11 major organs including adipose tissue, artery,
77 brain, heart, immune tissue, intestine, kidney, liver, lung, muscle, and pancreas. To compare
78 organ age gaps to organ-agnostic measures of biological age, we also derived age gaps from an
79 "organismal" aging model trained on non-organ-specific proteins and a "conventional" aging
80 model trained on all proteins on the Olink assay. We confirmed the top proteins in the conventional
81 aging model overlapped with a previous proteomic aging model developed on the UK Biobank
82 dataset⁹.

83

84 Data from ten of twenty-one plasma collection centers were used for model training and the
85 remaining eleven for testing (**Fig. 1a**). Model performance was highly stable across train and test
86 centers (**Extended Data Fig. 1a-b**). Age gaps were z-scored per aging model to allow for direct
87 comparison between organs in downstream analyses (**Fig. 1a**). We observed some sex
88 differences between organ age gaps with males having older kidneys, immune systems, and
89 intestines, while females had older adipose tissue, arteries, and hearts (**Extended Data Fig. 1c-**
90 **d**).

91
92 After deriving organ age gaps, we first determined the uniqueness of each measure. If organs
93 truly aged at different rates, then the age gap of one organ should be independent from the age
94 gap of another in the same individual. Thus, we calculated pairwise correlations between organ
95 age gaps. As expected, based on previous literature, we found organ age gaps were only mildly
96 correlated (mean $r=0.21$; **Fig. 1b**). Of note, organ age gaps were largely different from the
97 conventional age gap, suggesting they capture information not measured by conventional
98 proteomic aging models in the field. Instead, the conventional age gap was strongly correlated
99 with the organismal age gap ($r=0.87$). Estimated organismal, brain, and artery age were sufficient
100 to explain 97% of the variance in estimated conventional age, with organismal age carrying 74%
101 of the weight (**Fig. 1c**).

102
103 We previously identified extreme organ agers who displayed especially fast aging in just a single
104 organ or many organs⁴. We searched for extreme agers in the UK Biobank by identifying
105 individuals with age gaps above or below 1.5 standard deviations from the population average in
106 any organ (top and bottom ~6-7% percentiles). Indeed, we found groups of fast (≥ 1.5 z-age gap)
107 and slow (≤ -1.5 z-age gap) organ agers who had extreme age gaps in only a single organ (1-
108 2% of samples each, 33% total; **Fig. 1d**; **Extended Data Fig. 1e**). We also identified multi-organ
109 agers who had two or more extreme organ age gaps (26% of samples; **Extended Data Fig. 1e**).
110 14% of samples were ambiguous, with both positive and negative extreme age gaps and 27% of
111 remaining samples were defined as normal agers (**Extended Data Fig. 1e**). Multi-organ agers
112 were significantly older than normal and single organ agers, suggesting aged organs accumulate
113 over time (**Extended Data Fig. 1f-g**). Youthful agers were not identified in our previous study⁴
114 based on SomaScan data, potentially due to limited sample size and detection of different proteins
115 between platforms.

116
117 We next sought to determine the longitudinal stability of organ age gaps over several years within
118 an individual. In other words, does a person with a biologically older heart at age 50 still have an
119 older heart at age 60? We analyzed a subset of 937 individuals who had plasma proteomics data
120 from two to three visits, spanning 1 to 15 years from baseline. We assessed the correlations
121 between age gaps at baseline versus visit two, for each organ. We found medium to strong
122 correlations across visits (mean $r=0.6$), suggesting age gaps are relatively stable, while also likely
123 reflecting dynamic alterations to biological age based on lifestyle and disease as well as technical
124 variability (**Extended Data Fig. 2a**).

125
126 Examining longitudinal stability of extreme ager status, we found that individuals who were
127 extreme agers in a given organ at visit 1 were 3-22 times more likely to be an extreme ager in
128 that same organ at visit 2, compared to individuals who were not extreme agers in that organ at
129 visit 1 (**Extended Data Fig. 2b**). Still, a considerable proportion (68%) of visit 1 extreme agers
130 were no longer categorized as extreme agers for their respective organs in visit 2. Therefore, we
131 examined changes in age gap status by bins separated by 0.5 standard deviations up to ± 1.5 ,
132 rather than binary extreme ager status. We found that the vast majority of visit 1 extreme agers
133 stayed within the same signed bins across visit 2 (76%) and visit 3 (72%), suggesting that the
134 overall directionality of their age gaps was stable (**Extended Data Fig. 2c-e**).

135
136 Together, these data show that organ-specific biological age estimates can be derived from
137 plasma proteomic data in the UK Biobank, and that each organ age estimate provides unique
138 information about the individual, perhaps related to organ-specific health. Moreover, within 2
139 independent visits, deviation from chronological age tends to be stable within individuals.

141 142 **Organ age estimates predict future age-related disease**

143 For an estimate of biological age to be informative, it must robustly associate with the
144 physiological state of the organ or individual and consequently, with age-related health and
145 disease outcomes. Hence, we sought to determine whether organ age gaps could predict future
146 diseases in their respective organs. We tested the associations between all 13 z-scored age gaps
147 and 15 incident age-related diseases (2-17 year follow-up) using Cox proportional hazard
148 regression, while adjusting for age and sex. Following Benjamini-Hochberg correction for multiple
149 hypothesis testing, we identified 176 positive and 4 negative significant associations out of 195
150 tests (**Fig. 2a; Supplementary Table 5**).

151
152 We discovered highly significant associations between heart aging and atrial fibrillation (hazard
153 ratio [HR]=1.75, $q < 1 \times 10^{-230}$) and heart failure (HR=1.83, $q = 1.39 \times 10^{-230}$), pancreas aging
154 (HR=1.77, $q = 5.03 \times 10^{-220}$) and kidney aging (HR = 1.64, $q = 5.25 \times 10^{-217}$) with chronic kidney
155 disease, brain aging with Alzheimer's disease (HR=1.81, $q = 2.29 \times 10^{-72}$) and lung aging with
156 chronic obstructive pulmonary disease (HR=1.39, $q = 7.20 \times 10^{-32}$). Liver aging was associated with
157 chronic liver disease (HR=1.18, $q = 4.31 \times 10^{-11}$), albeit the strength of the association was modest
158 and similar compared to other organs. Importantly, organ-specific age gaps consistently exhibited
159 stronger predictive power than conventional age gaps across all diseases (**Fig. 2a**).

160
161 The widespread significant associations between organ aging (176/195) and disease underscore
162 the systemic nature of aging. While certain diseases may have notably systemic causes, others
163 may stem primarily from dysfunction in a single organ. Identifying the degree of systemic versus
164 local contributions in disease onset could yield insights into biological mechanisms and prevention
165 strategies. Thus, for each disease, we calculated the Gini-coefficient, a measure of statistical
166 dispersion (originally intended to measure income inequality), of organ age gap log hazard ratios.

167
168 Interestingly we found that chronic kidney disease, ischemic heart disease, heart failure, and
169 chronic obstructive pulmonary disease (COPD) were predicted by aging of many organs,
170 suggesting systemic underpinnings (**Fig. 2b**). Whether these diseases are caused by systemic
171 aging or the prodromal phases of these diseases induce aging across the body is unclear.
172 Conversely, Alzheimer's disease was predicted primarily by brain aging (**Fig. 2c-d**). Other more
173 organ-specific diseases included atrial fibrillation which was primarily predicted by heart aging
174 and type 2 diabetes which was predicted primarily by kidney (HR=1.58, $q = 2.54 \times 10^{-206}$), intestine
175 (HR=1.54, $q = 1.18 \times 10^{-126}$), and immune (HR=1.49, $q = 1.03 \times 10^{-103}$) aging (**Fig. 2c**).

176
177 We also investigated the associations between extreme organ age and disease risk (**Extended**
178 **Data Fig. 3a; Supplementary Table 6**). Individuals with more than one aged organ had
179 significantly increased risk for nearly every disease we examined. Individuals with only aged
180 brains, hearts, kidneys, or lungs also showed broad increased risk of disease. On the other hand,
181 individuals with 2-4 youthful organs were protected from some disease including chronic kidney
182 disease, osteoarthritis, and COPD; however, individuals with 5-7 youthful organs were not globally
183 significantly protected and instead had increased risk for diabetes and Parkinson's disease,
184 suggesting a youthful appearing aging signature is not always beneficial. Among youthful organ
185 profiles, only the brain and immune system were protective for at least three diseases (nominal

186 p-value<0.05) while not conferring increased risk of any other diseases. A youthful brain was
187 especially protective of Alzheimer's disease (HR=0.13, p=0.046, q=0.15) and other dementias,
188 while a youthful immune system was protective of diabetes (HR=0.52, p=0.0073, q=0.044), atrial
189 fibrillation, and cerebrovascular disease (**Extended Data Fig. 3a**).

190
191 We further examined all individuals with youthful or aged brains – regardless of single or multi-
192 organ age status – and their associations with Alzheimer's disease risk (**Fig. 2e**). We found that
193 individuals with aged brains had a 3.4-times increased risk (HR=3.43, p=7.26x10⁻³⁴) while those
194 with youthful brains had a striking 81% reduced risk (HR=0.19, p=4.21x10⁻⁵) of Alzheimer's
195 disease compared to those with normal aging brains (**Fig. 2e**). Regarding sample size, 121 of
196 2,618 individuals (4.6%) with aged brains developed Alzheimer's disease over 17 years, while
197 only 6 of 2,002 individuals (0.3%) with youthful brains developed the disease.

198
199 The specificity of the association between brain aging and dementia led us to determine whether
200 organ age gaps were associated with brain volume based on magnetic resonance imaging (MRI)
201 data from follow-up visits (**Extended Data Fig. 3b**). We confirmed that brain aging was uniquely
202 associated with increased volume of the ventricles and decreased volume of cortical regions.

203
204 We also assessed organ age gap associations with disease progression, by regressing age gaps
205 against years since diagnosis, for individuals who were diagnosed with disease before blood draw
206 (**Extended Data Fig. 3c**). We found that many organ age gaps increased throughout chronic
207 kidney disease progression. Interestingly, the brain age gap was not associated with dementia
208 progression (**Extended Data Fig. 3d**), suggesting the brain aging model uniquely captures age-
209 related changes leading up to dementia but not after.

210
211 Given these robust associations, we sought to gain further insights into organ aging by examining
212 aging model proteins and their weights (**Extended Data Fig. 4a**). The strongest weighted protein
213 in the brain aging model was neurofilament light chain (NEFL; **Fig. 2f**), which increases with age
214 and is a clinical biomarker of neurodegeneration that is often measured in clinical trials for
215 Alzheimer's disease^{10,11} and was recently approved as a surrogate endpoint for a clinical trial to
216 treat superoxide dismutase 1 amyotrophic lateral sclerosis (SOD1-ALS)^{12,13}. Our data suggest it
217 may also be a viable surrogate endpoint for functional deterioration of the brain, risk of dementia,
218 and brain aging. Other highly weighted brain aging proteins include myelin oligodendrocyte
219 protein (MOG), a component of the outer surface of myelin sheaths, and glial fibrillary acidic
220 protein (GFAP) a marker of reactive astrocytes, which both increased with age, as well as
221 brevican (BCAN), a brain extracellular matrix component produced by oligodendrocyte precursor
222 cells, and protein tyrosine phosphatase receptor type R (PTPRR), which decreased with age (**Fig.**
223 **2f**). Plasma NEFL, GFAP, and BCAN were previously highlighted as predictors of future dementia
224 risk¹⁴. Model weights between UK Biobank-Olink and SomaScan⁴ brain aging models were
225 moderately correlated (Spearman $\rho=0.5$), with NEFL, BCAN, and PTPRR being most aligned in
226 effect and directionality across platforms (**Extended Data Fig. 5a**). Using the permutation feature
227 importance for biological aging (FIBA) algorithm⁴, we found that all of the top seven most highly
228 weighted brain aging proteins contributed to the prediction of Alzheimer's disease risk, showing
229 the importance of leveraging the information from many brain-derived proteins to understand brain
230 aging and disease (**Extended Data Fig. 5b**).

231
232 We then sought to determine which cell types these proteins were likely derived from by analyzing
233 public human brain single-cell RNA-sequencing data¹⁵ (**Extended Data Fig. 5c-d**). Interestingly,
234 we found that around half of brain aging proteins were specific to the oligodendrocyte lineage,
235 with the rest expressed mostly in neurons, then astrocytes (**Extended Data Fig. 5d**), pointing to

236 white matter as a key aging region, as suggested by human brain MRI and mouse brain RNA-
237 sequencing studies^{16,17}.

238
239 Lung aging was explained primarily by lysosome-associated membrane glycoprotein 3 (LAMP3),
240 a protein expressed specifically in type II alveolar stem cells, secretoglobin family 1A member 1
241 (SCGB1A1) also known as club cell secretory protein (CCSP), a marker of club cells, and C-C
242 Motif Chemokine Ligand 18 (CCL18), a cytokine expressed by alveolar macrophages, potentially
243 reflective of stem cell dysfunction and inflammation in the lung with age. Heart aging was
244 explained primarily by N-terminal pro b-type natriuretic peptide (NT-proBNP), a vasodilating
245 hormone that increases in response to heart damage, while kidney aging was explained by renin
246 (REN), a protein involved in blood pressure regulation. Both NT-proBNP and REN were previously
247 identified as key heart and kidney aging proteins, respectively, based on SomaScan plasma
248 proteomics data⁴ and are well-established biomarkers of heart and kidney function. All aging
249 model protein weights are provided in **Supplementary Table 4** and the top 20 proteins for each
250 model are shown in **Extended Data Fig. 4a**.

251
252 Together, these data show that plasma protein-derived organ age estimates are linked with age-
253 related organ diseases and can reveal insights into the aging biology of their respective organs.

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255

256 **Organ age estimates are sensitive to modifiable lifestyle choices**

257 We next explored whether biological age estimates grounded in physiological states of organ
258 function are sensitive to changes in lifestyle. We tested the associations between all 13 z-scored
259 age gaps and 15 lifestyle factors (diet, alcohol, smoking, exercise), adjusted for age and sex using
260 linear regression (**Supplementary Table 7**). We found 66 positive and 79 negative significant
261 associations after correcting for multiple hypothesis testing. In line with their known health impacts,
262 smoking, alcohol, and processed meat intake were associated with age acceleration across
263 several organs, while “vigorous exercise” and oily fish consumption were associated with youthful
264 organs (**Fig. 4a**).

265
266 We also tested the associations between all 13 z-scored age gaps and consumption of 137
267 drugs/supplements (n cases ≥ 100; **Supplementary Table 8**). After multiple hypothesis test
268 correction, we found 5 products – Premarin, ibuprofen, glucosamine, cod liver oil, multivitamins,
269 vitamin C – that were significantly (q < 0.01) associated with more youthful age in at least two
270 organs (**Fig. 4b**). Ibuprofen, glucosamine, cod liver oil, multivitamins, and vitamin C products were
271 associated with youth primarily in the kidneys, brain, and pancreas (**Fig. 4b**).

272
273 Premarin is a conjugated estrogen medication typically prescribed to women experiencing post-
274 menopausal symptoms, and estrogen medication has been recently shown to be associated with
275 reduced mortality risk in the UK Biobank¹⁸. Thus, we wondered whether estrogen medications
276 may extend longevity by preventing menopause-induced accelerated aging of organs. We
277 grouped all post-menopausal estradiol/oestrogen medications together and identified 47 women
278 with normal, early, or premature menopause (but not late menopause) who were treated with
279 estrogen by the time of blood draw. We subsetted our analysis to women among these
280 menopausal groups and tested the independent associations of age at menopause and estrogen
281 treatment with organ age gaps using linear regression. Interestingly, women with earlier
282 menopause were age accelerated across nearly all organs, in line with the well-documented
283 adverse health consequences of early menopause¹⁹ (**Fig. 4c**). Conversely, estrogen treatment
284 was associated with more youthful immune systems, livers, and arteries suggesting intervention
285 with estrogen treatment may protect these organs from menopause-induced age acceleration
286 resulting in extended survival (**Fig. 4d**).

287
288 Though these cross-sectional findings should be interpreted with caution, they underscore the
289 sensitivity of plasma protein-derived organ age estimates to various lifestyle choices with known
290 health impacts and their potential utility in assessing the effects of novel interventions in more
291 rigorous experimental settings.

292
293
294 **Accrual of aged organs progressively increases mortality risk while brain and immune**
295 **system youth is associated with longevity**

296 We next sought to determine whether organ age estimates were associated with future mortality
297 risk. We tested associations between organ age gaps and all-cause mortality risk, adjusting for
298 age and sex, over a 2-17 year follow-up using Cox proportional hazards regression
299 (**Supplementary Table 9**). We found significant associations in all organs with a standard
300 deviation increase in age gaps conferring 20%-60% increased risk of death (**Fig. 4a**), similar to
301 findings from SomaScan-based organ aging models⁴. These associations were robust to
302 additional adjustment with blood cystatin-C, a marker of kidney filtration rate, and PhenoAge, an
303 established blood biochemistry/cell counts-based biological age estimate (whose age gap has a
304 mortality risk hazard ratio of 1.38 in the UK Biobank), suggesting that organ age estimates provide
305 independent information not captured by existing clinical biomarkers. Surprisingly, brain aging
306 was most strongly predictive of mortality (HR=1.58, $p=4.40 \times 10^{-291}$) (**Fig. 4a**), suggesting that the
307 brain may be a central regulator of lifespan in humans similar to findings in animal models (worms,
308 flies, mice)²⁰⁻²². Indeed, individuals with aged brains had increased risk for several diseases
309 beyond dementia including COPD and heart failure (**Extended Data Fig. 3a**) consistent with
310 previous studies showing that the brain regulates systemic inflammation²³⁻²⁷.

311
312 These data suggested that organ age estimates may provide additional predictive power for
313 mortality, beyond cystatin-C and PhenoAge. We compared the concordance-index, a metric of
314 Cox model performance equivalent to area under the curve (AUC), of regularized Cox proportional
315 hazard models trained on cystatin-C alone, PhenoAge alone, organ ages alone, and combinations
316 of these aging biomarkers, with chronological age and sex as covariates in each model. We found
317 that the model with all variables had the strongest performance, comparable to the performance
318 of the model with organ ages alone (**Fig. 4b**), suggesting that organ ages not only provide
319 additional predictive power, but also that they sufficiently capture the information from other
320 clinical aging biomarkers. Examination of the combined model coefficients revealed that
321 conventional age, brain age, PhenoAge, and biological sex were the strongest independent
322 predictors of mortality (Fig. 4c). Application of FIBA to understand contributions of brain and
323 conventional aging model proteins on mortality risk highlighted BCAN, NEFL, and PTPRR from
324 the brain as well as ectodysplasin A2 receptor (EDA2R, organismal protein), chemokine C-X-C
325 motif ligand 17 (CXCL17, organismal protein), and elastin (ELN, artery protein) from the
326 conventional aging model as important proteins (**Extended Data Fig. 6a-d**).

327
328 While each organ age gap was associated with risk of death, we wondered whether the accrual
329 of aged organs would be increasingly detrimental. Hence, we tested whether single-organ
330 extreme agers and multi-organ agers (bins of 2-4, 5-7, 8+ organs) had an increased risk of death
331 compared to normal agers, while adjusting for age and sex (**Supplementary Table 10**).
332 Interestingly, we found that while having a single aged organ (brain, lung, intestine, heart, immune,
333 kidney, liver, pancreas) conferred a 1.5-3 times increased risk, having 2-4, 5-7, and 8+ extremely
334 aged organs conferred a 2.3-, 4.5-, and 8.2- times ($q=3.52 \times 10^{-70}$, $q=1.11 \times 10^{-104}$, and $q=1.72 \times 10^{-123}$)
335 increased risk of death, respectively (**Fig. 4d-e**). Notably, over 60% of individuals with 8+
336 extremely aged organs at blood draw died within 15 years (**Fig. 4d**).

337

338 We then sought to determine whether youthful organ profiles were associated with longevity
339 (**Supplementary Table 10**). We found individuals with youthful appearing arteries had increased
340 mortality risk, and those with multi-organ youth had no difference in mortality risk compared to
341 normal agers (**Fig. 4d**). Using FIBA, we found that artery-protein thrombospondin 2 (THBS2), a
342 protein that decreases with age but has a positive association with mortality risk, was responsible
343 for the non-linear association between the artery age gap and mortality risk (**Extended Data Fig.**
344 **6c; Extended Data Fig. 4a**). Why individuals with broad multi-organ youth are not protected is
345 unclear.

346
347 Notably though, individuals with youthful brains (HR=0.53, $q=6.58 \times 10^{-3}$) and immune systems
348 (HR=0.63, $q=0.034$) had significantly reduced mortality risk (**Fig. 4d**), similar to their unique
349 protective associations with disease (**Extended Data Fig. 3a**). We therefore assessed individuals
350 with both youthful brains and immune systems and found that this group was most strongly
351 protected from mortality (HR=0.37, $p=0.027$; **Fig. 4d-e**), underscoring the additive longevity
352 benefits of having a resilient brain and immune system. Regarding sample size, 792 of 10,000
353 individuals (7.92%) of normal agers died within 17 years, while only 5 of 157 individuals (3.2%)
354 with youthful brains and immune systems died.

355
356 To probe the underlying mechanisms implicated in brain- and immune system- related longevity,
357 we performed gene ontology enrichment analyses of the top ten brain and immune aging model
358 proteins based on mortality risk FIBA scores (**Extended Data Fig. 6f-g; Fig. 4f-g**). Selection of
359 brain- or immune system- specific plasma proteins as background for the enrichment test did not
360 result in significant associations, so we used all genes as background. Perineuronal net was the
361 most enriched brain pathway (BCAN, PTPRZ1, NCAN) and secretory granule was the most
362 enriched immune system pathway. Intriguingly, neuroinflammation was another enriched immune
363 system pathway, composed of metalloproteinase-9 (MMP9), a regulator of perineuronal net
364 composition, as well as tumor necrosis factor receptor superfamily member 1B (TNFSRF1B), and
365 integrin alpha M (ITGAM) also known as CD11B. Youthful brain agers had higher levels of BCAN
366 and NCAN and youthful immune agers had lower levels of MMP9 (**Extended Data Fig. 6f-g**),
367 suggesting that global preservation of brain extracellular matrix partly due to reduced degradation
368 by peripheral inflammatory factors and reduced chronic inflammation partly regulated by the brain
369 could be crucial for promoting longevity.

370
371 Together, these data reveal that plasma-protein derived organ age estimates improve upon
372 existing aging biomarkers for mortality risk prediction, the accrual of aged organs progressively
373 increases mortality risk, and a youthful brain and immune system are key to longevity.

374
375

376 **DISCUSSION**

377 Our findings based on plasma proteomics data (~3,000 proteins) from nearly 45,000 individuals
378 in the UK Biobank establish plasma protein-derived organ age estimates as robust indicators of
379 organ age, health, and disease/mortality risk beyond gold-standard clinical aging biomarkers and
380 reveal key proteins implicated in the aging process. Furthermore, we show that organ age
381 estimates are stable across train/test centers and longitudinal visits and are cross-sectionally
382 associated with modifiable lifestyle choices and therapeutic use, and thus, lay the foundation for
383 human experiments testing the effects of novel longevity interventions on the biological age of
384 organs at the individual level.

385
386 Though we define correlates of organ aging that explain heterogeneity in disease and mortality,
387 future work is needed to understand the molecular and environmental determinants and sequence
388 of organ aging. Our discovery of multi-organ agers and their increased prevalence with age (**Fig.**

389 **1d, Extended Data Fig. 1g)** suggests that aged organs likely accumulate over time within an
390 individual, but how and why is unclear. Consistent longitudinal sampling combined with
391 comprehensive patient phenotyping regarding environmental stresses and genetic background
392 are needed to elucidate the dominant sequences and causes of organ aging at the population
393 and individual levels. Improved technologies that allow for the sampling of thousands of more
394 molecules (proteins, lipids, and metabolites) from human tissue will aid in obtaining a more global
395 understanding of human aging heterogeneity and its causes.

396
397 Furthermore, additional studies are needed to understand why individuals with youthful profiles in
398 many organs are not protected from disease and mortality (**Fig. 4d, Extended Data Fig. 3a**).
399 While this may be commonly assumed to be true, numerous studies have shown non-linear
400 associations between clinical biomarkers of health (ie. BMI, blood ALT, platelet count) and
401 mortality risk with extreme “youthful” phenotypes being associated with higher risk^{28–30}. This
402 observation emphasizes the complexities of biological age estimation and the importance of
403 investigating non-linear associations between aging signatures with disease and mortality to
404 derive interpretable and actionable insights.

405
406 Here, we find evidence that the brain and immune system may be central regulators of aging and
407 longevity in humans, as accelerated brain aging is most strongly predictive of earlier mortality and
408 a youthful brain and immune system is most predictive of longevity (**Fig. 4a-d**). After all, the brain
409 regulates numerous critical age-related functions throughout the body including circadian rhythm,
410 blood pressure, energy homeostasis, and stress response via the neuroendocrine and autonomic
411 nervous systems, and chronic inflammation has been heavily implicated in aging^{1,31}. Intriguingly,
412 recent studies show bidirectional communication between the brain and immune system in aging
413 and disease relevant contexts, such as chronic stress, atherosclerosis, and infection^{23–27}. These
414 observations suggest that accelerated aging or maintenance of youth in the brain and immune
415 system likely has broad age-related effects across the body, though additional studies are needed
416 to test this hypothesis more rigorously in humans.

417
418 Regarding the molecular alterations that occur with brain aging, we find many unexpected age-
419 and disease- associated changes in oligodendrocyte lineage- and extracellular matrix- proteins,
420 implying extensive changes beyond neuroinflammation and neurodegeneration. Indeed, myelin
421 degeneration and defective remyelination with mouse aging causes cognitive deficits³² and
422 aggravates Alzheimer’s disease pathology³³, and APOE4, the strongest genetic risk factor for
423 late-onset Alzheimer’s disease, impairs myelination via cholesterol dysregulation in
424 oligodendrocytes³⁴. Moreover, the observation that white matter regions exhibit the most
425 pronounced shifts in aging microglial transcriptomes¹⁷, coupled with the enrichment of genetic risk
426 variants for neurodegenerative diseases in microglial and oligodendrocyte genes³⁵, underscores
427 a potential link between oligodendrocyte aging and neuroinflammation, and their relevance to
428 neurodegeneration. Future studies exploring these multi-cellular interactions in the aging brain
429 and their interactions with the periphery may reveal key insights into human health and longevity.

430

431 **METHODS**

432

433 **Participants**

434 The UK Biobank is a population-based prospective cohort with 'omics and phenotypic data
435 collected on approximately 500,000 participants, aged 40 to 69 years at recruitment between
436 2006 and 2010. A subset of these had subsequent visits after the initial assessment 20,337
437 participants had a first repeat assessment (2012-2013), approximately 85,000 had a first MRI
438 imaging visit (from 2014 to ongoing), and approximately 9,000 had a second MRI imaging visit
439 (from 2019 to ongoing). Details on available phenotypes can be found online at
440 <https://biobank.ndph.ox.ac.uk/showcase/> and all participants provided informed consent.

441 A subset of these participants had their blood sample processed with the Olink proteomics
442 assessed, which selection, data processing and quality control are described in (Sun et al., 2023,
443 <https://www.nature.com/articles/s41586-023-06592-6>). Briefly, 53,014 samples were from the
444 initial assessment visit, 1,172 were from the first imaging visit, and 1,123 were from the second
445 imaging visit.

446

447 We defined participants' last-known-age as either age-at-death, or the difference between the
448 latest date available in ICD9, ICD10, operating procedure, cancer registry or UKB assessment
449 visit fields and birth date, this age corresponds to censoring in the following survival analyses.
450 Additionally, we define the age-at-onset of several groups of diseases based on a combination of
451 information in ICD10, ICD9, operating procedure, and cancer registry. The following disease
452 groups were defined, as in
453 (<https://www.medrxiv.org/content/10.1101/2023.09.13.23295486v1.full>), Type-2 diabetes (E11),
454 Ischemic heart disease (I20 to I25), Cerebrovascular disease (I60 to I69), Chronic liver disease
455 (K70, K73 to K76), Chronic kidney disease (N18), All cause dementia (A81, F00 to F03, F05, F10,
456 G30, G31, I67), Vascular dementia (F01, I67), Alzheimer's disease (F00, G30), Parkinson's
457 disease and parkinsonism (G20 to G22), Rheumatoid arthritis (M05, M06), Macular degeneration
458 (H35), Osteoporosis (M80, M81), Osteoarthritis (M15 to M19), Prevalent hypertension (I10 to I13,
459 I15), Colorectal cancer (C18, C19, C20), Lung cancer (C33, C34), Esophageal cancer (C15),
460 Liver cancer (C22), Pancreatic cancer (C25), Brain cancer (C71), Leukemia (C91, to C95), Non-
461 Hodgkin lymphoma (C82 to C86), Breast cancer (C50), Ovarian cancer (C56, C57), Prostate
462 cancer (C61). For heart-related diseases the group definitions were based on
463 <https://www.medrxiv.org/content/10.1101/2023.12.19.23300218v1>, Heart failure (ICD9: 4254,
464 4280, 4281, 4289, ICD10: I110, I130, I132, I255, I420, I428, I429, I500, I501, I509), and Atrial
465 fibrillation or flutter (ICD9: 4273, ICD10: I480, I481, I482, I483, I484, I489, OPCS4: K571, K621,
466 K622, K623, K624, X501, X502).

467

468 Medications reported in the verbal interview
469 (<https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100075>) were also analyzed with a minimum of
470 100 participants per medication.

471

472 Brain MRI-derived phenotypes extracted with Freesurfer
473 (<https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=110>) were analyzed, and age-at-MRI as well as
474 estimated-total-intracranial volume were regressed out.

475

476 UK Biobank data were analyzed under Application Number 45420.

477

478 **Identification of organ-specific plasma proteins**

479 We used the same methods we developed in our previous study⁴ to identify organ-specific plasma
480 proteins. Briefly, we identified organ-enriched genes: genes that were expressed at least four
481 times higher in a single organ compared to any other organ based on human tissue bulk RNA-

482 seq data from the Gene Tissue Expression Atlas (GTEx). We refer to our previous study for details.
483 Our classification of organ-enriched genes are provided in **Supplementary Table 1**. We mapped
484 these genes to proteins measured by Olink to identify organ-specific plasma proteins in the UK
485 Biobank dataset (**Supplementary Table 2**).

486

487 **Organ age estimation**

488 We used LASSO regression models to build chronological age predictors, a.k.a. aging models, to
489 estimate biological age. The LassoCV function from the scikit-learn³⁶ Python package was used
490 to identify the optimal lambda parameter value using 5-fold cross validation. The lambda value
491 that achieved 95% of the performance of the highest performing lambda value was applied to
492 scikit-learn's Lasso function to derive sparse aging models. Each organ aging model was trained
493 using a distinct set of organ-specific plasma proteins. An organismal aging model was trained
494 using non-organ-specific proteins. A conventional aging model was trained using all proteins. Age
495 gaps were calculated as the residual of predicted age linearly regressed against actual age. Age
496 gaps were z-scored per aging model to normalize for differences in age prediction accuracy. Z-
497 scored age gaps were used for all analyses. Extreme agers were defined as individuals with an
498 age gap z-score > 1.5 or z-score < -1.5 in a given aging model. Conventional age gaps were not
499 included in the extreme ager analyses due to their high similarity to organismal age gaps (**Fig.**
500 **1b-c**).

501

502 Aging models were trained and tested on 44,526 baseline assessment plasma samples which
503 had measurements for 2,923 proteins from Olink Explore proteomics. 7 proteins with missing
504 values in over 10% of samples were removed, leaving 2,916 proteins for model development.
505 Remaining missing values were imputed using scikit-learn's KNNImputer function. The knn-
506 imputer was trained on 21,504 samples from 10 randomly selected sample collection centers
507 (train centers: 11013, 11009, 11014, 11008, 11018, 11007, 11017, 11005, 11002, 11023) and
508 tested on 23,022 samples from the remaining 11 centers (test centers: 11010, 11011, 11016,
509 11020, 11021, 11004, 11003, 11006, 11012, 11001, 11022, 10003). The number of neighbors
510 used for the knn-imputer was set to the square root of the sample size of the training dataset
511 ($n=147$). Protein values were z-score normalized based on the means and standard deviations of
512 proteins in the training split (**Supplementary Table 3**) prior to model training. Aging models were
513 trained and tested using the same train-test split as the knn-imputer. Aging models performed
514 near equally across train and test samples (**Extended Data Fig. 1b; Fig. 4b**), demonstrating
515 robustness of missing value imputation and biological age estimation. Aging model weights are
516 provided in **Supplementary Table 4**.

517

518 **Longitudinal age gap analyses**

519 Longitudinal age gap analyses (**Extended Data Fig. 2**) required use of plasma proteomics data
520 collected across multiple visits from the same individual. However, proteomics data from post-
521 baseline samples were obtained from an earlier version of the Olink assay with 1,459 proteins
522 and were not compatible with models trained on the ~3k protein platform. Therefore, for
523 longitudinal age gap analyses, we trained a distinct set of organ aging models using the subset
524 of ~1.5k proteins that were measured across all visits.

525

526 1,463 proteins were measured across all visits. 4 proteins with missing values in over 10% of
527 samples were removed, leaving 1,459 proteins for model development. Missing values for
528 baseline samples were knn-imputed as described above. Post-baseline samples were not
529 imputed to prevent biased imputation towards baseline data from the same individual. 1.5k-
530 protein-based aging models were trained on 44,406 baseline samples from individuals who did
531 not have follow-up proteomics data. Importantly, samples from individuals with longitudinal
532 proteomics data were not included in model training to prevent model training-evaluation

533 contamination. 1k-protein-based aging models were LASSO regression models trained to predict
534 the predicted age from the 3k protein-based organ aging models. The lambda value that achieved
535 90% of the performance of the highest performing lambda value was used for sparsity. Recursive
536 feature elimination using scikit-learn's RFECV function was additionally used to further simplify
537 the models to maximize the number of testable samples with unimputed data. Liver and muscle
538 1k-based aging models were removed due to low correlation ($r < 0.8$) with 3k-based aging models.
539 Models were tested and evaluated on longitudinal data from 1,176 unique individuals who had
540 non-missing values for all remaining aging model proteins (880 baseline, 843 imaging-visit-1, and
541 786 imaging-visit-2 samples). The mean number of years between imaging-visit-1 and baseline
542 was 9.1 years (st. dev.=1.8), and the mean number of years between imaging-visit-2 and imaging-
543 visit-1 was 3.3 years (st. dev.1.6).

544 545 **Statistical analyses**

546 Cox proportional hazards regression (CoxPHFitter function from lifelines³⁷ Python package) was
547 used to assess the associations between organ age gaps and future disease or mortality risk.
548 Linear regression (OLS function from statsmodels³⁸ Python package) was used to assess the
549 associations between organ age gaps and lifestyle factors recorded at the time of blood draw. All
550 Cox and linear regression models included age and sex as additional covariates. Multiple
551 hypothesis testing correction was applied, when appropriate, using the Benjamini-Hochberg
552 method, and the significance threshold was a 5% false discovery rate. Corrected p-values are
553 referred in the manuscript as q-values. Results and sample sizes for these statistical tests are
554 provided in **Supplementary Tables 5-10**.

555 556 557 **DATA AVAILABILITY**

558 Organ age estimates for all UK Biobank participants will be returned to the UK Biobank and
559 available through Showcase.

560 561 562 **CODE AVAILABILITY**

563 Organ aging models can be accessed in a Python package called organageUKB (at the time of
564 publication) to easily estimate organ age from any Olink plasma proteomics sample. All aging
565 model weights are provided in **Supplementary Table 4**. Means and standard deviations to z-
566 score protein levels before applying model weights are provided in **Supplementary Table 3**.

567 568 569 **AUTHOR CONTRIBUTIONS**

570 H.S.O., J.R., and T.W.-C conceptualized the study. H.S.O. led study design and analyses. Y.L.G.
571 led data processing of UK Biobank clinical phenotypes and advised on analyses. N.R. aided in
572 longitudinal organ age gap analyses and figure generation. D.Y.U. aided in disease progression
573 analyses and figure generation. J.R., A.B., and M.D.G. provided key insights. H.S.O. produced
574 figures and wrote the manuscript. T.W.-C. edited the manuscript. T.W.-C supervised the study.
575 All authors critically revised the manuscript for intellectual content. All authors read and approved
576 the final version of the manuscript.

577 578 579 **ACKNOWLEDGEMENTS**

580 We thank B. Lehallier, A. Antebi, L. Gold, and members of the Wyss-Coray laboratory for
581 feedback and support and D. Channappa for laboratory management. This work was supported
582 by the Stanford Alzheimer's Disease Research Center (National Institute on Aging grants

583 P50AG047366 and P30AG066515), the National Institute on Aging (AG072255, T.W.-C), the
584 Milky Way Research Foundation (T.W.-C.), and the Knight Initiative for Brain Resilience (T.W.-
585 C.). It is further supported by the Stanford Graduate Fellowship (H.S.O.), the National Science
586 Foundation Graduate Research Fellowship (H.S.O.), and the NIH Center for Clinical and
587 Translational Education and Research award, Biostatistics, Epidemiology and Research Design
588 (BERD) Program (UL1TR003142, Y.L.G.).

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591 **CONFLICTS OF INTEREST**

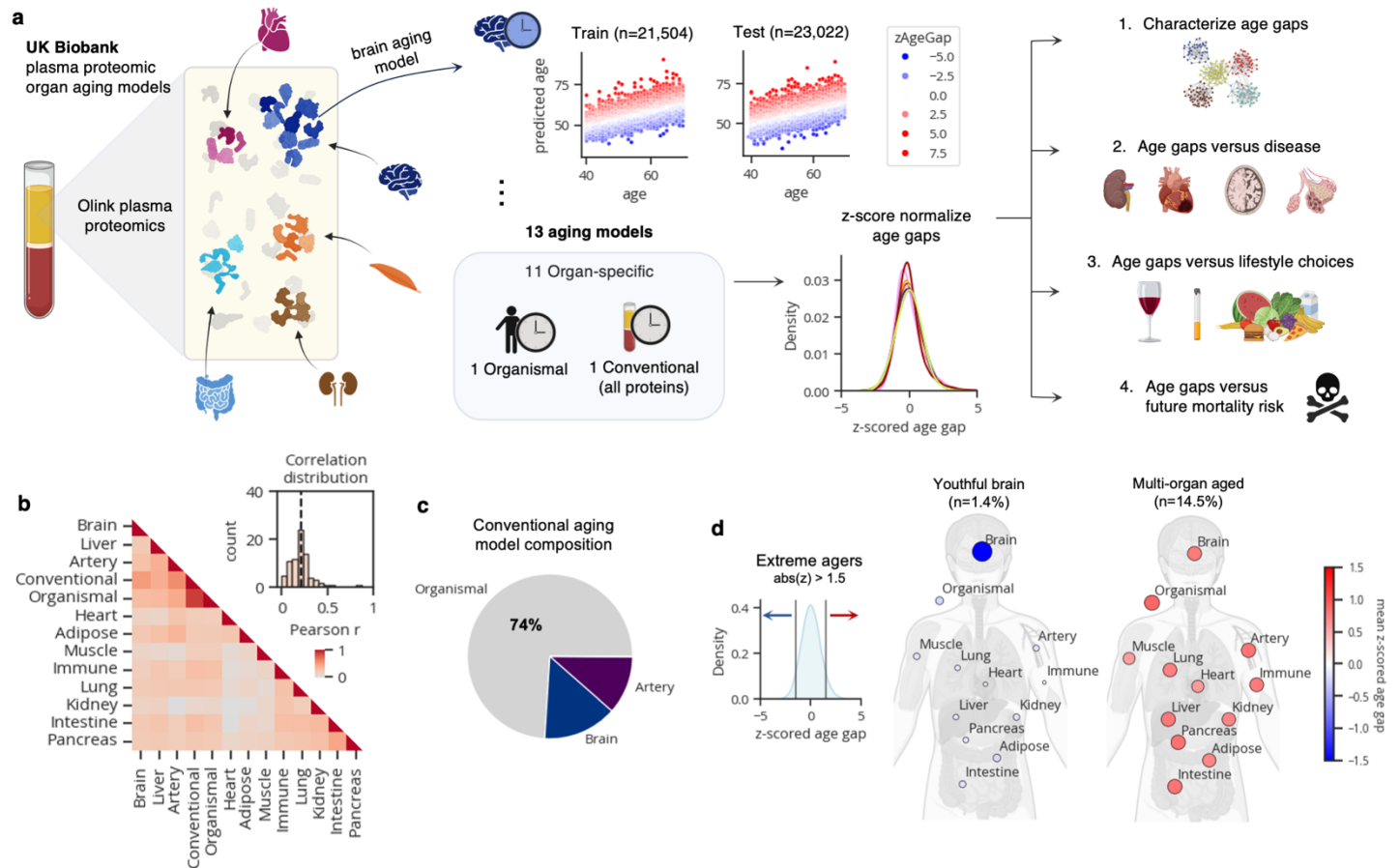
592 T.W.-C., H.S.O. and J.R. are co-founders and scientific advisors of Teal Omics Inc. and have
593 received equity stakes. T.W.-C. is a co-founder and scientific advisor of Alkahest Inc. and
594 Qinotto Inc. and has received equity stakes in these companies.

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- 681

682 **Figures**



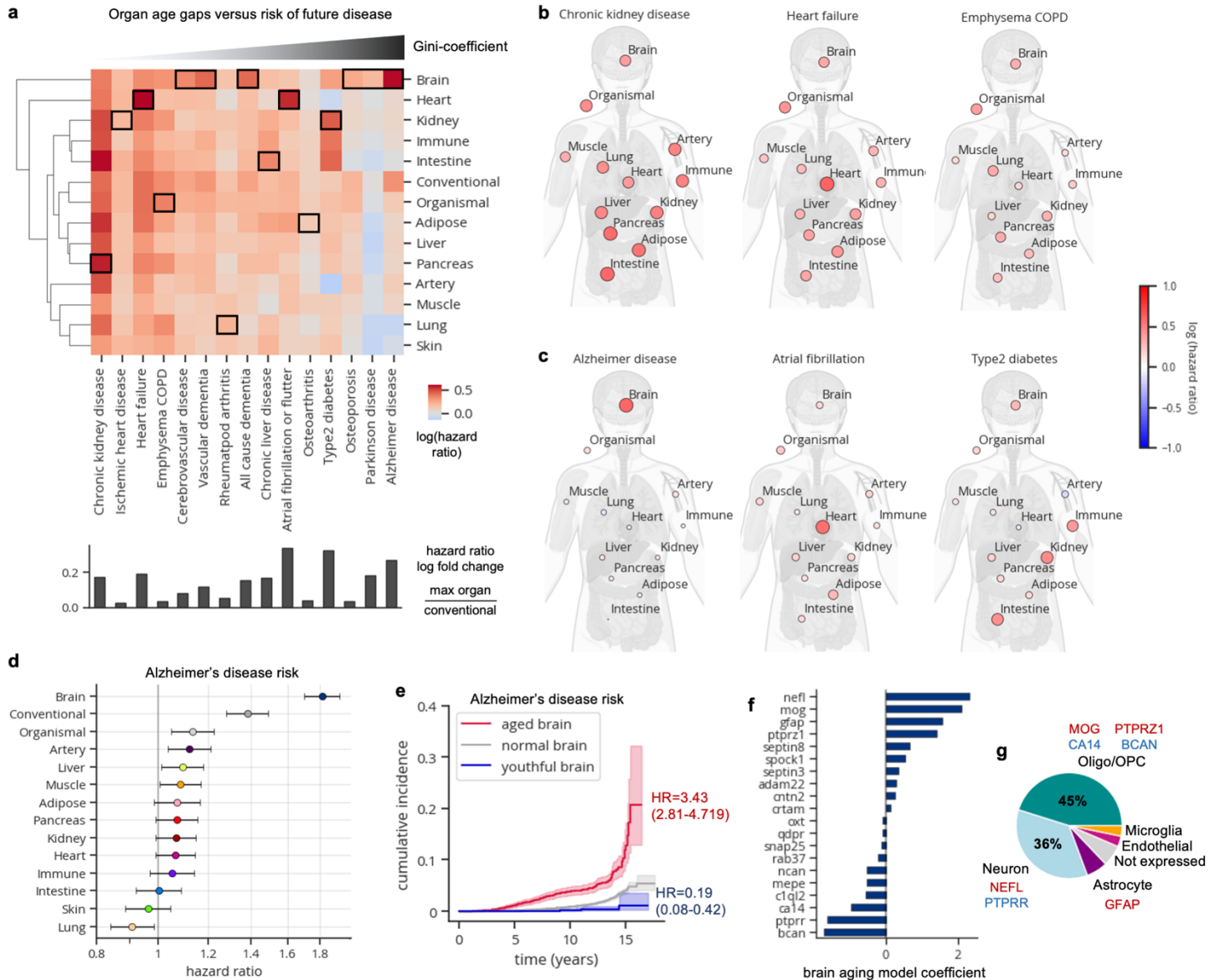
683
684 **Figure 1. Plasma protein-derived organ age estimates in the UK Biobank.**

685
686 **a**, Study design to estimate organ-specific biological age from plasma proteomics data in the UK Biobank.
687 A protein was called organ-specific if the gene encoding the protein was expressed at least four-fold
688 higher in one organ compared to any other organ in the GTEx organ bulk RNA-seq atlas. Organ-specific
689 protein sets were used to train LASSO chronological age predictors. Samples from 10/21 centers
690 ($n=21,504$) were used for training and the remaining samples ($n=23,022$) were used for testing. An
691 'organismal' model, which was trained on the levels of non-organ-specific (organ-shared) proteins, and a
692 'conventional' model, which was trained on all proteins on the Olink assay, were also developed and
693 assessed. Model age gaps were calculated and then z-score normalized per organ to allow for direct
694 comparisons across organs. Age gaps were characterized (**Fig. 1**), and tested for associations with
695 disease risk (**Fig. 2**), modifiable lifestyle choices (**Fig. 3**), and mortality risk (**Fig. 4**).
696

697 **b**, Pairwise correlation of organ age gaps from all samples. Inset histogram shows the distribution of all
698 pairwise correlations, with the dotted line representing the mean.
699

700 **c**, A Lasso regression model was used to predict conventional age based on organ ages and organismal
701 age. Organismal, brain, and artery ages were sufficient to predict conventional age with $r^2=0.97$. Relative
702 weights are shown as a pie chart.
703

704 **d**, Extreme agers were defined by a 1.5 standard deviation increase or decrease in at least one age gap.
705 The mean organ age gaps of extremely youthful brain agers and accelerated multi-organ agers are
706 shown.



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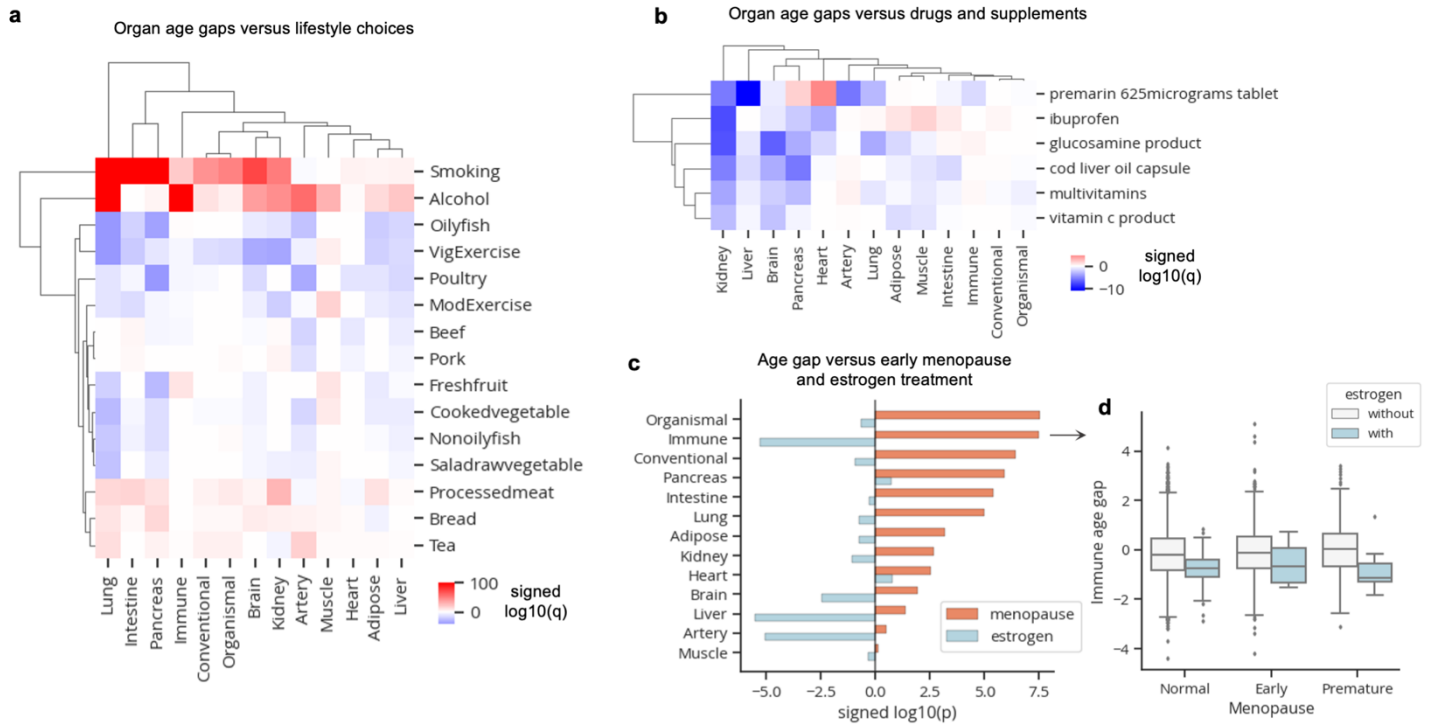
Figure 2. Organ age estimates predicts future age-related disease.

a, Cox proportional hazards regression was used to test the association between age gaps and future disease risk, adjusted for age-at-blood-draw and sex. Heatmap colored by age gap $\log(\text{hazard ratio})$ is shown. Heatmap columns are ordered by the Gini-coefficient of age gaps per disease. The most significant associations per disease are highlighted with black borders. The conventional age gap was never the most significant. The log fold change in hazard ratios between the organ with the most significant age gap versus the conventional age gap is shown below the heatmap.

b, Body plots showing log hazard ratios from the heatmap in **a**, are shown for diseases of systemic aging.

c, Body plots showing log hazard ratios from the heatmap in **a**, are shown for diseases of single-organ aging.

- 723 **d**, Forest plot visualizing the results from the heatmap in **a**, for Alzheimer's disease risk. Age gap hazard
724 ratios and 95% confidence interval shown.
725
- 726 **e**, Cumulative incidence plot showing increased risk of Alzheimer's disease in extreme accelerated brain
727 agers and decreased risk in youthful brain agers.
728
- 729 **f**, Bar plot displaying the top 10 protein coefficients in the brain aging model.
730
- 731 **g**, Pie chart displaying proportion of brain aging proteins assigned to each brain cell-type based on single-
732 cell RNA-sequencing. Cell type was assigned based on cell type with the maximum expression of a given
733 gene.
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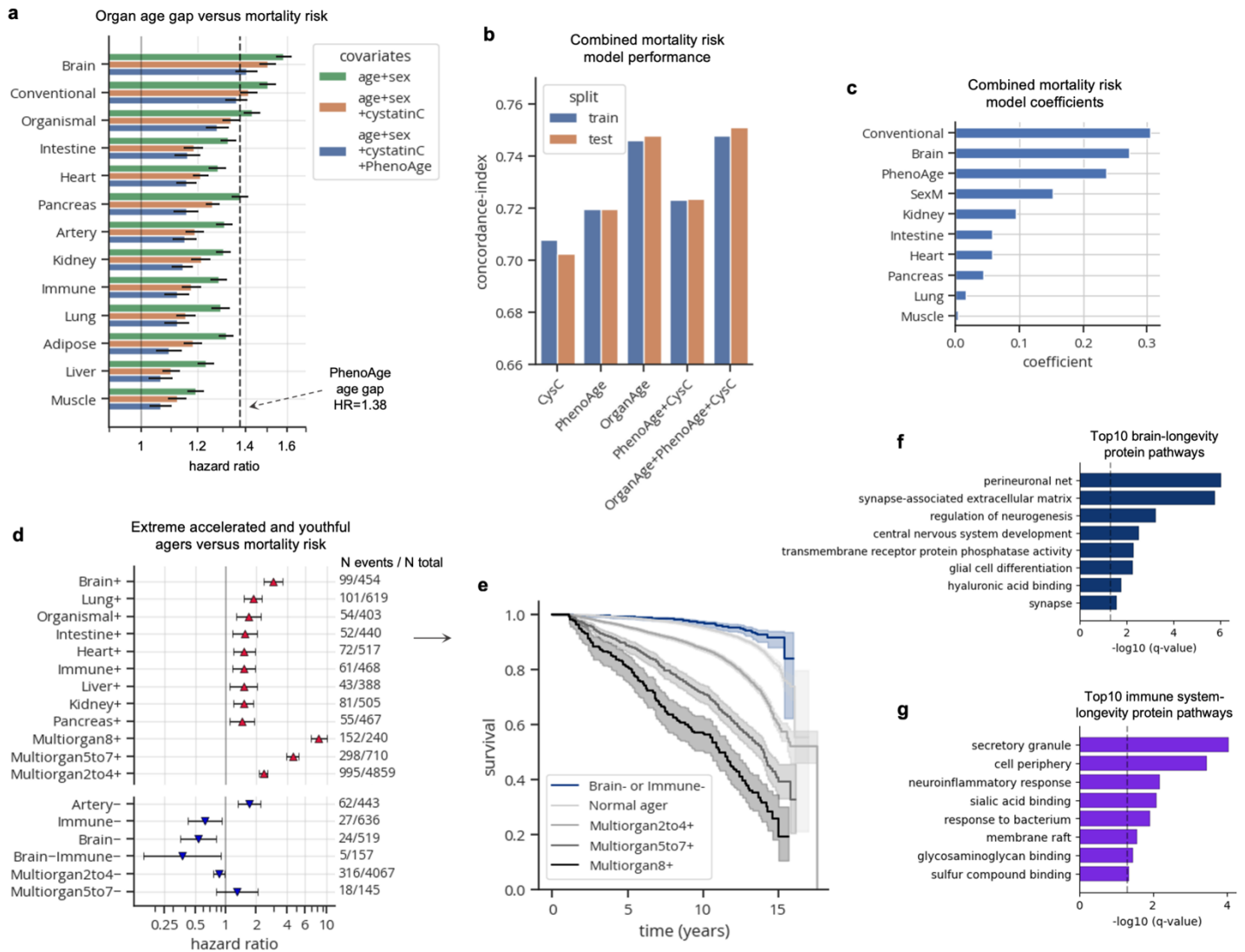
Figure 3. Organ age estimates are sensitive to modifiable lifestyle choices

a, Linear regression was used to determine the association between age gaps and modifiable lifestyle choices while accounting for age and sex. Heatmap colored by signed $\log_{10}(q)$ -value is shown. Only significant ($q < 0.05$) values are colored.

b, Linear regression was used to determine the association between age gaps and drugs/supplement intake while accounting for age and sex. Only drugs with significant ($q < 0.05$) youthful associations in at least two organs are shown. Heatmap is colored by signed $\log_{10}(q)$ -value. Only significant ($q < 0.05$) values are colored.

c, Linear regression was used to determine the association between age gaps versus early menopause and estrogen treatment together. Bar plot showing signed $\log_{10}(p)$ -value for menopause and estrogen covariates is shown.

d, Boxplot visualization of immune age gaps in individuals stratified by menopause status and estrogen treatment. Standard boxplot structure was used.



755

756

757 **Figure 4. Accrual of aged organs progressively increases mortality risk while brain and**
 758 **immune system youth is associated with longevity**

759

760 **a**, Bar plot showing results from Cox proportional hazards regression analyses, testing the associations
 761 between age gaps and future all-cause mortality risk, controlling for age, sex, (and blood cystatin C; and
 762 PhenoAge). Hazard ratios and 95% confidence intervals are shown. PhenoAge age gap hazard ratio
 763 (1.38) is shown as a dotted line for reference.

764

765 **b**, Concordance indices from various Lasso-regularized Cox proportional hazard models trained to predict
 766 mortality risk. Performance across train and test centers is shown. Covariates for each model, in addition
 767 to age-at-blood-draw and sex, are labeled on the x-axis.

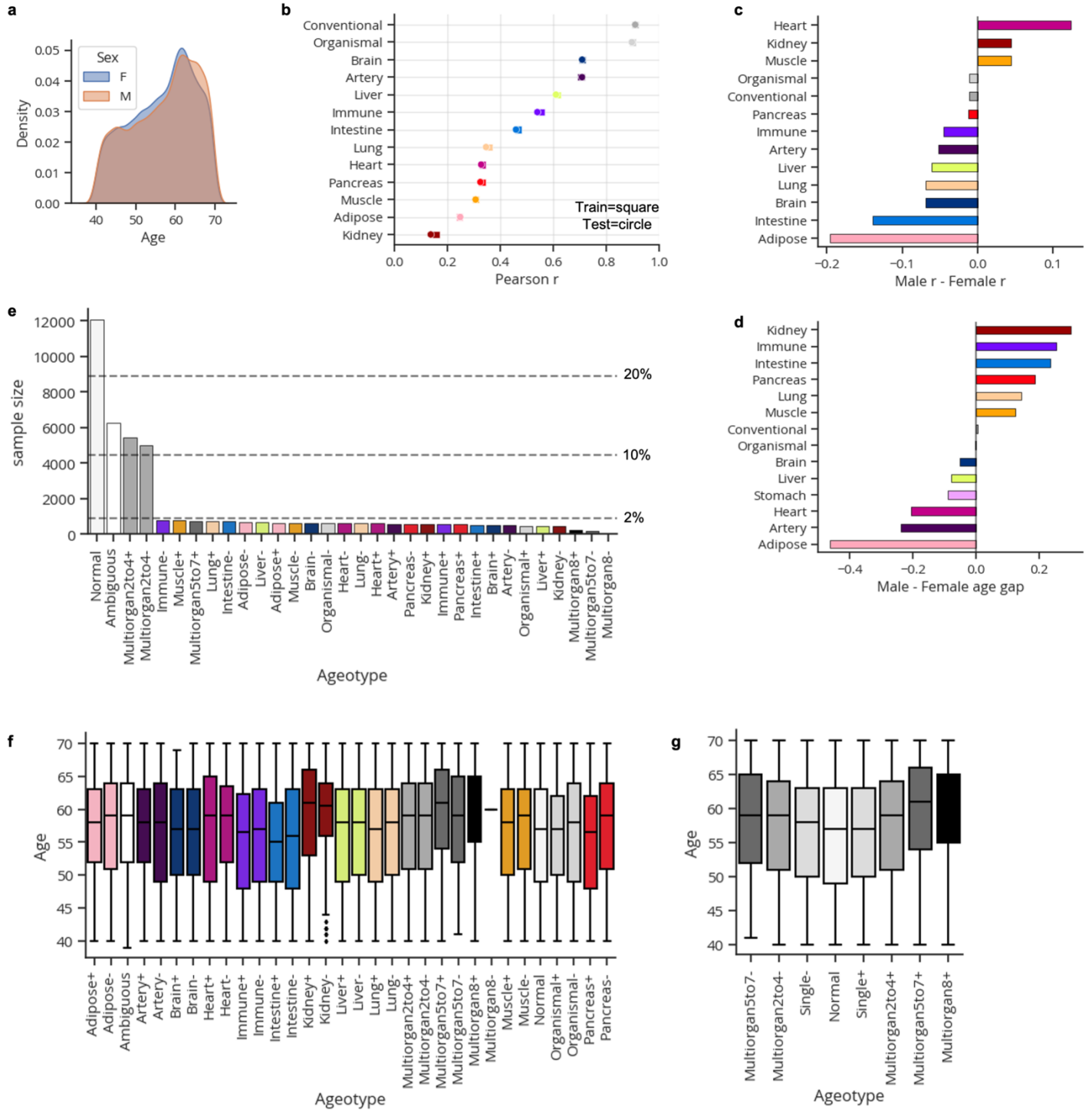
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769 **c**, Model coefficients shown for the combined model (OrganAge+PhenoAge+CysC) from **b**.

770

771 **d**, Forest plot showing results from Cox proportional hazards regression, testing the associations between
 772 extreme ager status and future all-cause mortality risk, controlling for age-at-blood-draw and sex. Only

773 significant ($q < 0.05$) associations are shown. Age gap hazard ratios, 95% confidence intervals, number of
774 events out of the total sample size are shown.
775
776 **e**, Kaplan-Meier curves showing survival over 17-year follow-up of normal agers, progressive levels of
777 multi-organ agers (2-4, 5-7, 8+ aged organs), and individuals with youthful brains or immune systems.
778
779 **f-g**, Gene ontology pathway enrichment results (with all genes as background) from top ten brain (**f**) and
780 immune (**g**) aging proteins by mortality risk FIBA score.
781



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783

784 **Extended Data Figure 1. Organ aging models in the UK Biobank.**

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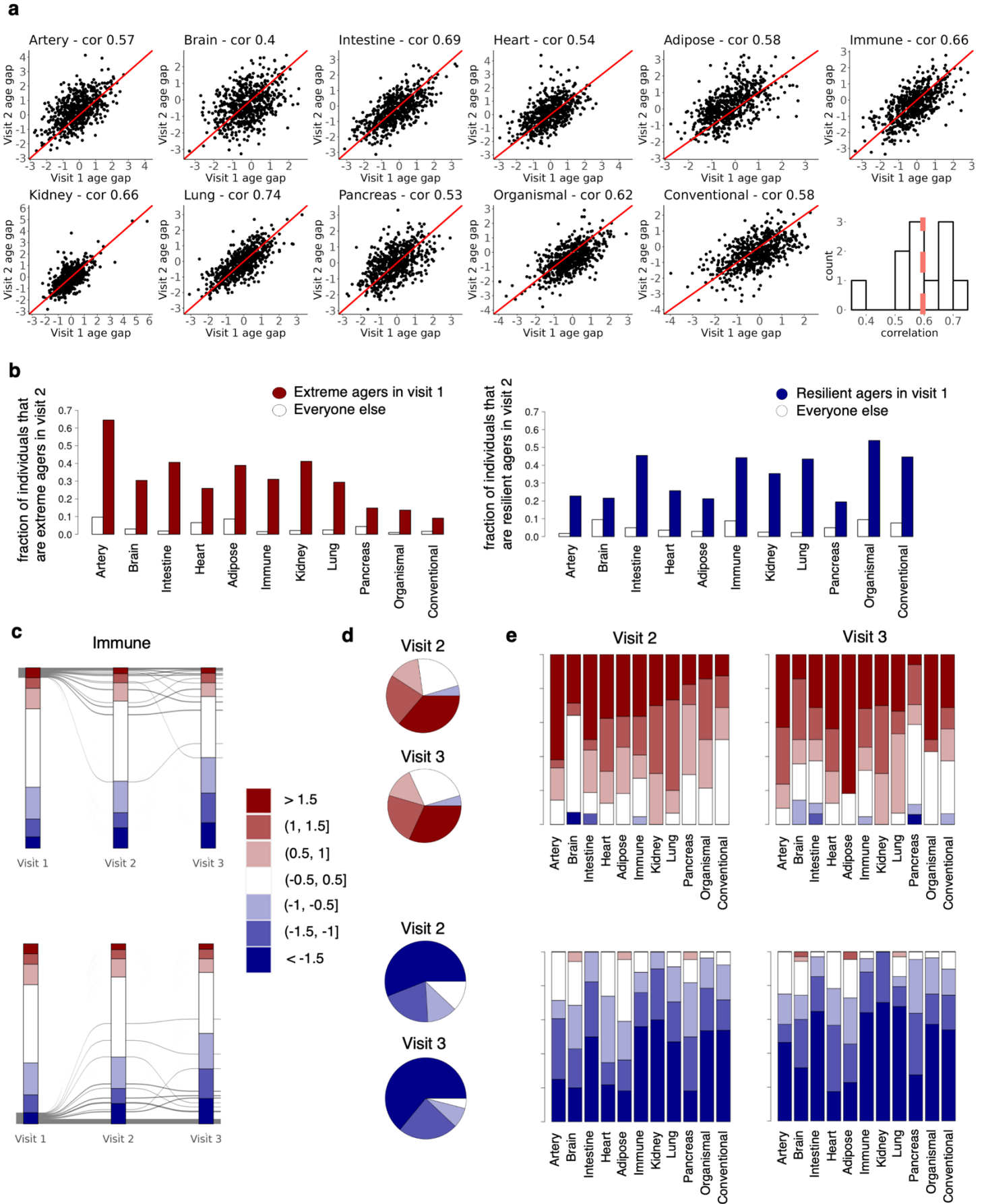
786 **a**, Age-at-blood-draw distribution by biological sex.

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788 **b**, Correlation between predicted and actual age across all aging models and train/test splits.

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- 790 **c**, Difference in correlation between predicted and actual age by biological sex.
791
792 **d**, Mean difference in organ age gaps between males and females.
793
794 **e**, Extreme ager ageotype sample sizes and proportions.
795
796 **f**, Age distributions per extreme ager ageotype
797
798 **g**, Age distributions per aggregated extreme ager ageotype. Individuals with many aged or youthful
799 organs are significantly older than normal and single organ agers.
800



802 **Extended Data Figure 2. Age gaps are stable across longitudinal visits.**

803

804 **a**, Longitudinal proteomics data from a subset of 937 individuals were analyzed. Longitudinal data were
805 available only on the 1k-protein platform, so new aging models trained on the 1k-platform were
806 developed. New aging models were trained on 44,406 samples without longitudinal data and tested on
807 samples with longitudinal data (937 unique individuals). Only 1k-aging models with age estimates that
808 were correlated $r^2 \geq 0.8$ with 3k-based age estimates were included for downstream analyses. Correlation
809 between visit 1 (baseline, 2006-2010) and visit 2 (imaging visit 1, 2014+) age gaps are shown.

810

811 **b**, Bar plot showing fractions of visit 1 extreme agers and non-visit 1 extreme agers that are extreme
812 agers in the same organ in visit 2. Equivalent plot for youthful agers is shown on the right.

813

814 **c**, Age gaps were grouped into bins of 0.5 standard deviation to determine changes in age gap bins
815 across visits. Individual trajectories across visits for extreme immune agers are shown. Equivalent plot for
816 youthful immune agers is shown at the bottom.

817

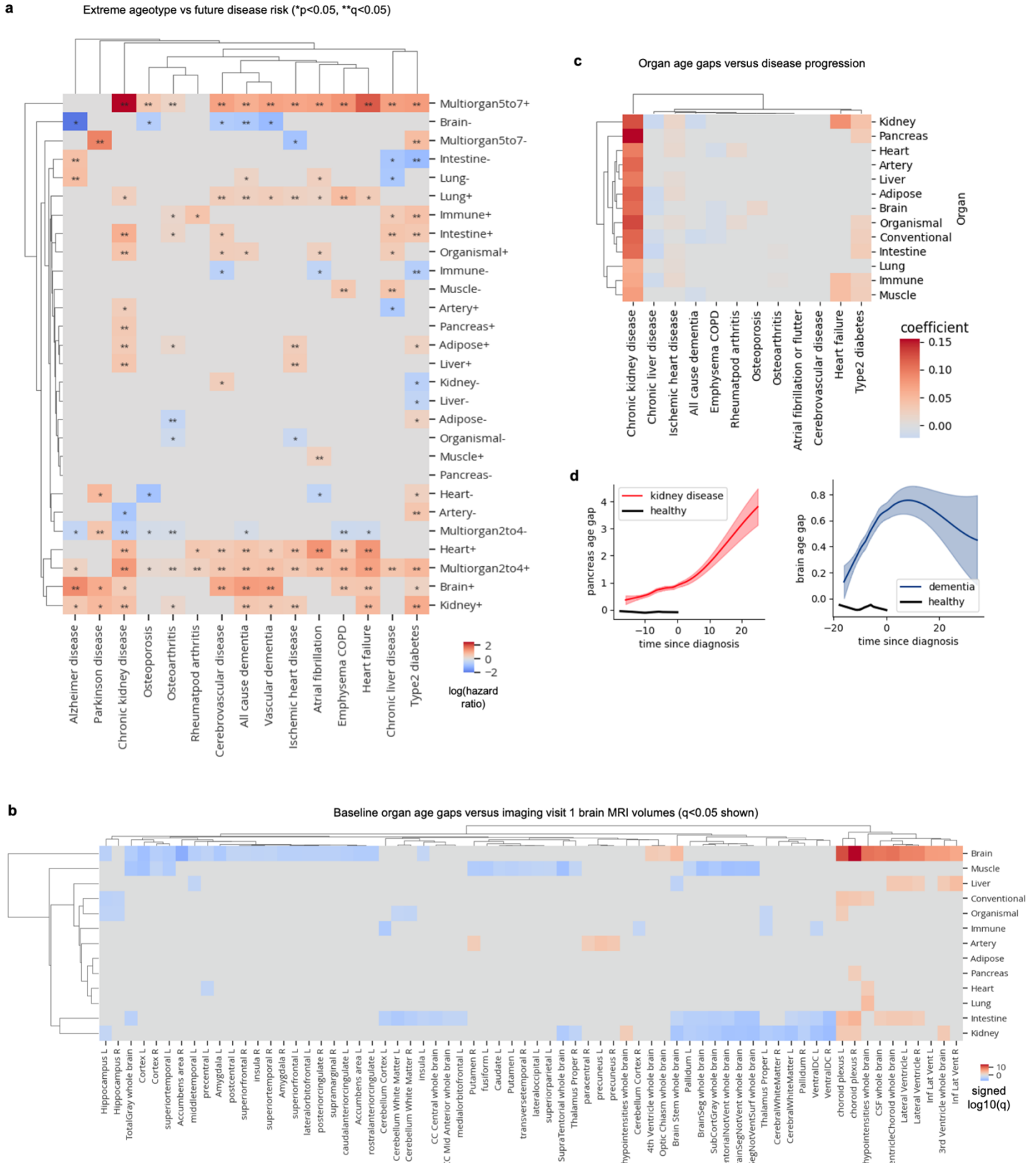
818 **d**, Pie chart showing percent distribution of immune age gap bins in visit 2 (2014+) and visit 3 (2019+) for
819 individuals who are extreme immune agers in visit 1. Equivalent plot for youthful immune agers is shown
820 at the bottom.

821

822 **e**, Stacked bar plot showing percent distribution of age gap bins in visit 2 and visit 3 for individuals who
823 are extreme agers in visit 1. Equivalent plot for youthful agers is shown at the bottom.

824

825



827 **Extended Data Figure 3. Ageotypes versus disease risk and age gaps versus brain volume.**

828

829 **a**, Cox proportional hazards regression was used to determine the association between extreme
830 ageotypes and future disease risk, controlling for age and sex. Heatmap colored by age gap $\log(\text{hazard}$
831 $\text{ratio})$ is shown. * $p < 0.05$, ** $q < 0.05$. Non-significant hazard ratios ($p < 0.05$) were set to zero.

832

833 **b**, Linear regression was used to determine the association between baseline organ age gaps and
834 imaging visit 1 brain MRI volumes, controlling for age-at-blood-draw, age-at-imaging-visit-1, sex, and
835 estimated total intracranial volume. Non-significant effect sizes ($q < 0.05$) were set to zero. Red indicates
836 positive associations, while blue indicates negative associations.

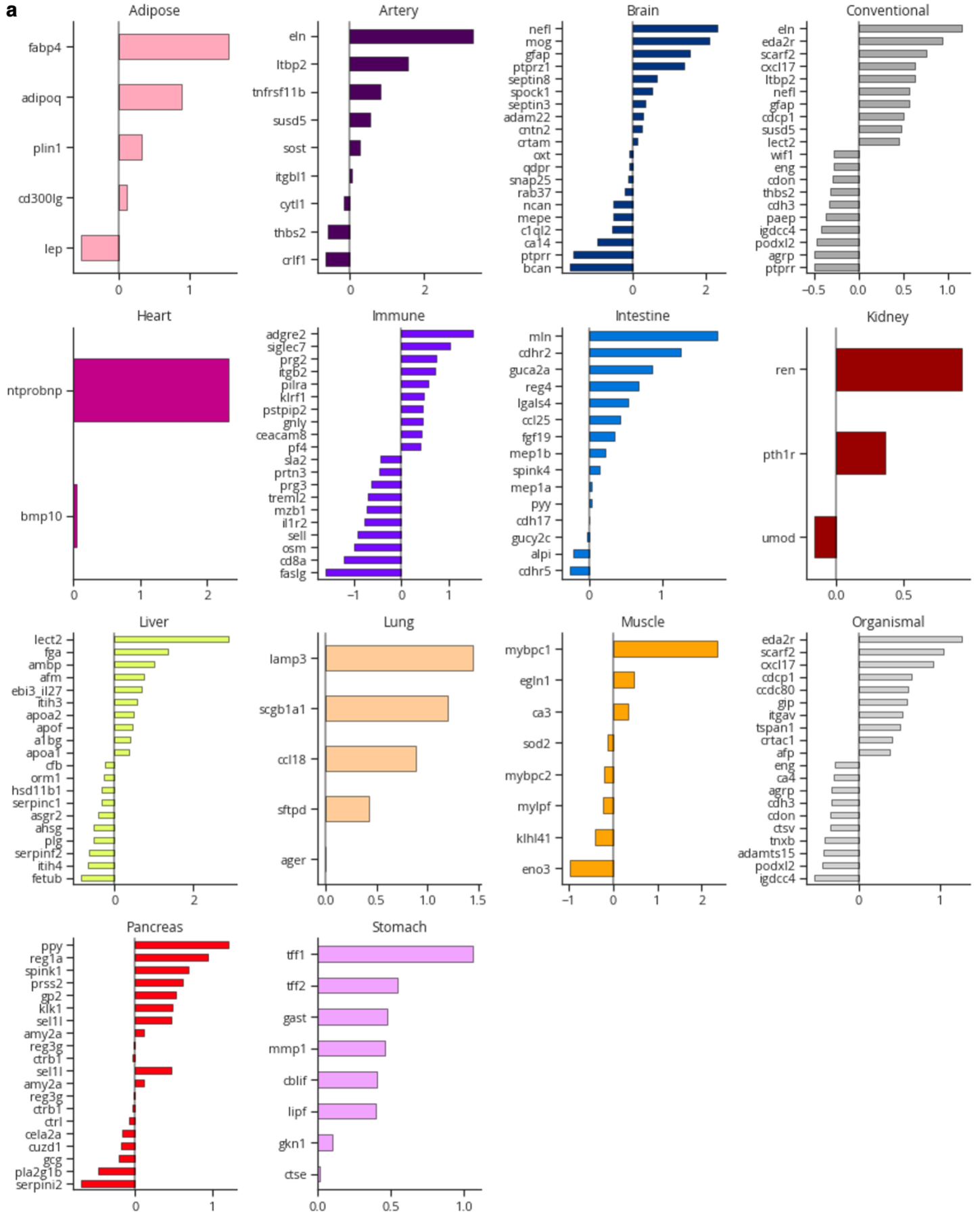
837

838 **c**, Linear regression was used to determine the association between organ age gaps and years since
839 disease diagnosis. Non-significant effects ($q < 0.05$) were set to zero.

840

841 **d**, Visualization of results from **c**. Organ age gap versus years since diagnosis shown.

842



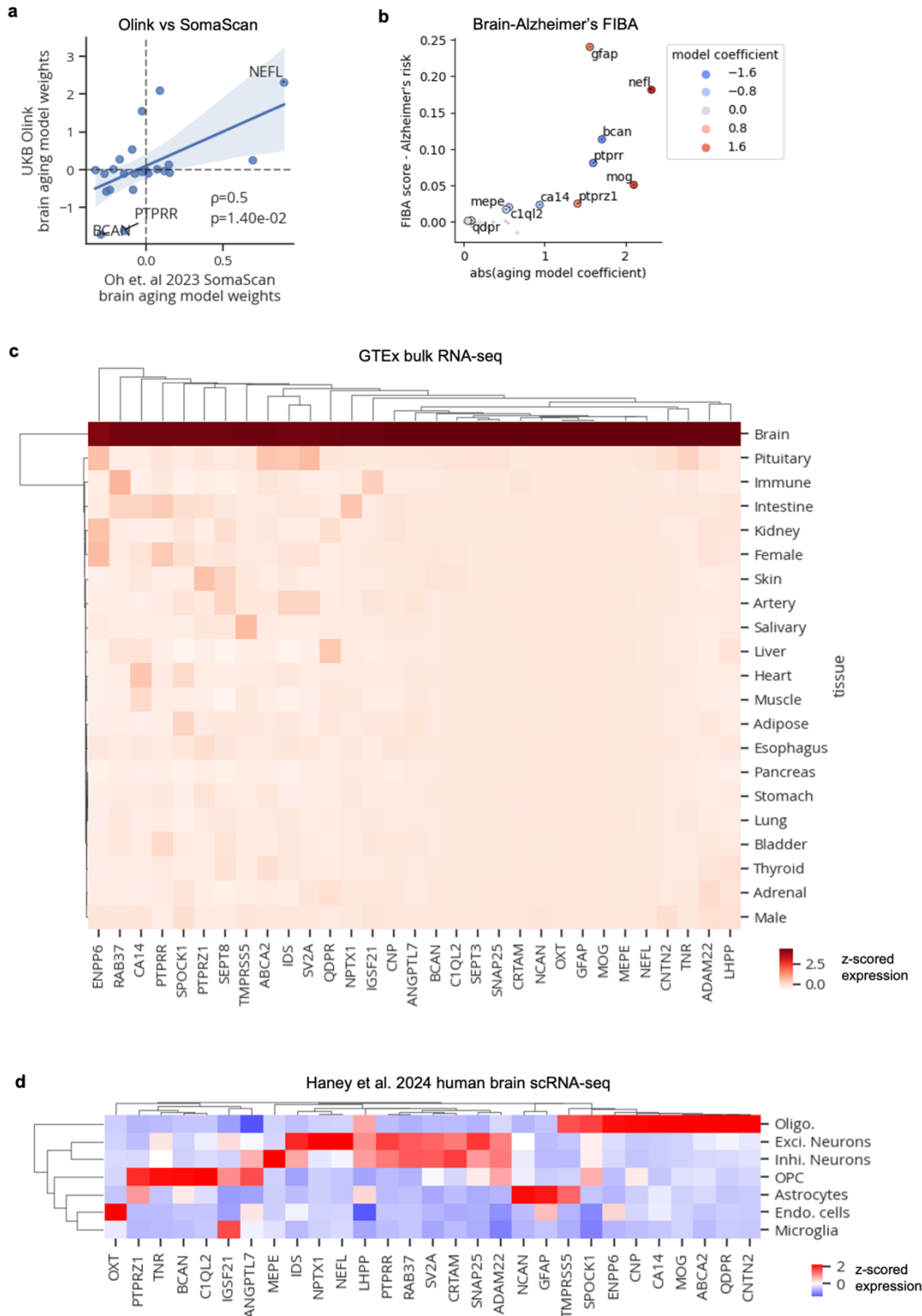
844 **Extended Data Figure 4. Aging model coefficients**

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846 **a,** For all aging models, the top 20 aging model proteins and their weights are shown.

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850 **Extended Data Figure 5. Brain aging proteins.**

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852 **a**, Scatterplot showing model weights from this study's Olink-based aging model (y-axis) and Oh et al

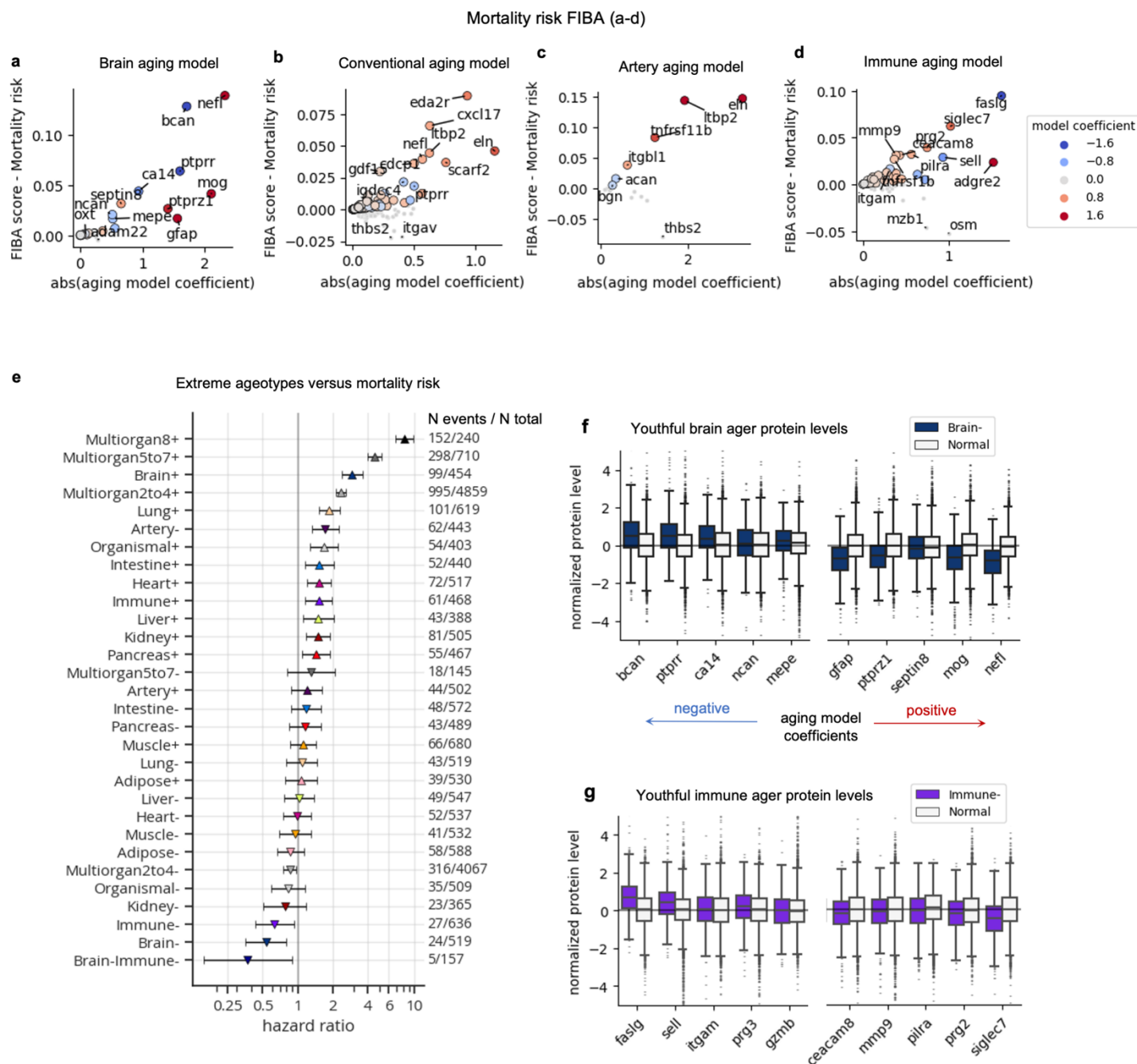
853 2023's SomaScan-based brain aging model (x-axis). Spearman correlation and p-value shown.

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b, Scatterplot showing results from feature importance for biological aging (FIBA) algorithm to identify proteins in the brain aging model contributing to the brain age gap's association with Alzheimer's disease risk. FIBA score (y-axis) indicates Alzheimer's disease risk effect size loss after permutation of protein values. X-axis indicates absolute protein weight in the brain aging model. Color indicates protein weight in the brain aging model.

c, Mean gene expression of brain aging protein-encoding genes in GTEx tissue bulk RNA-seq data.

d, Mean gene expression of brain aging protein-encoding genes in Haney et al. 2024 human brain scRNA-seq data.



866 **Extended Data Figure 6. Aging-mortality risk proteins.**

867

868 **a-d**, Scatterplots showing results from feature importance for biological aging (FIBA) algorithm to identify

869 proteins in the brain (**a**), conventional (**b**), artery (**c**), and immune (**d**) aging models that contribute to the

870 model age gap's association with future mortality risk. FIBA score (y-axis) indicates mortality risk effect

871 size loss after permutation of protein values. X-axis indicates absolute protein weight in the aging model.

872 Color indicates protein weight in the aging model.

873

874 **e**, Forest plot showing results from Cox proportional hazards regression, testing the associations between

875 extreme ager status and future all-cause mortality risk, controlling for age and sex. Age gap hazard ratios,

876 95% confidence intervals, number of events out of the total sample size are shown.

877

878 **f**, Protein levels of youthful brain agers versus normal agers. The top ten (5 decrease with age, 5 increase
879 with age) proteins based on mortality risk FIBA score are shown. Each protein was linearly adjusted for
880 age, sex, and every other protein in the brain aging model before plotting. Proteins are ordered by the
881 aging model coefficient.
882
883 **g**, As in **f**, but for the immune aging model.