Mendelian randomization of genetically independent aging phenotypes identifies LPA and VCAM1 as biological targets for human aging

Paul R. H. J. Timmers 1,2,3✉, Evgeny S. Tiys 3,4, Saori Sakaue 5,6,7,8, Masato Akiyama 9,10, Tuomo T. J. Kiiskinen 8,11, Wei Zhou 8,12,13, Shih-Jen Hwang 14,15, Chen Yao 14,15, Biobank Japan Project*, FinnGen*, Joris Deelen 16,17, Daniel Levy 14,15, Andrea Ganna 8,11,12, Yoichiro Kamatani 9,18, Yukinori Okada 6, Peter K. Joshi 2, James F. Wilson 1,2,20 and Yakov A. Tsepilov 3,19,20

Length and quality of life are important to us all, yet identification of promising drug targets for human aging using genetics has had limited success. In the present study, we combine six European-ancestry genome-wide association studies of human aging traits—healthspan, father and mother lifespan, exceptional longevity, frailty index and self-rated health—in a principal component framework that maximizes their shared genetic architecture. The first principal component (aging-GIP1) captures both length of life and indices of mental and physical wellbeing. We identify 27 genomic regions associated with aging-GIP1, and provide additional, independent evidence for an effect on human aging for loci near HTT and MAML3 using a study of Finnish and Japanese survival. Using proteome-wide, two-sample, Mendelian randomization and colocalization, we provide robust evidence for a detrimental effect of blood levels of apolipoprotein(a) and vascular cell adhesion molecule 1 on aging-GIP1. Together, our results demonstrate that combining multiple aging traits using genetic principal components enhances the power to detect biological targets for human aging.

Aging affects us all, from the personal, progressive loss of health to the collective burden of chronic age-related disease and frailty on society. In humans, the body undergoes a systemic functional decline after reaching adulthood, which manifests itself as age-related disease, infertility and eventually death. The factors determining the rate of aging and death are complex and interlinked, and include genetics, lifestyle, environmental exposures and chance. Quantifying the aging process is not straightforward. A variety of aging-related phenotypes has been studied as proxies, from chronological measurements such as the length of time from birth until the occurrence of a major disease (healthspan) or death (lifespan), to cellular deterioration measurements such as telomere attrition and loss of the Y chromosome, to holistic measurements such as the frailty index, encompassing multiple functional impairment indicators. Although the genetic component of these aging-related traits tends to be estimated at <15%, recent progress has been made on characterizing this component using large genome-wide association studies (GWASs), and combining similar GWASs to increase statistical power.

The benefit of combining GWASs of several aging phenotypes, especially in different populations, is the ability to detect biological mechanisms that influence multiple core components of aging, while downweighing population- and trait-specific features. For example, a recent multivariate analysis of healthspan, parental lifespan and longevity GWASs found that genetic loci that were not shared between traits often associated with population-specific, behavioral risk factors such as smoking and skin cancer. On the other hand, that analysis showed that genetic loci shared between traits were associated with biological pathways such as cellular homeostasis and heme metabolism.

However, to date, large aging-related trait GWASs have been combined only using multivariate analysis of variance, which detects...
a genetic variation that is either shared between multiple traits or strongly associated with a single trait\(^1\)\(^2\). This mixture generates heterogeneous SNP effect sizes, complicating the downstream analysis\(^3\). An alternative is to perform principal component analysis on the genetic covariance between traits and use the component loadings to construct new, genetically independent phenotypes (GIPs)\(^4\). As their name implies, GIPs capture the genetic covariance between phenotypes while being genetically uncorrelated to each other. In practice, this means that the first principal component (GIP1) maximizes the genetic overlap between all traits, whereas each subsequent GIP contains genetic variation distinguishing the traits from each other\(^4\).

In the present study, we cluster 11 large aging-related trait GWASs by genetic similarity, and explicitly quantify their common and unique genetic architecture using the GIP methodology. We then characterize this common genetic aging phenotype, identify robust genomic loci and highlight proteins that may be potential drug targets for improving the length and quality of life.

**Results**

**Aging-related traits cluster based on genetic correlations.** We gathered publicly available GWAS summary statistics on aging-related traits measured in at least 10,000 European-ancestry individuals. These included self-rated health\(^5\), healthspan\(^6\), father lifespan\(^7\), mother lifespan\(^7\), exceptional longevity\(^8\), frailty index\(^9\), perceived age\(^10\), Hannum epigenetic age acceleration\(^11\), Horvath epigenetic age acceleration\(^12\), telomere length\(^13\) and mosaic loss of the Y chromosome\(^14\) (Supplementary Table 1). A variety of UK and European individuals is represented between these studies, from children (aged 10+) to centenarians (aged 100+), with birth years spanning the twentieth and early twenty-first century. The largest sample consists of UK Biobank participants and their parents (see Supplementary Note for details of each GWAS, and Extended Data Fig. 1 for correlations between studies due to sample overlap).

Calculating genetic correlations \((r_s)\) from summary statistics, and performing hierarchical clustering based on the magnitude of these correlations, we find that the first six traits—mostly chronological and holistic measures of aging—form a cluster of high genetic similarity \((|r_s| \geq 0.5, P < 5 \times 10^{-10})\). In contrast, the cellular measures of aging show low or no correlations with other traits \((|r_s| \leq 0.3)\), although the epigenetic age acceleration phenotypes correlate strongly with each other \((r_s = 0.5; 95\%\) confidence interval \((CI) = 0.2–0.8\); Fig. 1 and Supplementary Data 1).

Testing the 6 aging-related traits in the main cluster for correlations with 728 other traits from the GWAS-MAP platform\(^5\), we find that their genetic similarity may be largely explained through strong, shared genetic correlations \((|r_s| \geq 0.5, false discovery rate \((FDR) < 0.05, P_{adj} > 0.05, F < 0.50)\) with chest pain, cardiovascular disorders, smoking-related disease, type 2 diabetes, and general illness or medication use in UK Biobank (Supplementary Data 2). However, each core aging trait also has several genetic correlations that differ substantially (Methods) from the other aging-related phenotypes and may reflect population- or trait-specific risk factors. For example, self-rated health correlates more strongly with physical fitness, body mass index and a noisy work environment, healthspan correlates more strongly with skin and breast cancers, father lifespan correlates more strongly with hypertension, mother lifespan uniquely correlates with lower childhood height, longevity uniquely lacks a negative correlation with chronic knee pain, and frailty correlates more strongly with hearing aid usage, daytime napping and allergic disease (eczema/dermatitis and hayfever/rhinitis) (Supplementary Data 2).

**Aging-GIPs capture distinct elements of wellbeing.** We combined the six GWASs in the main correlation cluster using the loadings from the principal components of the genetic correlation matrix (Fig. 2), yielding association summary statistics for six aging-GIPs (available at https://doi.org/10.7488/ds/2972). As expected, high-definition likelihood (HDL)\(^5\) estimated aging-GIP1 to be the most heritable of the aging-GIPs \((h^2_{GIP1} = 0.20; standard\ error = 0.005)\), capturing >70% of the genetics of healthspan, paternal lifespan and longevity, and 90% of the genetics of self-rated health and the inverse of frailty (henceforth referred to as ‘resilience’) (Fig. 3). A leave-one-out analysis confirms that the GIP analysis is highly robust to the selection of GWAS, with the genetic architecture of aging-GIP1 remaining largely the same, after excluding any one of the six chronological and holistic aging-related trait GWASs (estimates range from \(r_s = 0.950\) (s.e. = 0.024) when excluding resilience, to \(r_s = 0.996\) (0.023) when excluding healthspan; Supplementary Table 2).

Apart from the genetic correlations with its component traits, aging-GIP1 shows significant correlations, with 459 of 729 traits tested \((P_{adj} < 0.05, Bonferroni-adjusted for 6 GIPs and 729 traits)\). These suggest that, in addition to length of life, aging-GIP1 also captures mental and physical wellbeing. For example, among the largest negative aging-GIP1 correlations are mental illness, taking medications and diseases of old age (such as cardiometabolic disorders, cancers and osteoarthritis; \(r_s \leq -0.5; P_{adj} < 1 \times 10^{-10}\)). Inversely, fitness and education are among the largest positive correlations \((r_s \geq 0.5; P_{adj} < 1 \times 10^{-10}\)). Aging-GIP1 also shows moderate negative correlations with infectious diseases, including N39 (International Classification of Diseases, 10th revision\(^5\)) urinary tract infections \((r_s = -0.66; 95\%\) CI = -0.42 to -0.90; \(P_{adj} = 3 \times 10^{-5}\)), coughing on most days \((r_s = -0.39; 95\%\) CI = -0.30 to -0.04).
to $-0.49$; $P_{\text{adj}} = 1 \times 10^{-11}$) and severe COVID-19 hospitalization (that is, resulting in respiratory support or death; $r_g = -0.33$; 95% CI = $-0.20$ to $-0.46$; $P_{\text{adj}} = 0.004$). However, aging-GIP1 also retains some strong correlations with socioeconomic factors, such as smoking behaviors (for example, current tobacco smoking: $r_g = -0.50$; 95% CI = $-0.45$ to $-0.55$; $P_{\text{adj}} = 0.004$).
and having a job involving manual or physical work ($r_s = -0.49$; 95% CI = -0.44 to -0.54; $P_{adj} = 2 \times 10^{-6}$; Fig. 3 and Supplementary Data 3). Although such socioeconomic risk factors are partlyheritable⁶, they could also reflect social stratification or geographic confounding shared between the original six studies used to construct aging-GIP1 (refs. 24,25). Therefore, as a sensitivity analysis, we used the GIP methodology to remove all genetic correlations with UK Biobank GWASs of household income and socioeconomic deprivation from the aging-GIPs—recognizing that this may remove some of the true signal as well (Extended Data Fig. 2).

The SNP heritability of the adjusted aging-GIP1 phenotype is substantially attenuated (h²_{SNP} = 0.09; s.e. = 0.003) and, consequently, genetic correlations with all phenotypes are reduced. However, most traits that were significantly associated at 5% FDR remain associated with the residual phenotype (Extended Data Fig. 3). As expected, the largest reductions in genetic correlations are with socioeconomic, educational and smoking/drinking traits, which are reduced by ≥0.30 (Supplementary Data 3).

The remaining aging-GIPs have much lower heritability (h²_{SNP} < 0.065) and are of less interest to the present study because they capture genetic variance shared between fewer traits and do so with higher degrees of uncertainty. In short, aging-GIP2 correlates mainly with nonlethal causes of poor self-rated health, such as chronic pain (neck, back, stomach), negative emotions and hearing problems (59 traits; $P_{adj} < 0.05$); aging-GIP3 correlates mainly with measures of socioeconomic deprivation and body composition (73 traits); and aging-GIP4 captures healthspan-specific correlations with cancer and diabetes (7 traits). Although aging-GIP5 and aging-GIP6 are underpowered due to their low heritabilities, they appear to distinguish parental lifespan from longevity (possibly through educational attainment), and between father lifespan and mother lifespan (possibly through risk taking and cardiovascular factors), respectively (Fig. 3).

Characterizing the genomics of aging-GIP1. Across the genome, 27 loci in the aging-GIP1 GWAS pass the genome-wide significance threshold, Bonferroni's adjusted for 6 GIPs ($P < 8.3 \times 10^{-5}$). The strongest lead SNPs in these loci are rs429358 ($P = 2 \times 10^{-10}$) and rs660695 (P = 2 \times 10^{-2}) RLOD, located nearest to the APOE and HLA-DRB1/DQA1 genes, respectively (Fig. 4 and Table 1). Genetic fine-mapping with SuSiE²⁶ highlights three independent 95% credible sets of causal variants for the APOE locus: the APOE ε4 and ε2 alleles at single variant resolution, and a set of three variants intrinsic or near to APOCI. Three other loci have a credible set containing only one variant. These variants are rs9271300 (intergenic between HLA-DRB1 and HLA-DQA1), rs34811474 (a nonsynonymous ANAPC4 exon variant) and rs2165702 (an intergenic variant near PHB; Supplementary Table 3 and Supplementary Data 4).

Most lead SNPs are strongly associated with self-rated health and resilience, in line with the large loadings of these traits in the construction of aging-GIP1 (Fig. 4 and Supplementary Table 4). Seventeen aging-GIP1 loci overlap with genome-wide significant ($P < 5 \times 10^{-8}$) loci from the original aging-related trait GWAS, showing evidence of a shared causal variant (coloc posterior probability (PP) ≥80%; Supplementary Table 5). For the other loci, the GIP framework either increases power (n = 4) or indicates that there may be a different causal variant (coloc PP < 80%; n = 6; Supplementary Data 5).

Loci near APOE, HLA-DRB1/DQA1, LPA and CDKN2B/AS1 have previously been validated using the same trait in an external cohort²⁴. For the remaining 23 loci, we measured lead SNP effects on participant survival in FinnGen (release 5; n = 203,244; 6.94% deceased) and BioBank Japan (n = 135,983; 24.1% deceased), to provide additional evidence of their association with human aging traits in independent samples. Combining both cohorts to achieve adequate power, we find that aging-GIP1-increasing alleles of lead SNPs near HTT and MAML3 have a protective effect on survival in these cohorts (one-sided $P < 0.0022$, that is, taking into account the 23 loci tested), increasing average lifespan by around 2.53 (95% CI = 0.91–4.15; one-sided $P = 0.001$) and 2.51 (95% CI = 0.79–4.23; one-sided $P = 0.002$) months per allele, respectively. Although we are underpowered to confirm the remaining 21 loci individually, we find that, collectively, their aging-GIP1-increasing alleles are also associated with increased Finnish and Japanese survival (one-sided $P = 0.044$; Supplementary Table 6).

Again, we find aging-GIP1 genetics are stable when performing a leave-one-out analysis: lead SNP effects of most aging-GIP1 loci do not change significantly when excluding one of the six aging traits. The exceptions are for previously replicated loci and SLCT22A1/A2, where exclusion of one of the traits can reduce the aging-GIP1 effect size, although loci near HLA-DRB1/DQA1, LPA and CDKN2B/AS1 remain genome-wide significant in all leave-one-out scenarios (Supplementary Data 6). Similarly, when completely removing genetic correlations with household income and socioeconomic deprivation, we find that aging-GIP1 effect sizes are attenuated but, in all cases, remain associated with the residual trait ($P < 0.0019$, that is, taking into account the 27 loci tested; Extended Data Fig. 4 and Supplementary Data 7).

We further looked up all lead aging-GIP1 SNPs and close proxies ($r^2 > 0.8$) in PhenoScanner⁷ and the GWAS catalog⁸, excluding associations discovered solely in UK Biobank, which showed that 24 of 27 aging-GIP1 loci had previously been associated with one or more traits at genome-wide significance. Most of these loci were associated with cardiometabolic, immune-related or neuropsychiatric disorders, although several were also associated with measures of educational attainment and household income. Of specific interest are loci near APOE, HLA-DRB1/DQA1, CDKN2B/AS1 and ZNF652/PHB, which show aging-GIP1-increasing alleles are associated with a reduction in multiple diseases, but do not appear to associate with socioeconomic factors, suggesting that these loci largely capture intrinsic sources of aging (Supplementary Data 8).

Aggregating SNP association statistics across the genome into gene scores using the Pathway Scoring Algorithm (PASCAL)⁹, we find that high-scoring genes for aging-GIP1 (Supplementary Data 9) appear to be overrepresented in the heme metabolism Hallmark gene set, as well as 300 gene ontology (GO) pathways (FDR = 5%), regardless of adjustment for socioeconomic correlations. These GO pathways cluster into 20 groups, related to: neuronal development, organization and function; transcriptional regulation; chemical homeostasis; cellular growth, differentiation and apoptosis; proteolysis; protein phosphorylation; intracellular signaling and transport; immune system development; the muscle system; and lipoprotein metabolism (Supplementary Data 10). Similarly, aging-GIP1 heritability appears to be enriched in genomic regions containing histone marks associated with the central nervous system (Supplementary Table 7).

Causal inference of blood protein levels on aging-GIP1. Mendelian randomization (MR) uses genetic variation as instrumental variables to estimate the causal effect of exposures of interest on an outcome⁵. We used a set of well-validated blood protein quantitative trait loci (pQTLs) for 857 proteins¹⁰ as genetic instruments in a two-sample MR¹¹ and colocalization¹² framework to infer putative causal links between protein levels and aging-GIP1 (Supplementary Data 11). We find robust evidence for a detrimental effect on aging-GIP1 (FDR < 5%) for the levels of four proteins in blood (Table 2), with pQTL instruments passing sensitivity and causal directionality tests, and additionally colocalizing with the aging-GIP1 signal (Methods). Three of these proteins—apolipoprotein(a) (LPA), olofartinemid-1 (OLFML1) and low-density lipoprotein (LDL) receptor-related protein 12 (LRP12)—were instrumented by a cis-pQTL and encoded by genes that appeared significantly enriched in the
gene score analysis. The remaining protein, vascular cell adhesion molecule 1 (VCAM1), was instrumented by a trans-pQTL shared with β₂-microglobulin (β₂M); however, only VCAM1 protein levels colocalized with the signal at this locus (Supplementary Data 11). When performing the same MR analysis on aging-GIP1 adjusted for household income and socioeconomic deprivation, protein effects remained significant (Extended Data Fig. 5). Among the discovered proteins, LPA shows the most significant effect on aging-GIP1 ($P_{\text{MR}} = 2\times10^{-8}$), with an increase of 1 s.d. in genetically predicted blood protein levels, causing a decrease of 0.035 (95% CI = 0.025–0.045) s.d. in aging-GIP1. This significance appears to be driven by a consistent detrimental effect across all six aging-GIP1 component traits ($\beta_{\text{MR}}$, range 0.013–0.035; all nominal $P < 0.05$; Fig. 5). For a sense of scale, when performing the same MR analysis on aging-GIP1 adjusted for survival in two additional, independent samples. Across the genome, we found genes enriched for associations of SNPs across the genome with aging-GIP1, with the y axis showing the strength of the association and the x axis the genomic position of the SNP. The line represents the genome-wide significance threshold, Bonferroni’s adjusted for 6 GIPs ($P = 8.3 \times 10^{-9}$). The lead SNP of each independent locus is marked with a cross and annotated with the nearest (upstream) gene, or the cytogenetic band if there are no genes within 250 kb. The y axis has been capped at $P = 1 \times 10^{-20}$. The following loci exceed this cap and are represented as triangles: APOE ($P = 1.5 \times 10^{-49}$) and HLA-DRB1 ($P = 1.4 \times 10^{-22}$). Significance of the association of each lead SNP with the aging-related trait GWASs used to construct aging-GIP1. Bonf–GWS, Bonferroni’s adjusted genome-wide significance ($P < 8.3 \times 10^{-5}$); GWS, genome-wide significance ($P < 5 \times 10^{-8}$); Bonferroni’s, $P < 0.05$ adjusted for 6 traits and 27 SNPs ($P < 3 \times 10^{-8}$); nominal, $P < 0.05$; NS, not significant. $P$ values are derived from two-sided Wald’s test with one degree of freedom.

**Discussion**

We combined European-ancestry GWASs of healthspan, father lifespan, mother lifespan, longevity, frailty and self-rated health using a framework that maximized power to detect associations with their shared genetic component while downweighing trait-specific genetic associations. The resulting aging-GIP1 trait captured the genetics underlying physical and mental wellbeing, and showed strong inverse genetic correlations with cardiovascular, inflammatory and neuropsychiatric disease traits. We highlight 27 loci with genome-wide significant effects on aging-GIP1, including two new loci near HTT and MAML3 which showed directionally consistent evidence of an effect on survival in two additional, independent samples. Across the genome, we found genes enriched for association with aging-GIP1 to be overrepresented in heme metabolism and pathways related to (among others) neurogenesis, homeostasis,
proteolysis, immunity and the muscle system in human aging. Last, we performed MR of predicted blood protein levels on aging-GiP1, which revealed that the levels of LPA, VCAM1, OLFM1 and LRP12 proteins may be detrimental to multiple indices of healthy aging.

LPA is a glycoprotein making up the main component of large lipoprotein(a) particles. It is a well-known risk factor for atherosclerotic disease33,34 and a target of ongoing clinical trials with regard to cardiovascular outcomes35. A recent MR study used 27 genetic instruments for LPA and found a link between genetically elevated LPA levels and reduced healthspan and parental lifespan36, in line with our results. Our analysis suggested that the detrimental effect of LPA may apply to aging more generally, and stringent colocalization and reverse MR tests provided additional evidence for causalit y. It is interesting that human endothelial cell culture experiments revealed that the levels of LPA, VCAM1, OLFM1 and LRP12 were significantly elevated in response to pro-inflammatory stimuli7,11, and a target of ongoing clinical trials with regard to cardiovascular outcomes35.

### Table 1 | Twenty-seven independent genomic loci associated with the first genetic principal component of aging-related trait GWASs (aging-GiP1)

| Nearest gene(s) | rsID | Chromosome | Position | A1 | Freq1 | β1 (s.e.) | P | Het |
|-----------------|------|------------|----------|----|-------|-----------|---|-----|
| NEGR1           | rs2815748 | 1 | 72816147 | G | 0.20 | 0.028 (0.004) | 7 × 10⁻¹⁰ |
| PHTF1           | rs1230682 | 1 | 114293526 | A | 0.63 | 0.023 (0.004) | 4 × 10⁻¹⁰ |
| AFF3            | rs7690978 | 2 | 100490363 | A | 0.37 | 0.023 (0.004) | 3 × 10⁻¹⁰ |
| TRAIP           | rs227196 | 3 | 49878113 | T | 0.50 | 0.027 (0.004) | 8 × 10⁻¹⁴ |
| ADD1            | rs16843603 | 4 | 2928577 | C | 0.28 | 0.025 (0.004) | 1 × 10⁻⁰⁶ |
| HTT             | rs362273 | 4 | 3227419 | G | 0.32 | 0.024 (0.004) | 4 × 10⁻¹⁰ |
| ANAPC4          | rs34811474 | 4 | 25408838 | A | 0.23 | 0.025 (0.004) | 3 × 10⁻⁰⁹ |
| 4q13.2          | rs10434248 | 4 | 67842921 | A | 0.57 | 0.021 (0.004) | 8 × 10⁻⁹ |
| MAML3           | rs56172573 | 4 | 140919381 | C | 0.38 | 0.021 (0.004) | 7 × 10⁻⁹ |
| C6orf47/GPANK1  | rs805262 | 6 | 31628733 | C | 0.52 | 0.027 (0.004) | 1 × 10⁻¹² |
| HLA-DRB1/DQA1   | rs660895 | 6 | 32577380 | A | 0.79 | 0.043 (0.004) | 1 × 10⁻²² |
| SLC22A1/A2      | rs9456508 | 6 | 160958596 | T | 0.98 | 0.082 (0.012) | 4 × 10⁻¹¹ |
| LPA             | rs118039278 | 6 | 160985526 | G | 0.92 | 0.045 (0.007) | 1 × 10⁻¹³ |
| MADIL1/SNORA1T4 | rs11764780 | 7 | 2020904 | C | 0.19 | 0.029 (0.005) | 3 × 10⁻¹⁰ |
| FOX2            | rs12705966 | 7 | 114248851 | G | 0.34 | 0.023 (0.004) | 7 × 10⁻¹⁰ |
| CSM3            | rs560719 | 8 | 113032374 | T | 0.50 | 0.021 (0.004) | 5 × 10⁻⁹ |
| CDKN2B/AS1      | rs9632885 | 9 | 22072638 | G | 0.52 | 0.025 (0.004) | 5 × 10⁻¹² |
| CTSF            | rs2924807 | 11 | 66341005 | G | 0.50 | 0.021 (0.004) | 5 × 10⁻⁹ |
| CCDC90B/DLG2    | rs2512690 | 11 | 83145469 | C | 0.34 | 0.023 (0.004) | 7 × 10⁻¹⁰ |
| TTC12/ANK1K1    | rs2186800 | 11 | 113242860 | A | 0.54 | 0.022 (0.004) | 2 × 10⁻⁹ |
| USP28/HTR3B     | rs61907878 | 12 | 113751052 | C | 0.90 | 0.037 (0.006) | 1 × 10⁻¹⁰ |
| MIR6074         | rs7306710 | 12 | 66376091 | T | 0.48 | 0.023 (0.004) | 4 × 10⁻¹⁰ |
| 12q21.31        | rs6539846 | 12 | 8481127 | A | 0.49 | 0.022 (0.004) | 8 × 10⁻¹⁰ |
| LINCO1065       | rs8002970 | 13 | 53924489 | C | 0.45 | 0.024 (0.004) | 6 × 10⁻¹¹ |
| ZNF652/PH2      | rs28394864 | 17 | 47450775 | G | 0.54 | 0.021 (0.004) | 6 × 10⁻⁹ |
| APOE            | rs429358 | 19 | 45411941 | T | 0.84 | 0.066 (0.005) | 2 × 10⁻⁰⁹ |
| ZFP64           | rs67442863 | 20 | 5103131 | T | 0.18 | 0.029 (0.005) | 6 × 10⁻¹⁰ |

Loci were defined as 500-kb regions centered on a lead genome-wide significant SNP (P < 8.3 × 10⁻¹⁰) in linkage equilibrium (r² < 0.1) with other lead locus SNPs. Nearest gene(s), closest genes upstream/downstream to the lead SNP (within 250 kb) or, if none, the closest cytogenetic band; rsID, the lead SNP within the locus; Position, base-pair position (GRCh37); A1, effect allele, associated with higher aging-GiP1; Freq1, allele frequency of the effect allele in UK Biobank; β1, effect estimate (and s.e.) of the A1 allele on aging-GiP1 in s.d. units; P, two-sided nominal P-value from Wald’s test; Het, evidence of heterogeneity; asterisks indicate that aging-GiP1 effect size changes significantly when leaving out one of the core aging traits from the GIP1 calculation (*all but one leave-one-out effects are the same; **all but two effects are the same; *** all but three effects are the same).

### Table 2 | MR of genetically predicted blood levels of four proteins suggesting that they have a causal detrimental effect on aging-GiP1

| Exposure | β_steiger (s.e.) | P | FDR | P_steiger | P_reverse | Coloc PP (%) | LD check |
|----------|-----------------|---|-----|-----------|-----------|--------------|----------|
| LPA      | −0.035 (0.005)  | 2 × 10⁻¹¹ | 2 × 10⁻⁸ | 6 × 10⁻¹²⁴ | 0.556 | 100 | Pass |
| VCAM1    | −0.095 (0.019)  | 7 × 10⁻⁷ | 2 × 10⁻⁴ | 9 × 10⁻¹² | 0.063 | 99 | Pass |
| OLFM1    | −0.111 (0.024)  | 3 × 10⁻⁶ | 6 × 10⁻⁴ | 1 × 10⁻⁶ | - | - | Pass |
| LRP12    | −0.078 (0.021)  | 7 × 10⁻⁶ | 2 × 10⁻⁴ | 3 × 10⁻¹⁰ | - | - | Pass |

In bold are exposures passing all quality checks, including reverse MR and coloc, which required access to genome-wide summary statistics. β_steiger MR effect with s.e. in parentheses. P, two-sided nominal Wald’s test P-value for the MR effect. FDR, FDR-adjusted P-value taking into account the 857 proteins tested. P_steiger, two-sided nominal Wald’s test P-value for the MR-Steiger test assessing whether the exposure-outcome pair has the correct causal direction. P_reverse, two-sided nominal Wald’s test P-value for the MR effect of aging-GiP1 on the exposure, that is, evidence of reverse causality. Coloc PP (%) posterior probability of colocalization estimated by coloc. LD check, a secondary check for colocalization, which requires at least 1 of the 30 strongest aging-GiP1 SNPs within 500 kb of the pQTL to be in strong LD (r² < 0.8) with the pQTL itself.
show that the addition of LPA increases cell-surface expression of VCAM1 (ref. 9) and can increase endothelial cell contraction and permeability.

VCAM1 is a cell adhesion glycoprotein localized predominantly on endothelial cell surfaces and its expression is upregulated in response to inflammatory signals, which mediate adhesion and transduction of leukocytes across endothelial walls. The link that we established between VCAM1 and human aging relied on a trans-pQTL instrument shared with βM and is therefore more susceptible to horizontal pleiotropy, that is, the genetic variant may influence VCAM1 levels indirectly, and its effect on human aging traits could be caused by factors independent of VCAM1 levels. However, only VCAM1 colocalized with the pQTL signal, and experimental evidence from mouse studies suggests that the effect of VCAM1 on aging is likely to be causal. Specifically, VCAM1 levels in blood are known to increase with age in both humans and mice, and treatment with anti-VCAM1 antibodies or an inducible deletion of Vaim improves cognitive performance of aged mice. Of note, similar results have been found for βM abundance and mouse knockouts and, as such, identification of robust genetic instruments for βM levels is also warranted.

We were unable to robustly assess colocalization and reverse causality for the LRP12 and OLFM1 signals because genome-wide association summary statistics were not available, so the effects of these proteins on human aging should be interpreted with additional caution. LRP12 belongs to the LDL-receptor superfamily and is therefore more difficult to study at scale (although progress is being made). The sample sizes of exposure GWASs were 6,861 for LPA, 3,301 for VCAM1, and 3,200 for OLFM1 and LRP12.

Fig. 5 | MR of blood protein expression levels on aging-related GWASs. Exposures that showed causal evidence of an effect on aging-GIP1 were tested for association with each of the aging-related traits used to construct aging-GIP1. The x axis shows the MR effect estimate, with lines representing 95% CIs, as estimated by TwoSampleMR. The sample sizes of exposure GWASs were 6,861 for LPA, 3,301 for VCAM1, and 3,200 for OLFM1 and LRP12. The effect of injecting old blood in mice is counteracted when anti-VCAM1 antibodies are concomitantly injected. As such, the blood currently remains one of the most promising tissues to detect aging-related proteins.

Heme metabolism and iron levels were previously hypothesized to play a role in human aging, and in the present study we identify the same pathway using new methods and additional data. It is of interest that both the heme pathway and the proteins we uncovered using MR are strongly linked to vascular and endothelial damage. Across the genome, we also found an enrichment for brain tissues and pathways related to neuronal integrity. Given that endothelial cells are central to both the cardiovascular system and the blood–brain barrier, and that endothelial function declines with age, progressive endothelial dysfunction may manifest itself as an age-related disease. Indeed, recent findings suggest that the detrimental effects of theAPOEε4 allele—the largest genetic determinant of human aging—are mediated by an accelerated breakdown of the blood–brain barrier, independent of amyloid-β and tau accumulation. We therefore speculate that molecules involved in maintaining or repairing endothelial integrity may be key to avoiding both age-related cardiovascular injury and neurodegeneration, and recommend further research into this area.

Our study demonstrates that GIP analysis of genetically correlated GWASs can increase power to detect shared genetic architecture and can identify genetic loci that would have been missed by any individual GWAS. For example, regions near AFF3, MAML3, USP28/HTR3B and MIR6074 reached genome-wide significance only in the combined analysis, and validation of MAML3 in an external survival cohort suggests that these findings may hold across populations and aging measurements. In addition, USP28 within the USP28/HTR3B locus resembles CDKN2A within the well-known CDKN2B/-AS1 locus, because both have been implicated in cellular proliferation and senescence. In fact, short hairpin RNA knockdown of USP28 in vitro results in decreased CDKN2A expression. However, additional validation and functional investigation of aging-GIP1 loci are warranted.

A secondary advantage of the GIP method is the high stability of the resultant aging-GIP1 GWAS, which appears to be largely robust to the selection of component traits. Nevertheless, we note that our analysis focused on chronological and disease measures of aging and did not include the cellular measures of aging due to their modest genetic correlations and lack of power. Whether aging-GIP1 loci and pathways accurately reflect the aging process overall, or only capture specific domains of aging, is unknown. Inclusion of future
aging-related GWASs performed on Biobank-scale samples should provide insight into how well aging-GIP1 captures human aging.

An important limitation of the aging-GIP1 GWASs, and GWASs of aging-related traits more generally, is the potential confounding of aging genetics with social stratification. Socioeconomic factors exhibiting geographical clustering can induce gene–environment correlations that could inflate trait heritability and may bias results, especially for UK Biobank studies. In our study, we found that genetic correlations of the six aging-related GWASs with socioeconomic deprivation were moderately high (up to 61% for self-rated health). This confounding can be inadvertently propagated and even amplified in the shared genetic component captured by aging-GIP1. Indeed, when explicitly removing genetic correlations with two UK Biobank GWASs of socioeconomic factors, aging-GIP1 heritability is halved.

After adjustment, genetic correlations with mental and physical health traits are also somewhat reduced, although the overall patterns remain stable. Similarly, effect sizes of blood protein levels and aging-GIP1 loci—including loci that have been confidently linked to aging-related traits previously—were only slightly reduced after adjustment.

The shift of these effect sizes after adjustment was almost equal for all SNPs and MR signals. Together with the highly decreased heritability and stable genetic correlations, this suggests that the adjustment removed the unspecific polygenic background induced by UK Biobank microstructure and social confounding. We therefore consider this procedure to be a suitable approach for confounder correction, although it may be somewhat conservative for also removing the genetic background of the adjusting traits, which may genuinely be associated with aging. An alternative solution to the confounding problem could be the inclusion of a more ancestrally diverse set of aging-related GWASs from a larger variety of populations.

Despite these limitations, modeling the shared genetic component of human aging proxies has allowed us to downweigh nonbiological features, and propose pathways and proteins that may causally influence the human aging process. We share the full aging-GIP1 summary statistics without restrictions to encourage further MR analysis using other biomarkers, and accelerate the discovery of drug targets able to prolong mental and physical wellbeing throughout life.

Methods

Data sources. We searched PubMed and Google Scholar in April 2020 for GWASs of aging measures, including only studies for which we could obtain autosomal genome-wide summary statistics measured in at least 10,000 European-ancestry individuals. If multiple studies were performed on similar traits, we kept the study with the largest sample size. GWASs meeting inclusion criteria included self-reported health traits, socioeconomic factors, aging-GIP1 loci—incorporating loci that have been confidently linked to aging-related traits previously—were only slightly reduced after adjustment.

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where s.e.(B) is the vector of SNP s.e.s of the core aging trait effect estimates. Effective sample sizes were then estimated based on the median z statistic and allele frequencies, that is, solving equation (1) for n. Full technical details of the GIP method are described in Supplementary Note.

Aging-GIP summary statistics were calculated for the 7,324,133 SNPs shared between quality-controlled GWAS statistics, of which 5,353,660 were common (MAF ≥ 5%) and 1,970,474 were rare (MAF < 5%). Finally, s.e.s of each aging-GIP GWAS were adjusted to account for the LDSC regression intercept, which ranged from 0.99 (GIP1) to 1.03 (GIP4).

Adjusting for genetic correlations with socioeconomic factors. UK Biobank GWAS summary statistics for household income and Townsend’s deprivation index were downloaded from the Neale Lab GWAS collection19 and subjected to the same SNP filters used for aging-related trait quality control. Genetic correlations between GWASs of aging-GIPs and the two socioeconomic GWASs were calculated using the HDL R package27 v.1.3.4. As before, phenotypic correlations were estimated from the correlation between independent null z statistics.

For each aging-GIP, adjustment loadings were then calculated as:

\[
\alpha_i = \left(1 - \beta_i - \beta_j\right)
\]

where \(\beta\) refers to \(\beta = \text{Cov}(X)\) - \(\text{Cov}(\text{GIP}, X)\). Here, Cov(X) is the genetic covariance matrix of UK Biobank GWASs for household income and Townsend’s deprivation index, and Cov (GIP, X) is the genetic covariance matrix between the aging-GIP and the two GWASs.

These loadings were used as weights in the linear combination framework to calculate new aging-GIP summary statistics, which—by definition—were uncorrelated to the UK Biobank GWAS of household income and Townsend’s deprivation index. Last, s.e.s were adjusted to account for the LDSC regression intercept, which ranged from 0.99 (GIP3) to 1.02 (GIP1).

Characterization of genome-wide significant aging-GIP1 loci. Genome-wide significant loci were defined as 500-kb regions centered on a lead genome-wide significant SNP \((P < 8.3 \times 10^{-7})\) in linkage equilibrium \((r^2 < 0.1)\) with other lead loci SNPs. The LD between SNPs was calculated using a random 10,000 subset of unrelated, genomically British individuals from UK Biobank20. The susiR package20 v.0.11.8 was used to perform genetic fine-mapping of the association signals within each aging-GIP1 locus, allowing for up to ten causal variants. We report posterior inclusion probabilities for SNPs within 95% credible sets. Positional annotations of credible set SNPs were retrieved using ANNOVAR27 v.2019Oct24.

SNPs within each 500-kb locus were looked up in the six aging-related trait GWASs used to construct the aging-GIPs. Any region containing an SNP associated with an aging-related trait at genome-wide significance \((P < 5 \times 10^{-8})\) was tested for colocalization between the trait and the aging-GIP1 signal. For this, we used the coloc R package25 v.4.9-4 with its default parameters, denoting a posterior colocalization probability (PP) of 80% as evidence of a shared GWAS signal.

Association of loci with Finnish and Japanese survival. Loci were considered to be previously replicated if they had been associated at genome-wide significance with one of the core aging traits and also had evidence of an effect in an independent cohort on the same trait \((P < 0.05)\). We attempted to find additional evidence for an effect on aging for the aging-GIP1 loci, which had not been previously replicated.

Effects were first looked up in a GWAS of survival of FinnGen study participants21. The FinnGen study associated SNPs across the genome with the survival of 218,396 Finnish-anxiety individuals (203,244 censored, 15,152 deceased) using Genetic Analysis of Time-to-Event phenotypes (GATE) v.0.40. SNP effects were log(hazard ratios), calculated from a mixed-effect frailty model that adjusted for sex, genotyping batch, birth year and the first ten genomic principal components as fixed effects, and cryptic relatedness using the genetic relatedness matrix as random effects.

Analogously, the same SNPs (if polymorphic) were regressed against the survival of 135,983, unrelated, Japanese-anxiety individuals (97,365 censored, 30,976 deceased) from BioBank Japan26. In this analysis, a fixed-effect Cox proportional hazards model was fitted using the survival R package v.2.241.

\[
h(t) = h_0(t) \exp \left( \sum_i \beta_i X_i + \beta_{GIP} \times GIP + G \right)
\]

where \(h(t)\) is the hazard at time \(t\), given that the subject is alive at time \(t\) and \(h_0(t)\) is the baseline hazard at time \(t\); \(X_1, X_2, \ldots, X_n\) are the vectors of covariates with fixed effects \(\beta_1, \beta_2, \ldots, \beta_n\); and \(G\) is the effect of the vector of SNP dosage \(G\). Covariates were sex, disease status and the first 20 principal components, where disease status refers to 1 of 47 common diseases in Japan used to recruit the individuals. Each SNP was tested in a separate model. The SNP effects from both studies were converted from log(hazard ratios) to approximate years of life by inverting the sign and multiplying the effect estimate and s.e.s by ten. For each SNP, a combined effect was calculated by meta-analyzing the cohort-specific effects in a fixed-effect framework (weighted using inverse variance), implemented in the meta R package27 v.4.15-1. One-sided P values were adjusted for multiple testing of 23 loci using Bonferroni’s correction. The collective effect of the 21 remaining loci was calculated using a random-effect framework, to allow for heterogeneity in effect size estimates.

Aging-GIP1 leave-one-out sensitivity analyses. Leave-one-out sensitivity analyses were performed for aging-GIP1, where, one at a time, a core aging trait was excluded and aging-GIP1 loadings and summary statistics were recalculated using the remaining five traits. Genetic and nongenetic correlations were calculated between the original aging-GIP1 and each leave-one-out aging-GIP using HDL inference and null SNP z statistics, as described above.

To test for heterogeneity in genome-wide significant aging-GIP1 loci, we estimated the difference between the lead SNP effect in aging-GIP1 and the effect in the leave-one-out aging-GIP GWAS, taking into account null correlations between traits. The s.e. of the difference in effects was calculated as follows:

\[
\text{s.e.}(\hat{\beta}_1 - \hat{\beta}_2) = \sqrt{\text{s.e.}(\hat{\beta}_1)^2 + \text{s.e.}(\hat{\beta}_2)^2 - 2 \times r \times \text{s.e.}(\hat{\beta}_1) \times \text{s.e.}(\hat{\beta}_2)}
\]

where s.e. (\(\hat{\beta}_1\)) and s.e. (\(\hat{\beta}_2\)) are the s.e.s of the SNP for aging-GIP1 and the leave-one-out GIP1, respectively, and \(r\) is the nongenetic correlation between GWASs. Statistical significance of the difference was assessed using Wald’s test and adjusted for multiple testing of 27 loci using Bonferroni’s correction.

Lookup of known SNP associations. Lead SNP and close proxies \((r^2 > 0.8)\) of the aging-GIP1 loci were looked up in PhenoScanner22 and the GWAS catalog\(^2\) (accessed 3 December 2020), keeping only the traits with genome-wide significance \((P < 5 \times 10^{-8})\). Trimmed GWASs and associations with treatments or medications were discarded, before converting associations with the lack of a phenotype into the phenotype itself by inverting the sign (for example, ‘Qualifications: none’ to ‘Qualifications: yes’). We then further grouped the traits based on similarities in trait names, keeping the strongest association in the group. This grouping was done by partial matching of trait names—verified manually—and keeping the shortest name. For example, ‘Melanoma’, ‘Malignant melanoma’ and ‘Malignant melanoma of skin’ were grouped and renamed to ‘Melanoma’.

Tissue enrichment. Stratified LDSC regression v.1.0.0 was used to stratify aging-GIP1 SNPs into categories and test whether the proportion of SNP heritability in a category exceeded that expected from the proportion of SNPs in the category\(^2\). We kept only HapMap SNPs, excluding the MHC region and SNPs with MAF < 0.05, and used the 1000 Genomes Phase 3 LDSC reference as weights. Categories tested included the 10 groups summarizing 220 cell-type specific annotations from Finucane et al.\(^2\), adjusting for the baseline model (v.1.2).

Gene and pathway enrichment. PASCAL\(^2\) was used to aggregate aging-GIP1 SNP-level P values (with and without adjustment for socioeconomic correlations) into gene scores for enrichment against predefined gene sets. Gene sets were Hallmark (C1) and Gene Ontology Biological Process (C5.BP) sets from v.7.2 of the Molecular Signatures Database\(^2\).

Aging-GIP1 summary statistics were first aligned to the 1000 Genomes SNp (build matching the PASCAL LD reference), before being tested with default PASCAL parameters, which includes discarding SNPs with MAF < 5% and SNPs in the MHC region. Gene results passing a 5% FDR threshold were considered to be significant. For each pathway in the C1 and C5.BP datasets, PASCAL calculated two measures of significance based on \(\chi^2\) and permutation statistics. We separately adjusted C1 and C5.BP for multiple testing and considered a pathway with both \(\chi^2\) and permutation statistics passing a 5% FDR threshold to be significant.

Significant C5.BP pathways (with and without adjustment for socioeconomic correlations) were clustered based on their Jaccard’s similarity coefficient (that is, the size of the intersection of genes divided by the size of the union of genes). The multich R package\(^2\) v.5.4.1 was used to maximize the Bayesian information criterion of Jaccard’s similarity matrix to identify the optimal number of clusters (up to a maximum of 100). We used the number of clusters selected by most multich models to group the pathways.

MR of blood protein levels. Genetic instruments for blood protein levels (pQTLs) were retrieved from Zheng et al.\(^2\). We included all tier 1 instruments: cis- and trans-pQTLs shown to influence ≤ 5 proteins (specificity) with no evidence of heterogeneity in effect sizes between multiple protein expression studies (consistency). A total of 857 proteins had nonalpineid SNIP SNP instruments (889 total pQTLs) present in the aging-GIP1 summary statistics. Two-sample MR of blood protein levels as exposures and aging-GIP1 as outcome was performed using the TwoSampleMR R package\(^2\) v.0.5.5. If multiple pQTL instruments were available for a protein, heterogeneity and MR Egger sensitivity tests were also performed. This analysis was repeated with the six standardized aging-GIP1 component traits as outcome, as well as the unstandardized, combined parental lifespan GWAS from Timmers et al.\(^2\) to provide an intuitive measure of the effect.
The MR effects and s.e.s from the latter were multiplied by 10 to convert them from units of negative log(hazard ratio) to approximate years of life. Aging-GIP1 MR results passing a 5% FDR threshold and sensitivity tests (P > 0.05 and P < 0.05, if applicable) were taken forward for follow-up. SNPs from aging-GIP1 (shared between GWASs and replacing missing or palindromic SNPs with the next most significant SNP) as instruments and the protein expression statistics as outcome. Proteins significant for the MR-Steiger test (P < 0.05) and showing no evidence of reverse causality in the bidirectional MR (P > 0.05), if applicable, were considered to have robust causal effects on aging-GIP1.

Ethical oversight. BioBank Japan participants provided written informed consent and survival study protocols were approved by BioBank Japan Project ethical review boards from the Institute of Medical Sciences, University of Tokyo and the RIKEN Center for Integrative Medical Sciences. All other data were publicly available and approved by ethical committees as described in their respective publications. See Supplementary Note for FinnGen ethical approval.

Statistical reproducibility. The statistical methods used to analyze the data are described fully in Methods, with basic data processing done using R v.3.6.0 only if specified otherwise. We used the independent FinnGen and BioBank Japan cohorts to successfully replicate 2 of the 23 new aging-related loci. Predetermination of sample size, randomization of experiments and blinding of investigators to experiments were not applicable for our type of study.

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

Data availability
Aging-related trait GWAS summary statistics can be retrieved or requested from the study authors at http://www.nealelab.is/uk-biobank (self-rated health; field 2178), https://www.longevitygenomics.org/downloads (longevity), and the following: https://doi.org/10.5281/zenodo.1302861 (healthspan), https://doi.org/10.6084/m9.figshare.9204998.v3 (frailty index), https://doi.org/10.5523/bris.21crwscw4xw3w2q4q8chaltha (perceived age), https://doi.org/10.7488/dc/2463 (parental lifespan), https://doi.org/10.7488/ds/2631 (epigenetic age acceleration), https://doi.org/10.1038/ng.3821 (healthspan). Summary statistics for aging-GIP1 calculated in the present study have been deposited in the Edinburgh DataShare repository, available without restrictions at https://doi.org/10.7488/ds/2972. Summary statistics of the GWAS-MAP phenotypes used to calculate phenome-wide genetic correlations are available from GeneAtlas (http://geneatlas.robin.io.uk), NealeLab (http://www.nealelab.is/uk-biobank) or their respective publications. The COVID-19 GWAS summary statistics have been made available by the COVID-19 Host Genetics Initiative at https://www.covid19hostgenomics.org/results. GWAS catalog and Phenoscanner associations can be found at https://www.ebi.ac.uk/gwas and http://www.phenoscanner.medschl.cam.ac.uk, respectively. Curated gene sets (Hallmark Genes) are available from the Molecular Signatures Database (https://www.genessignatures.org). Source data are provided with this paper, or are available in the supplementary documents and upon request from the corresponding author.

Code availability
The following codes are available: HDL: https://github.com/zhenhui/HDL1; LDSC: https://github.com/bulik/llds; SuSiLo: https://stephsabeslab.github.io/sussR; ANNOVAR: https://www.openbioinformatics.org/PASCAL; https://www.ncbi.nlm.nih.gov/chp/index.html?pmid=Pascal; TwoSampleMR: https://mrcieu.github.io/TwoSampleMR. This code can be accessed without restrictions.

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References
1. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. The hallmarks of aging. Cell 153, 1194–1217 (2013).
2. Zien, A. et al. Identification of 12 genetic loci associated with human healthspan. Commun. Biol. 2, 41 (2019).
3. Joshi, P. K. et al. Genome-wide meta-analysis associates HLA-DQA1/DRB1 and LPA and lifestyle factors with human longevity. Nat. Commun. 8, 910 (2017).
4. Timmers, P. R. H. J. et al. Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. eLife 8, e38956 (2019).
5. Li, C. et al. Genome-wide association analysis in humans links nucleotide metabolism to leukocyte telomere length. Am. J. Hum. Genet. 106, 389–404 (2020).
6. Forsberg, L. A. et al. Mosaic loss of chromosome Y in peripheral blood is associated with shorter survival and higher risk of cancer. Nat. Genet. 46, 624–628 (2014).
7. Wright, D. J. et al. Genetic variants associated with mosaic Y chromosome loss highlight cell cycle genes and overlap with cancer susceptibility. Nat. Genet. 49, 674–680 (2017).
8. Atkins, J. et al. A genome-wide association study of the frailty index highlights synaptic pathways in aging. Aging Cell 20, e13459 (2021).
9. Mitnitski, A. B., Mogilner, A. J. & Rockwood, K. Accumulation of deficits as a proxy measure of aging. Sci. World J. 1, 325–336 (2001).
10. Ruby, J. G. et al. Estimates of the heritability of human longevity are substantially inflated due to assortative mating. Genetics 210, 1109–1124 (2018).
11. Timmers, P. R. H. J., Wilson, J. F., Joshi, P. K. & Deelen, J. Multivariate genomic scan implicates novel loci and haem metabolism in human ageing. Nat. Commun. 11, 3570 (2020).
12. Bender, D., Pilling, L. C. & Ferrucci, L. The genetics of human ageing. Nat. Rev. Genet. 21, 88–101 (2020).
13. Shen, X. et al. Multivariate discovery and replication of five novel loci associated with immunoglobulin G N-glycosylation. Nat. Commun. 8, 447 (2017).
14. Ning, Z. et al. Beyond power: multivariate discovery, replication, and interpretation of pleiotropic loci using summary association statistics. Preprint at bioRxiv https://doi.org/10.1101/2022.09.15.435971 (2021).
15. Tsepilov, Y. A. et al. Analysis of genetically independent phenotypes identifies shared genetic factors associated with chronic musculoskeletal pain conditions. Commun. Biol. 3, 329 (2020).
16. Harris, S. E. et al. Molecular genetic contributions to self-rated health. Int. J. Epidemiol. 46, 994–1009 (2017).
17. Deelen, J. et al. A meta-analysis of genome-wide association studies identifies multiple longevity genes. Nat. Commun. 10, 3669 (2019).
18. Roberts, V., Main, B., Timpson, N. J. & Haworth, S. Genome-wide association study identifies genetic associations with perceived age. J. Invest. Dermatol. 140, 2380–2385 (2020).
19. Gibson, I. et al. A meta-analysis of genome-wide association studies of epigenetic age acceleration. PLoS Genet. 15, e1008104 (2019).
20. Shashkova, T. I. et al. The GWAS-MAP platform for aggregation of results of genome-wide association studies and the GWAS-MAP homo database of 70 billion genetic associations of human traits. Var liv Genet. 24, 876–884 (2020).
21. Ning, Z., Pawitan, Y. & Shen, X. High-definition likelihood inference of genetic correlations across human complex traits. Nat. Genet. 52, 859–864 (2020).
22. ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision, 2nd edn (World Health Organization, 2004); ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision, 11th edn (World Health Organization, 2019).
23. Deelen, J. et al. A meta-analysis of genome-wide association studies of epigenetic age acceleration. PLoS Genet. 15, e1008104 (2019).
24. Abbott, A. et al. The GWAS-MAP platform for aggregation of results of genome-wide association studies and the GWAS-MAP homo database of 70 billion genetic associations of human traits. Var liv Genet. 24, 876–884 (2020).
25. Ning, Z., Pawitan, Y. & Shen, X. High-definition likelihood inference of genetic correlations across human complex traits. Nat. Genet. 52, 859–864 (2020).
26. Wang, G., Sarkar, A., Carbonetto, P. & Stephens, M. A simple new approach to variable selection in regression, with application to genetic fine mapping. J. R. Stat. Soc. Ser. B Stat. Methodol. 82, 1273–1306 (2020).
27. Kamat, M. A. et al. PhenoScanner V2: an expanded tool for searching human genotype–phenotype associations. Bioinformatics 35, 4851–4853 (2019).
28. Buniello, A. et al. The NHGRI-EBI GWAS catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res. 47, D1095–D1012 (2019).
29. Lamparter, D., Marbach, D., Ruedei, R., Kutilak, Z. & Bergmann, S. Fast and rigorous computation of gene and pathway scores from SNP-based summary statistics. PLoS Comput. Biol. 12, e1004714 (2016).
30. Hemani, G. et al. The MR-base platform supports systematic causal inference across the human phenotype landscape. Nat. Rev. Genet. 17, e3448 (2018).
31. Zheng, J. et al. Phenome-wide Mendelian randomization mapping the influence of the plasma proteome on complex diseases. Nat. Genet. 52, 1122–1131 (2020).
32. Giambartolomei, C. et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet.* **10**, e1004383 (2014).
33. Roffa, M. B., Marcovina, S. M. & Koschinsky, M. L. Lipoprotein(a) as a risk factor for atherosclerosis and thrombotic mechanistic insights from animal models. *Clin. Biochem.* **37**, 333–343 (2004).
34. Nordestdaag, B. G. et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur. Heart J.* **31**, 284–2853 (2010).
35. Roffa, M. B. et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet* **388**, 2239–2253 (2016).
36. Arsenault, B. J. et al. Association of long-term exposure to elevated lipoprotein(a) levels with parental life span, chronic disease-free survival, and mortality risk: a Mendelian randomization analysis. *JAMA Netw. Open* **3**, e201129 (2020).
37. Allen, S. et al. Expression of adhesion molecules by Lp(a): a potential novel mechanism for its atherogenicity. *FASEB J.* **1** 12, 1765–1776 (1998).
38. Cho, T., Jung, Y. & Koschinsky, M. L. Apolipoprotein(a) through its strong lysine-binding site in KIV 10, mediates increased endothelial cell contraction and permeability via a rho/ rho kinase/MYPT1-dependent pathway. *J. Biol. Chem.* **283**, 30503–30512 (2008).
39. Kong, D. H., Kim, Y. K., Kim, M. R., Jang, J. H. & Lee, S. Emerging roles of vascular cell adhesion molecule-1 (VCAM-1) in inflammatory disorders and cancer. *Int. J. Mol. Sci.* **19**, 13–18 (2018).
40. Yousef, H. et al. Aged blood impairs hippocampal neural precursor activity and activates microglia via brain endothelial cell VCAM1. *Nat. Med.* **25**, 988–1000 (2019).
41. Smith, L. K. et al. B2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis. *Nat. Med.* **21**, 932–937 (2015).
42. Grote, A. et al. LRP12 silencing during brain development results in cortical dyslamination and seizure sensitization. *Neurobiol. Dis.* **65**, 170–176 (2016).
43. Bethge, N. et al. A gene panel, including LRP12, is frequently hypermethylated in major types of B-cell lymphoma. *PLoS ONE* **9**, e104249 (2014).
44. Garnis, C., Coe, B. P., Zhang, L., Rosin, M. P. & Lam, W. L. Overexpression of LRP12, a gene contained within an 8q22 amplicon identified by high-resolution array CGH analysis of oral squamous cell carcinomas. *Oncogene* **23**, 2582–2586 (2004).
45. Nakaya, N., Sultana, A., Lee, H. S. & Tomarev, S. I. Olfactomedin 1 interacts with the Nogo A receptor complex to regulate axon growth. *J. Biol. Chem.* **287**, 37171–37184 (2012).
46. Shi, W. et al. Olfactomedin 1 negatively regulates NKB signaling and suppresses the growth and metastasis of colorectal cancer cells. *J. Pathol.* **240**, 352–365 (2016).
47. Cheng, A. et al. Pancarin-2 interacts with WAVE1 and Bcl-xl in a mitochondria-associated protein complex that mediates ischemic neuronal death. *J. Neurosci.* **27**, 1519–1528 (2007).
48. Yang, C. et al. Genome atlas of the proteome from brain, CSF and plasma prioritizes proteins implicated in neurological disorders. *Nat. Neurosci.* **24**, 1302–1312 (2021).
49. Rebo, J. et al. A side heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood. *Nat. Commun.* **7**, 13363 (2016).
50. Katsimparis, L. et al. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. *Science* **344**, 630–634 (2014).
51. Balla, J. et al. Haem, haemoglobin and ferritin in vascular endothelial cell injury. *Nephrol. Dial. Transplant.* **18**, v9–v12 (2003).
52. Higashi, Y. & Yoshizumi, M. Endothelial function. *Jpn. J. Clin. Med.* **61**, 1138–1144 (2003).
53. Engelhardt, B. Development of the blood–brain barrier. *Cell Tissue Res.* **314**, 119–123 (2003).
54. Lakatta, E. G. & Levy, D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises. Part I: aging arteries: a ‘set up’ for vascular disease. *Circulation* **107**, 139–146 (2003).
55. Montagne, A. et al. APOE4 leads to blood–brain barrier dysfunction predicting cognitive decline. *Nature* **581**, 71–76 (2020).
56. Popov, N. et al. The ubiquitin-specific protease USP28 is required for MYC stability. *Nat. Cell Biol.* **9**, 765–774 (2007).
57. Serrano, M. The tumor suppressor protein p16INK4a. *Exp. Cell. Res.* **237**, 7–13 (1997).
58. Li, F. et al. USP28 regulates deubiquitination of histone H2A and cell proliferation. *Exp. Cell. Res.* **379**, 11–18 (2019).
59. Baker, D. J. et al. Naturally occurring p16INK4a-positive cells shorten healthy lifespan. *Nature* **530**, 184–189 (2016).
60. Timmers, P. R. H. J. et al. Mendelian randomization of genetically independent aging phenotypes identifies LPA and VCAM1 as biological targets for human aging [dataset]. *University of Edinburgh* https://doi.org/10.1093/fix/fgaa072 (2020).
61. Zenin, A. et al. Genome-wide association summary statistics for human healthspan (Version 1) [dataset]. *Zenodo* https://doi.org/10.5281/zenodo.1302861 (2018).
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Competing interests
P.R.H.J.T. is a salaried employee of BioAge Labs Inc. P.K.J. is a paid consultant for Humanity Inc. and Global Gene Corporation. The remaining authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Paul R. H. J. Timmers.

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Biobank Japan Project
Yoichiro Kamatani

A full list of Biobank Japan Project members and their affiliations appears in the Supplementary Information.

FinnGen
Tuomo T. J. Kiiskinen, Wei Zhou and Andrea Ganna

A full list of FinnGen members and their affiliations appears in the Supplementary Information.
Extended Data Fig. 1 | Non-genetic correlations between ageing-related GWASs. Off-diagonal values show the phenotypic correlation between GWASs observed due to sample overlap. Correlations were calculated using the Z scores of independent SNPs (provided by the MultiABEL R package)\textsuperscript{13} that were non-significant in both studies (|z| < 1.96). The number of SNPs used for each pairwise correlation is reported in Supplementary Data 1. EAA, Epigenetic Age Acceleration; mLOY, mosaic Loss of Y chromosome.
Extended Data Fig. 2 | Adjustment of aging-GIPs to remove genetic correlations with socioeconomic status and household income. a) Genetic correlations of aging-GIPs with UK Biobank GWASs of Townsend’s deprivation index and household income. In black are the original correlations before adjustment, in red are the correlations after adjustment. Error bars represent 95% confidence intervals based on 1,027,336 SNPs (99.75%) from the HDL R package’s LD reference panel. b) LD score plot showing the relationship between LD scores and $\chi^2$ statistics of aging-GIP1 SNPs, before and after adjustment. Each dot represents an LD score percentile. The x-axis shows the mean LD score of variants in each LD score percentile, and the y-axis shows the mean $\chi^2$ statistics of SNPs in that LD score percentile. The weighted slope of the regression can be used as a measure of the trait heritability.
Extended Data Fig. 3 | Phenome-wide genetic correlations of aging-GIPs adjusted for household income and Townsend's deprivation index. Shown are the genetic correlations of the 25 GWAS-MAP clusters (defined in Fig. 3) with aging-GIPs adjusted for socioeconomic status and household income (as measured in UK Biobank). Values failing to pass nominal significance (two-sided Wald test $P \geq 0.05$) are greyed out. See Supplementary Data 3 for the full list of correlations.
Extended Data Fig. 4 | Effect sizes of lead aging-GIPI SNPs adjusted for household income and Townsend's deprivation index. The x-axis shows the mean effect size estimate of the lead SNPs associated with aging-GIPI at Bonferroni-corrected genome-wide significance (P < 8.3 x 10^-9), with 95% confidence intervals represented by lines. The estimated sample sizes are 154,478 and 195,015 for the original and adjusted aging-GIPI GWAS, respectively. The y-axis is annotated with the nearest gene(s) or cytogenetic band to each locus, with the lead SNP and the aging-GIPI-increasing allele in parentheses. In black are the original aging-GIPI estimates, while in red are the estimates after removing all genetic correlations with GWASs of UK Biobank socioeconomic status and household income.
Extended Data Fig. 5 | MR of blood protein levels on aging-GIP1 adjusted for household income and Townsend’s deprivation index. Exposures significant for a causal effect on aging-GIP1 were tested for their effect on the aging-GIP1 residual phenotype, which was adjusted to remove all genetic correlations with GWASs of socioeconomic status and household income in UK Biobank. The x-axis shows the MR effect estimates, with lines representing 95% confidence intervals, as estimated by TwoSampleMR\(^3\). The sample sizes of exposure GWASs were 6,861 for LPA; 3,301 for VCAM1; and 3,200 for OLFM1 and LRP12. In red is the original aging-GIP1 causal effect estimate, while in red is the effect with the adjusted aging-GIP1 phenotype. LPA—apolipoprotein(a). VCAM1—vascular cell adhesion molecule 1. OLFM1—olfactomedin 1. LRP12—LDL receptor related protein 12.
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- Estimates of effect sizes (e.g. Cohen’s d, Pearson’s r), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection  No software was used to collect the data.

Data analysis  High-definition likelihood (HDL) R package v1.3.4; LD-score regression (LDSC) v1.0.0; meta R package v4.15-1; Genetic Analysis of Time-to-Event phenotypes (GATE) v0.40; survival R package v2.41; Stratified LD-score regression v1.0.0; PASCAL v1; mclust R package v5.4.1; susieR R package v.0.11.8; ANNOVAR v.2019Oct24; TwoSampleMR R package v0.5.5; R v3.6.0

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Ageing-related trait: GWAS summary statistics can be retrieved or requested from study authors at http://www.nealelab.is/uk-biobank/ (self-rated health; field 2178), https://www.longevitygenomics.org/downloads(longevity), and the following DOI: 10.5281/zenodo.1902861 (healthspan), 10.6084/m9.figshare.9204988.v3 [frailty index], 10.5523/brs.21crwuj4wujm2q4o8chbthn (perceived age), 10.7488/ds/2178 (parental lifespan), 10.7488/ds/2631 (epigenetic age acceleration), 10.1016/j.ajhg.2020.02.006 (telomere length), 10.1038/ng.3821 [mLOY], Summary statistics for Ageing-GIP1 calculated in this study have been deposited in the Edinburgh DataShare repository, available without restrictions at https://doi.org/10.1488/ds/2972. Summary statistics of the GWAS-MAP phenotypes used to calculate phenotype-wide genetic correlations are available from GeneAtlas (http://geneatlas.rosin.ed.ac.uk/), NealeLab (http://www.nealelab.is/uk-biobank/), or
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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size: Sample sizes were not predetermined. Instead, sample sizes (i.e. the total number of individuals in each study) were reported in the age-related GWAS publications or their summary statistics. See http://www.nealelab.is/uk-biobank; https://doi.org/10.7554/eLife.39856; https://doi.org/10.1101/19007559; https://doi.org/10.1371/journal.pgen.1008104; https://doi.org/10.1038/s42003-019-0290-0; https://doi.org/10.1038/s41467-019-11558-2; https://doi.org/10.1038/s41387-019-0223-z; https://doi.org/10.1016/j.aje.2020.02.006. Sample sizes for the Ageing-GIPs were estimated based on the median z statistic and the allele frequencies of null SNPs.

Data exclusions: For each set of summary statistics, we discarded SNPs that were poorly imputed ([INFO < 40%], rare [MAF < 0.5%], or poorly measured [N individuals < 1% of total]. This was to restrict our analysis to reliable SNPs and prevent poorly measured outliers from biasing downstream analyses.

Replication: We measured long SNP effects on FinnGen participant survival (Release 5; N = 203,244; 6.94% deceased) and BioBank Japan participant survival (N = 135,983; 24.1% deceased), to provide additional evidence of their association with human age traits in independent samples. We found evidence for a directionally concordant and statistically significant effect for two of the 23 loci tested. As is common for genome-wide association analyses, larger samples may be needed to confirm or reject the remaining loci.

Randomization: Recruitment and analysis of the cohorts used to generate the GWAS summary statistics are described in the Supplementary Note and referenced publications. As is standard, GWAS analyses rely on observational data which is not randomised but is corrected for population stratification and familial relatedness using genetic principal components as fixed effects and/or genetic kinship as random effects. Our study does not compare experimental groups, so additional randomisation is not applicable.

Blinding: Blinding was not relevant to our study: analysis of genetically independent phenotypes does not use group allocation. GWAS of genetically independent phenotypes is a hypothesis-free scan of the genome that does not require sample randomisation.

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  - [ ] Clinical data
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Methods

- [X] n/a
- [X] Involved in the study
  - [ ] ChiP-seq
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Human research participants

Policy information about studies involving human research participants

Population characteristics: Description of the population characteristics of age-related GWAS are described in the Supplementary Note and referenced publications. For individual-level BioBank Japan (BBJ) data, detailed sample descriptives can be found in Hirata et al [2017] J Epidemiol. https://doi.org/10.1016/j.je.2016.12.006. A total of 135,983 unrelated Japanese-ancestry individuals (65% male) were used for our analysis, recruited at a median age of 64, of which 30,976 had a death record at time of analysis.
Recruitment

BJJ individuals were recruited from June 2003 to March 2008 at 12 medical institutes if they presented with one of 47 common diseases in Japan. Diseases were identified by attending physicians and independent medical coordinators provided information to patients. As diseases did not include cognitive impairments, we expect little self-selection bias. However, while the survival model was adjusted for this disease status, the selection of unhealthy individuals could decrease SNP hazard ratios (as the baseline mortality hazard is higher). This potential bias is towards the null, causing our replication of GWAS findings to be conservative.

Ethics oversight

Biobank Japan participants provided written informed consent and survival study protocols were approved by Biobank Japan Project ethical review boards from the Institute of Medical Sciences, the University of Tokyo, and the RIKEN Center for Integrative Medical Sciences. All other data was publicly available and approved by ethical committees as described in their respective publications. See Supplementary Note for FinnGen ethical approval.

Note that full information on the approval of the study protocol must also be provided in the manuscript.