Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan.

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Abstract

Human genetics seeks a way to improve human health on a global scale. Expectations are running high for polygenic risk scores (PRSs) to be translated into clinical practice to predict an inborn susceptibility to health risks. While risk stratification based on PRS is one way to promote population health, a strategy to utilize genetics to prioritize modifiable risk factors and biomarkers driving heath outcome is also warranted. To this end, here we utilized PRSs to comprehensively investigate the association of the genetic susceptibility to complex traits with human lifespan in collaboration with three worldwide biobanks (n_{total} = 675,898). First, we conducted genome-wide association studies for 45 quantitative clinical phenotypes, constructed the individual PRSs, and associated them with the age at death of 179,066 participants in BioBank Japan. The PRSs revealed that the genetic susceptibility of high systolic blood pressure (sBP) was strongly associated with a shorter lifespan (hazard ratio [HR] = 1.03, $P = 1.4\times10^{-7}$). Next, we sought to replicate these associations in individuals of European ancestry in UK Biobank (n = 361,194) and FinnGen (n = 135,638). Among the investigated traits, the individuals with higher blood pressure-related PRSs were trans-ethnically associated with a shorter lifespan (HR = 1.03, $P_{meta} = 3.9\times10^{-13}$ for sBP) and parental lifespan (HR = 1.06, $P_{UKBB} = 2.0\times10^{-86}$ for sBP). Further, our trans-biobank study identified additional complex traits associated with lifespan (e.g., obesity, height, serum lipids, and platelet counts). Of them, obesity-related traits showed strikingly heterogeneous effects on lifespan between Japanese and European populations ($P_{heterogeneity} = 9.5\times10^{-8}$ for body mass index). Through trans-ethnic biobank collaboration, we elucidated the novel value of the PRS study in genetics-driven prioritization of risk factors and biomarkers which can be medically intervened to improve population health.

Main

Introduction

Human disease risks can be explained by the combinations and interactions of inherited genetic susceptibility, acquired environmental exposures, and lifestyle factors[1]. One of the goals of medical research is to identify individuals at health risks both at the time of birth and later in life, and to provide them medical attention when necessary. Polygenic risk scores (PRSs) have successfully shown their predictive ability to idenitify those with a several-fold higher inherited risk of a given disease or condition[2]. Both an increase in statistical power and ethnic diversity in genetic studies—accelerated by nation-wide biobanks—have been instrumental in accurately predicting disease onset by PRSs[3–6]. Stratification of health risks based on PRSs would be one of the strategies to improve population health through targeted prevention. Nevertheless, the genetic risk itself cannot be modified. For many complex human traits, environmental exposure and lifestyle are also of great importance, such as cigarette smoking[7] and dietary habits[8]. The accurate identification of risk factors that affect not only disease onset but also long-term health outcomes would contribute to population health, because these factors can be modified by medical intervention.

Observational studies have been attempting to identify monitorable risk factors and biomarkers that are correlated with the health outcomes (e.g., high low-density lipoprotein [LDL] cholesterol levels and the development of myocardial infarction). Nevertheless, the observational studies are inevitably laden with the pervasive issue of difficulty in inferring the cause-and-effect direction. A randomized controlled trial (RCT) is considered the gold standard to derive the effect of the exposure on the outcome free from unknown confounders[9]. In the above example, if a medical intervention to decrease the LDL cholesterol level leads

to the decreased incidence of myocardial infarction at the population level, we could estimate that the high LDL cholesterol levels cause the development of myocardial infarction. The limitations of RCTs are, however, that they require a considerable amount of human and economic resources and are not always ethically feasible.

To address this, we here aimed to identify complex human traits affecting human lifespan, a health outcome of extreme importance and interest, by utilizing PRSs. The association of genetic susceptibility with lifespan would enable the prioritization of common risk factors and biomarkers, which could drive mortality in the current generation, among a variety of phenotypes that could be monitored in clinics. Furthermore, integration with deep-phenotype records and follow-up data in biobanks would enable us to pinpoint specific comorbidities and death causes that lead this association. Given the large genetic and environmental differences among populations, trans-ethnic comparison is also warranted. A collaboration with three trans-ethnic nation-wide biobanks collecting genotype, phenotype and survival data (n_{total} = 675,898) has enabled us to uncover the modifiable risk factors and monitorable biomarkers affecting human lifespan across the populations, on an unprecedented scale and without any clinical intervention.

Results

Study overview

An overview of our study design is presented in **Supplementary Figure 1**. We collaborated with three nation-wide biobanks (BioBank Japan [BBJ], UK Biobank [UKBB], and FinnGen) to elucidate clinical biomarkers affecting the lifespan of the current generation, across the different populations. The BioBank Japan cohort consisted of 200,000 participants mainly of Japanese ancestry, with clinical phenotype, biochemical measurement, lifestyle, and genotype data. The detailed information of this cohort is described elsewhere[10–12] and in **Supplementary Table 1a**. Of them, 138,278 participants were followed up for their health record after an initial visit, including disease onset, survival outcome, and the cause of death if they died. The mean follow-up period was 7.44 years, and the number of deaths during the follow-up was 31,403. The UK Biobank project is a population-based prospective cohort consisting of approximately 500,000 people in the United Kingdom with deep phenotype and genotype data (summary in **Supplementary Table 1b**; see **URLs**). The biobank participants are linked to a death registry, which provides the age and cause of death when they die. In this study, we analyzed 10,483 deaths during a mean follow-up period of 6.97 years. FinnGen is a public-private partnership project combining genotype data from Finnish biobanks and digital health record data from Finnish health registries (see **URLs**). We analyzed 11,058 deaths in the national death registry among the 135,638 participants in this study.

We first sought to identify clinical biomarkers that were associated with lifespan in BioBank Japan and UK Biobank as an illustration of a conventional observational study. We then performed an association test of the PRSs (i.e., genetic susceptibility) of these biomarkers with lifespan in BioBank Japan, in order to elucidate the drivers, not the correlation, affecting

human lifespan. We next performed replication studies of the association of the PRSs with lifespan in UK Biobank and FinnGen. We finally meta-analyzed these associations across the three cohorts.

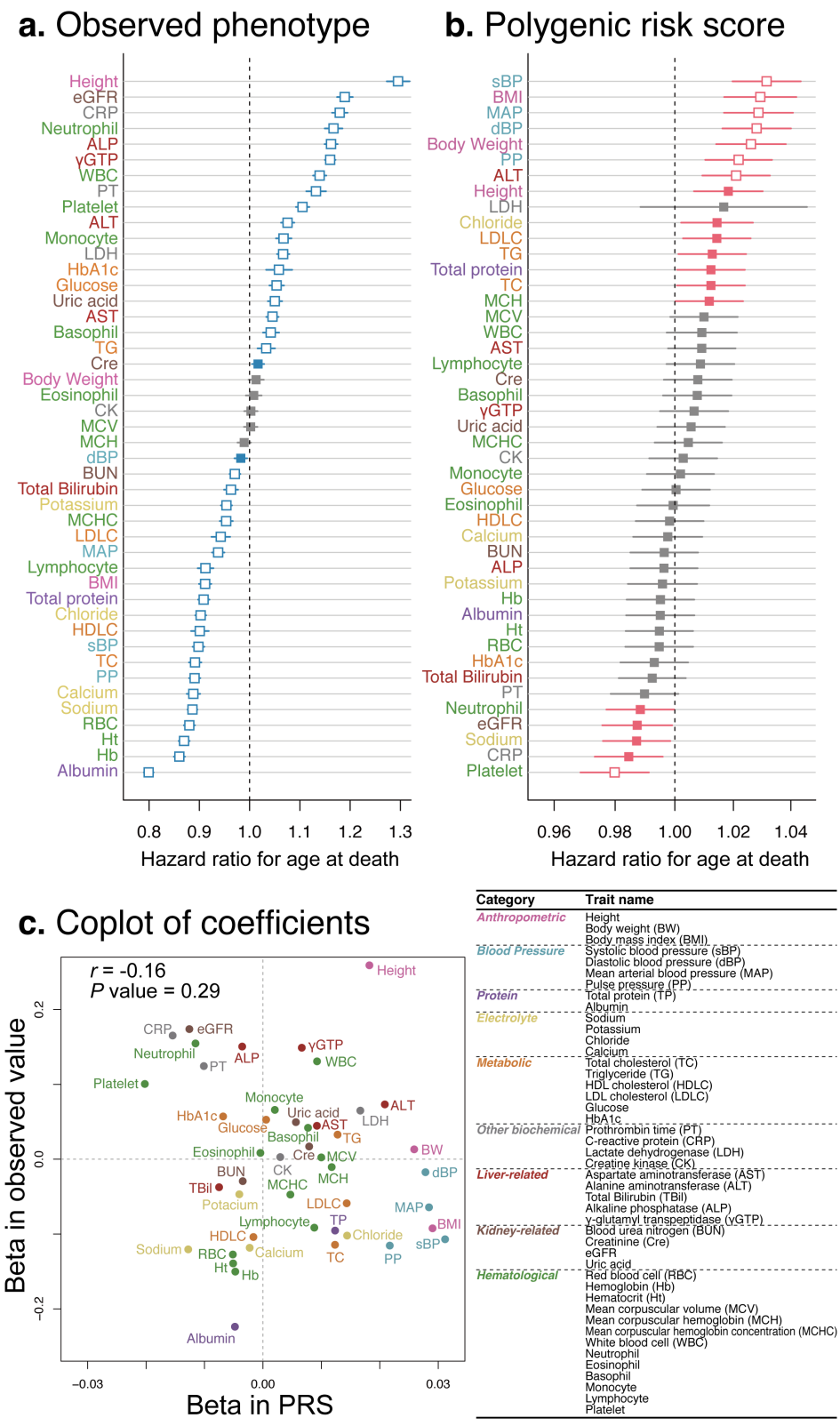
Association study of clinical biomarkers with human lifespan

First, in order to identify candidate clinical biomarkers correlated with human lifespan, we conducted an observational association study of these phenotypes with the lifespan on BioBank Japan. After the Bonferroni correction for multiple testing, 38 out of 45 clinical phenotypes showed a significant association with age at death (**Figure 1a**; Summary results are in **Supplementary Table 2**). The top traits associated with a shorter lifespan were low albumin, high γ-glutamyl transpeptidase, and increased height. The effect of a one standard deviation (SD) increase in each trait on mortality resulted in a hazard ratio (HR) of 0.80 [0.79–0.81], 1.16 [1.15–1.17], and 1.30 [1.27–1.32] ($P = 3.3 \times 10^{-287}$, 1.1×10^{-224}, and 8.3×10^{-186}), respectively. These results were consistent with the previous epidemiological studies in other cohorts[13–16].

To investigate how the association of clinical biomarkers with human lifespan is shared across different populations, we next performed the same observational study in UK Biobank using the 20 clinical phenotypes that were recorded in both UK Biobank and in BioBank Japan (**Supplementary Figure 2**). We again observed significant associations of the quantitative traits with lifespan in 17 out of 20 traits. Of note, 14 among the 15 traits with significant association in BioBank Japan showed directionally concordant associations with lifespan in UK Biobank. The only trait that showed directionally discordant association was body mass index (BMI). While a lower BMI was significantly associated with a shorter lifespan

in Biobank Japan, a higher BMI showed significant association with a shorter lifespan in UK Biobank. This discordant result could be attributed to differences in the participation criteria (i.e. hospital-based recruitment in BioBank Japan and healthy volunteers in UK Biobank) and differences in the health burden of obesity across populations, which warrants further replication studies in different cohorts.

A weakness of the epidemiological associations was, however, that it was difficult to conclude whether the variations in clinical measurements had caused the variations in lifespan, or they were just correlations. For example, a decreased albumin level was associated with a shorter lifespan, but this did not mean that low albumin caused high mortality. Rather, the decline in general health and nutritional status, which led to high mortality, might have resulted in low albumin levels.



Category	Trait name
Anthropometric	Height
	Body weight (BW)
	Body mass index (BMI)
Blood Pressure	Systolic blood pressure (sBP)
	Diastolic blood pressure (dBP)
	Mean arterial blood pressure (MAP)
	Pulse pressure (PP)
Protein	Total protein (TP)
	Albumin
Electrolyte	Sodium
	Potassium
	Chloride
	Calcium
Metabolic	Total cholesterol (TC)
	Triglyceride (TG)
	HDL cholesterol (HDLC)
	LDL cholesterol (LDLC)
	Glucose
	HbA1c
Other biochemical	Prothrombin time (PT)
	C-reactive protein (CRP)
	Lactate dehydrogenase (LDH)
	Creatine kinase (CK)
Liver-related	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Total Bilirubin (TBil)
	Alkaline phosphatase (ALP)
	γ-glutamyl transpeptidase (γGTP)
Kidney-related	Blood urea nitrogen (BUN)
	Creatinine (Cre)
	eGFR
	Uric acid
Hematological	Red blood cell (RBC)
	Hemoglobin (Hb)
	Hematocrit (Ht)
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
	White blood cell (WBC)
	Neutrophil
	Eosinophil
	Basophil
	Monocyte
	Lymphocyte
	Platelet

Figure 1. The hazard ratios for the age at death, according to clinical phenotypes and according to the PRSs and their correlations in BioBank Japan.

174 Shown are the adjusted HRs from Cox proportional-hazard models for lifespan, according to
175 clinical phenotypes **(a)** and according to the PRSs for the clinical phenotypes **(b)** in BioBank
176 Japan. The boxes indicate the point estimates, and the horizontal bars indicate the 95%
177 confidence interval. Boxes in blue **(a)** or red **(b)** indicate the nominal significance ($P < 0.05$),
178 and the white-out boxes indicate the statistical significance after correcting for multiple testing
179 by the Bonferroni method. **(c)** Co-plot of the coefficients from the Cox proportional-hazard
180 models for lifespan according to the PRS (x-axis) and those according to clinical phenotypes
181 (y-axis).
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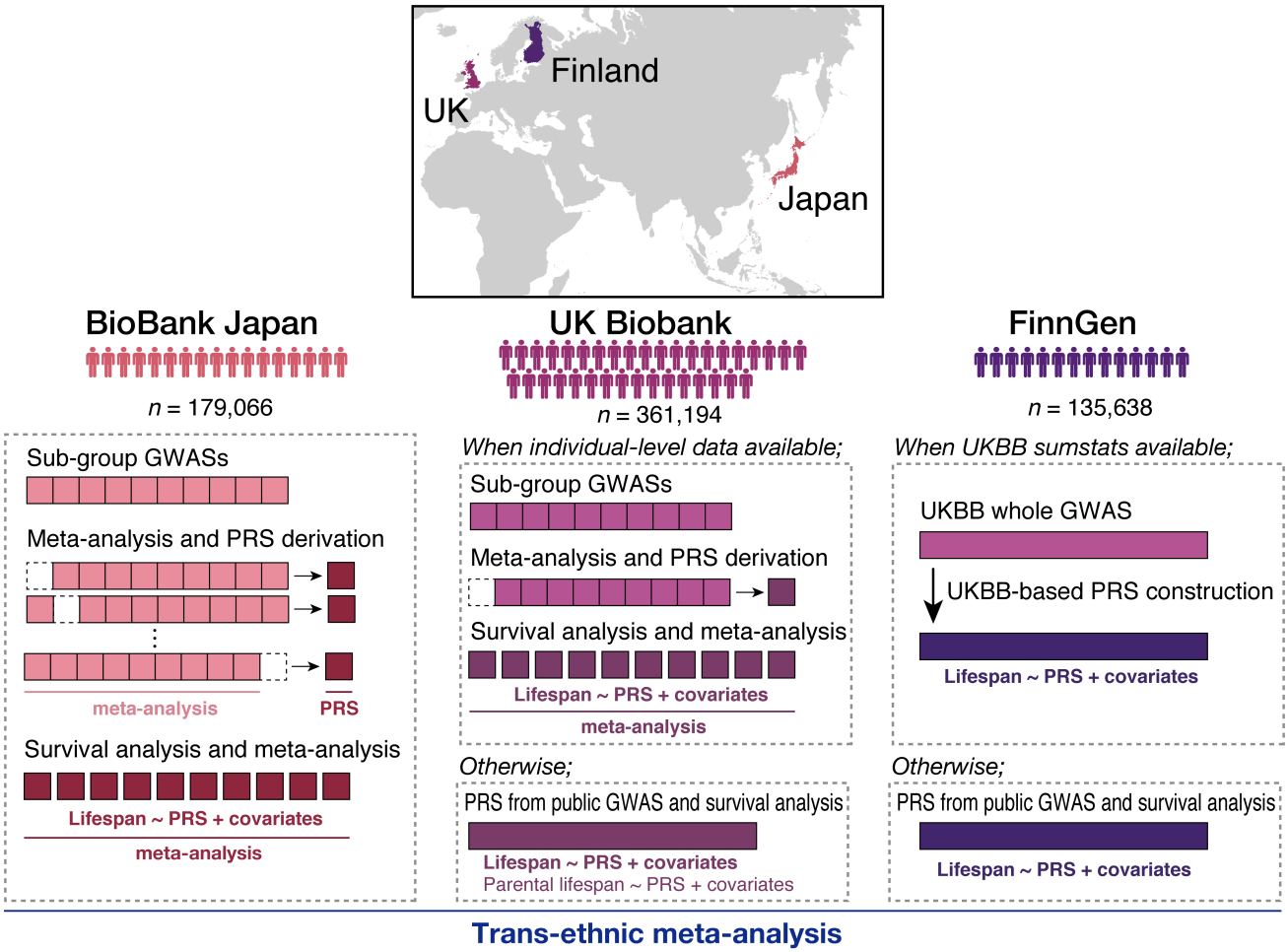

Figure 2. Overview of PRS-lifespan association study in collaboration with three nation-wide biobanks.

In BioBank Japan, we first randomly split the entire cohort into 10 sub-groups and performed genome-wide association studies (GWASs) on 45 quantitative traits. We then performed a 10-fold leave-one-group-out (LOGO) meta-analysis, derived the PRSs in one remaining sub-group, and associated them with lifespan. We meta-analyzed the statistics of the lifespan association obtained from the ten sub-groups. In UK Biobank, when individual-level phenotype data is available, we adopted the LOGO approach. Otherwise, we derived the PRSs from public large-scale GWAS statistics, and associated the PRSs with lifespan in the cohort. As a secondary analysis, we also associated the PRS with parental lifespan in UK

195 Biobank. In FinnGen, we derived the PRSs from UK Biobank GWAS summary statistics or
196 public large-scale GWAS statistics, and associated the PRS with lifespan in the cohort.
197 Finally, we performed trans-ethnic meta-analysis.

198 ***Association study of PRSs of complex traits with human lifespan in BioBank Japan***

199 Next, in order to prioritize the clinical traits affecting human lifespan, we utilized genetic
200 information. PRS is supposed to simulate the genetic predisposition towards the investigated
201 trait[1]. Thus, the association of the PRS of the investigated trait with lifespan can be
202 considered as less susceptible to the confounding factors such as a decline in general
203 health[17,18]. PRSs should be constructed from the genetic studies of the same population[5,19],
204 and BioBank Japan has been the largest study of East Asian populations to date.
205 Conventionally, when independent large-scale GWAS statistics with matched population and
206 a sufficient sample size are not available for constructing PRSs, a strategy to split the study
207 cohort into two groups (i.e., discovery group to conduct GWASs and a validation cohort to
208 derive the PRSs) has been used. This strategy compromises accurate estimates in GWAS
209 statistics using maximum samples or lowers the statistical power in PRS validations,
210 depending on how the cohort is split. To address this, we adopted a 10-fold leave-one-group-
211 out (LOGO) meta-analysis approach in the derivation of PRSs in order to validate the PRSs
212 in participants independent from GWAS while retaining as much sample size and statistical
213 power as possible. Briefly, we first conducted GWASs on 45 clinical phenotypes by randomly
214 splitting the whole cohort into ten sub-groups (**Supplementary Table 3** shows the detailed
215 phenotype information used in GWASs). Then, we meta-analyzed nine GWASs
216 (**Supplementary Table 4** for the GWAS summaries), constructed PRSs from the meta-
217 analyzed statistics by using a clumping and thresholding method, and performed survival
218 analyses to investigate the association of the derived PRS with individual lifespan (age at
219 death) in the one withheld sub-group. We repeated this analysis ten times and further meta-
220 analyzed the statistics of survival analyses in the 10 sub- groups (**Figure 2** and **Methods** for

the study design). Thus, we were able to maintain the sample size in GWASs at nine-tenths of the whole cohort and at the same time, validate the derived PRSs using all of the individuals in the cohort.

Among the investigated clinical phenotypes, higher PRSs of blood pressure-related traits (systolic blood pressure [sBP], diastolic blood pressure [dBP], and mean arterial pressure [MAP]) were significantly associated with a shorter lifespan (**Figure 1b;** summary results shown in **Supplementary Table 2**). In the case of sBP, whose PRS showed the strongest association with the age at death (HR of per SD increase in PRS on mortality = 1.03 [1.02–1.04], $P = 1.4\times10^{-7}$), individuals with the highest sBP PRS (in the top quintile) had indeed a 1.46-fold higher risk of being hypertensive (sBP > 130 mmHg or dBP > 80 mmHg) or being treated with anti-hypertensive medications when compared with those with the lowest PRS (in the bottom quintile; $P = 1.4\times10^{-84}$). A comparison between the standardized survival curves according to the observed phenotype and those according to the PRS of the phenotype is highlighted in **Figure 3**. Those with the highest PRS (in the top quintile) and thus with the genetic predisposition to cause increased blood pressure were significantly associated with an increased risk of standardized mortality than those with the lowest PRS (the standardized 10-year mortality rate was 0.210 and 0.217, respectively, **Figure 3b**, top). On the other hand, the measured blood pressure value showed U-shaped associations with lifespan, with those with the lowest and the highest sBP both harboring an increased risk of mortality (**Figure 3a** top and **Supplementary Figure 3**). By utilizing the genetic data, we disentangled the dose-dependent association of the genetic risk of high blood pressure with a short lifespan, while the observed association of the lowest-range blood pressure with a short lifespan might have been confounded by the consequence (i.e. decline in general health

caused low blood pressure[20]). This contrasts with the case of albumin. Although the measured low albumin level showed the strongest association with a short lifespan (**Figure 3a,** bottom), the PRS of the albumin did not show any association with the age at death (HR = 0.99 [0.98–1.00], *P* = 0.40, **Figure 3b,** bottom). Overall, there was no significant correlation of the effect size and directions between the association of clinical phenotypes on lifespan and the association of PRSs of clinical phenotypes on lifespan (*r* = -0.16, *P* = 0.29; **Figure 1c**), which was not confounded by the variance explained by PRSs in each trait (shown in **Supplementary Table 5**). To summarize, the PRSs have provided novel and distinct insights into prioritizing critical factors affecting human lifespan from the observational studies.

In addition to the overall survival outcome, we also tested the cause-specific mortality that drives the association with the sBP PRS, by leveraging the detailed follow-up data in BioBank Japan. Among the four most frequent causes of death in Japan[11], a high sBP PRS was significantly associated with death from cardiovascular diseases (I01–I02, I05–I09, I20–I25, I27 and I30–I52 [HR = 1.04 (1.01–1.08), *P* = 0.0064]) and nominally associated with death from cerebrovascular diseases (I60–69 [HR = 1.05 (1.01–1.10), *P* = 0.024]), as categorized by the International Classification of Diseases 10. We next performed comorbidity-stratified analysis in the association of sBP PRS with lifespan. We found that individuals with a past medical history of type 2 diabetes, cerebral infarction, or dyslipidemia strongly drove the association of sBP PRS with lifespan in Japanese individuals (HR = 1.05 [1.03–1.07), 1.06 [1.03–1.09), 1.05 [1.02–1.08), and $P = 2.6\times10^{-5}$, 1.9×10^{-4}, 4.0×10^{-3}, respectively). These results recapitulated the epidemiological knowledge that high blood pressure is one of the strongest risk factors of mortality among patients with cardiovascular[21], cerebrovascular [22,23],

266 and metabolic diseases[24]. It has been previously reported that healthy-aging individuals had

267 low genetic risk of coronary artery disease[25], which is in line with our findings.

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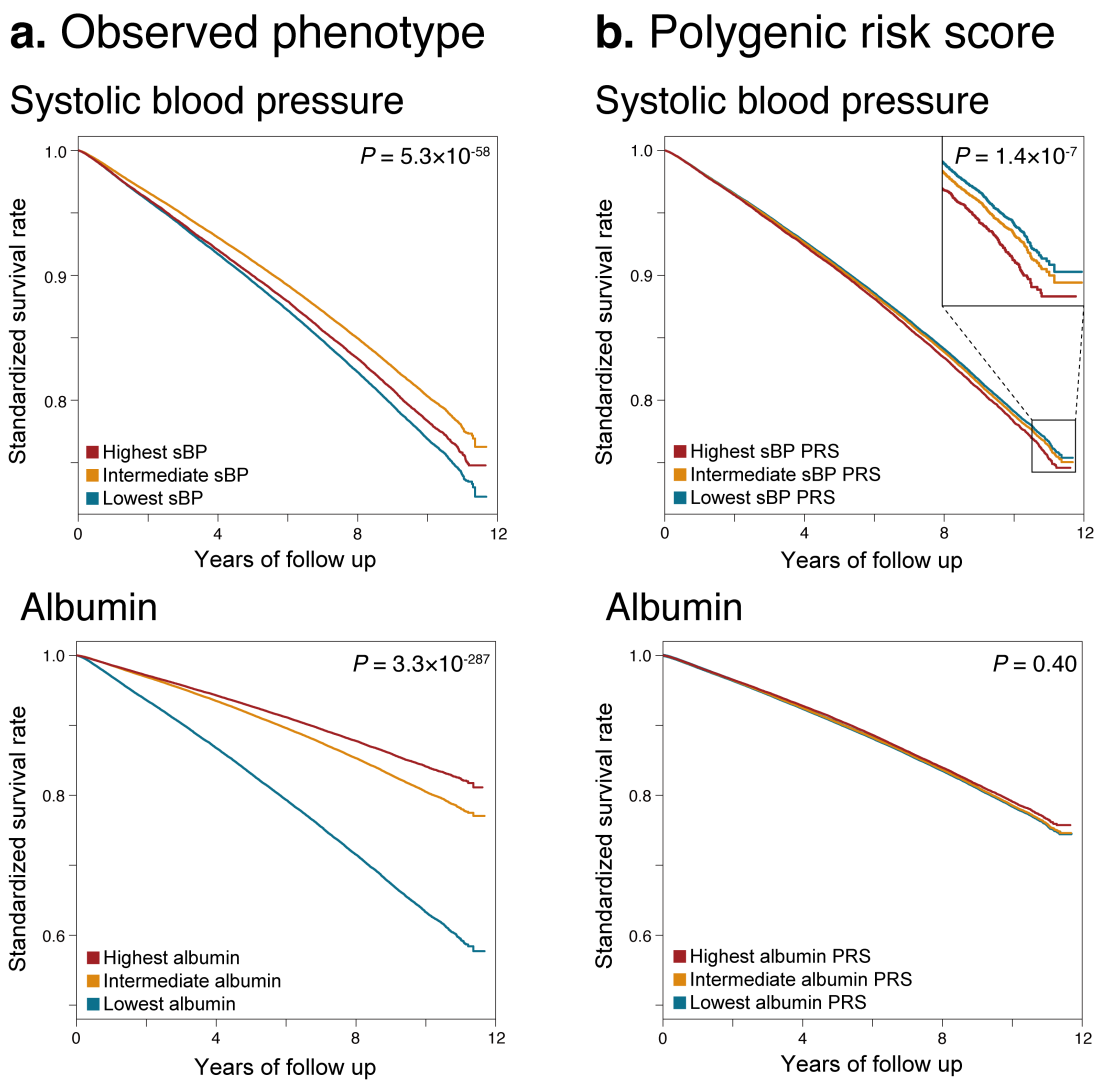


Figure 3. Standardized survival rate, according to systolic blood pressure (sBP) and albumin, and PRS status of both traits in BioBank Japan.

In each box, the standardized and adjusted survival curves according to three bins (lowest, first quintile; intermediate, 2–4 quintiles; and highest, fifth quintile) of the investigated trait or the PRS of the investigated trait are illustrated by analyzing mortality data in BioBank Japan. The standardization was performed using the mean of all the covariates. **(a)** Survival curves according to measured sBP value (top) and according to sBP PRS (bottom). **(b)** Survival curves according to measured serum albumin level (top) and according to albumin PRS.

Trans-ethnic association study of PRSs of complex traits with human lifespan

Next, we sought to replicate these associations in individuals of European ancestry using the individual-level data of UK Biobank (*n* = 361,194) and FinnGen (*n* = 135,638). We first constructed the PRSs by adopting the 10-fold LOGO meta-analysis approach when the individual-level phenotype was available (20 out of 33 traits in UK Biobank). Otherwise, we derived the PRSs by using independent publicly available large-scale GWAS summary statistics of European ancestry (13 out of 33 traits in UK Biobank and all the 33 traits in FinnGen) with a linkage disequilibrium (LD) reference of European individuals (**Figure 2** and **Methods** for the study design and **Supplementary Table 6** for public GWAS information). In this way, we could calculate the individual PRSs of 33 quantitative traits among the 45 investigated traits in BioBank Japan (**Supplementary Table 7** and **8** for phenotype and internal GWAS summary). We then associated the derived PRSs with lifespan in UK Biobank and FinnGen, and finally performed a trans-ethnic meta-analysis across the three cohorts (Summary results are shown in **Supplementary Table 9**). In UK Biobank and FinnGen, we successfully replicated the directional consistency of the association of a genetically increased risk of sBP with a shorter lifespan (HR = 1.02 [1.00–1.04], *P* = 0.083 in UK Biobank [**Figure 4b**] and HR = 1.03 [1.01–1.05], *P* = 0.0031 in FinnGen [**Figure 4c**]). A fixed-effect meta-analysis revealed a trans-ethnically robust association of higher PRSs of sBP with a shorter lifespan (HR = 1.03 [1.02–1.04], $P = 3.9\times10^{-13}$; **Figure 4d**). To further validate this finding, we also performed a secondary analysis using parental lifespan data in UK Biobank, which offered a much larger statistical power (see **Methods** for the detailed analysis method). The secondary analysis revealed that a genetically increased risk of sBP was also associated with a shorter parental lifespan (HR = 1.06 [1.06–1.07], $P = 2.0\times10^{-86}$).

Interestingly, the high PRSs of BMI and body weight (BW) were most significantly associated with short lifespan in UK Biobank and FinnGen (BMI: HR = 1.07 [1.05-1.09] and 1.06 [1.04-1.08], $P = 1.7\times10^{-11}$ and 1.5×10^{-8}, respectively), while they showed much smaller effect sizes and less significant associations in BioBank Japan (BMI: HR = 1.01 [1.00-1.02], $P = 0.094$). We noted that a strong effect of obesity on lifespan was consistent between the two of the European cohorts, UK Biobank and FinnGen, which would suggest the robustness of the result against the methods used for the calculation of PRSs (i.e., LOGO in UK Biobank and usage of independent GWAS summary statistics in FinnGen). Among all the investigated traits, the random effect meta-analyses only revealed a significant heterogeneity in association for BMI and BW ($P_{heterogeneity} = 9.5\times10^{-8}$ [BMI] and 1.5×10^{-8} [BW]). We did not observe apparent differences in the heritability and variance explained by the PRSs of BMI or BW between in BioBank Japan and UK Biobank (**Supplementary Table 4, 5, 8 and 10**). Thus, we considered that the reasons for this trans-ethnic heterogeneity was not attributed to the differences in GWASs utilized for the derivations of PRSs. The observed trait mean and SD were larger in the European cohorts before normalization (the mean for BMI was 23.3, 27.4, and 27.2, and the SD was 3.7, 4.8, and 4.1 in BioBank Japan, UK Biobank and FinnGen, respectively), and this was also the case in World Health Organization (WHO) data from 2016 (BMI: 22.8 [22.5–23.2] in Japan, 27.5 [27.2–27.8] in UK, and 26.6 [26.1–27.1] in Finland; see **URLs**). Obesity-related cardiovascular deaths are significantly prevalent among Europeans, and the epidemiological data revealed that the mortality rate of individuals in the in high BMI range was higher in Europeans than in East Asians[26]. The heterogeneity in the association of BMI or BW PRSs on lifespan between Japanese and Europeans might reflect the differences in the strength of the effect of obesity on mortality, on which further trans-

ethnic studies should be warranted.

To determine what is driving the association of BMI PRS on lifespan (i.e. mortality) in Europeans, we additionally investigated the cause-specific mortality and comorbidity information recorded in UK Biobank. When we tested the association of BMI PRS with the cause-specific mortality in UK Biobank, the BMI PRS was most strongly associated with cerebrovascular death (HR = 1.12 [1.08–1.17], P = 3.1×10^{-8}). When we stratified individuals based on the comorbid conditions (i.e., common disease affection status), we found that the association of BMI PRS with lifespan was strongest among those with unstable angina (HR = 1.17 [1.05–1.30], P = 3.1×10^{-3}). These analyses successfully pinpointed the target individuals who would be expected to benefit most from the modification of obesity.

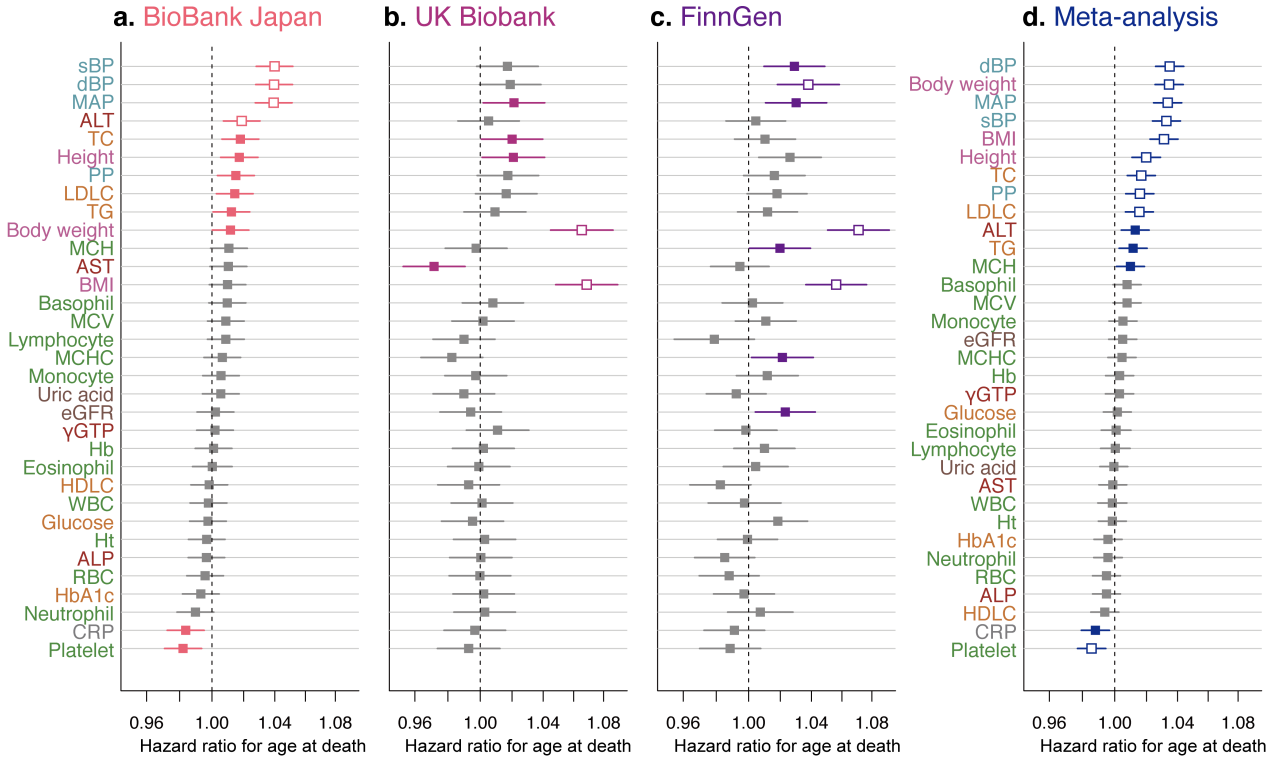
There were several additional traits where the PRSs showed significant associations with lifespan in trans-ethnic meta-analysis after the Bonferroni correction for multiple testing (P_{meta} < $1.5\text{x}10^{-3}$; i.e., lipid-related traits, height, and platelet count). The genetic burden of increased lipid-related traits (i.e. total cholesterol and LDL cholesterol) was associated with a shorter lifespan, which was concordant with the observational studies reporting the causal roles of cholesterol in worse health outcomes[27]. Height has been indicated as a risk factor for various cancers and linked with cancer-related mortality in both Europeans and Asians[15,16]. A lower platelet count was also reported as associated with an increased mortality in Europeans[28].

To test whether there existed differences in the effect sizes of PRS on lifespan between males and females, we performed a sex-stratified association study of PRSs with lifespan across the investigated traits and across the three cohorts. While we did not find any significant differences between sexes within each of the three cohorts (**Supplementary Figure 4a–c**), the sex-stratified trans-ethnic meta-analysis revealed that the effect of high

dBP PRS on a short lifespan, which was the largest among 33 traits in primary meta-analysis, was significantly larger in males than in females (HR_{male} = 1.05 [1.04-1.06], HR_{female}= 1.02 [1.00-1.03], $P_{heterogeneity}$ = 0.0013; **Supplementary Figure 4d**). This observation was in line with previous epidemiological studies showing that the excess mortality caused by hypertension was higher for men than for women in the Japanese population[29], and that women with hypertension not complicated by left ventricular hypertrophy had lower risk of clinical major cardiovascular events than men in Europeans[30].

Finally, in order to validate our findings, we conducted a trans-ethnic Mendelian randomization (MR) study of the 33 traits on which we had performed the trans-ethnic PRS-lifespan association study (see **Methods**). Two-sample MR with the inverse-variance weighted method revealed the following; (i) the significant causal effect of sBP and mean arterial blood pressure (MAP) on lifespan in BioBank Japan; (ii) the significant causal effect of BMI and BW on lifespan in UK Biobank and FinnGen; and (iii) that trans-ethnic meta-analysis further strengthened their significance (i.e. BMI, BW, sBP, and MAP; β_{causal} = 0.17, 0.17, 0.15, 0.15; and P_{meta} = 1.6×10^{-11}, 9.6×10^{-11}, 1.6×10^{-4}, 8.2×10^{-4} respectively; summary results shown in **Supplementary Figure 5**). While both methods (PRS and MR study) have their own limitations, such as pleiotropy and assumptions on instrumental variables[31,32], we consider that the consistent result from these two methods would complement each other and further support the robustness of our findings in identifying the driver biomarkers of human lifespan.

To summarize, these results collectively suggest the utility of PRSs in genetics-driven identification of both known and novel drivers for longevity, and could potentially pinpoint a group of individuals who could most likely benefit from the intervention.



Category	Trait name
Anthropometric	Height
	Body weight (BW)
	Body mass index (BMI)
Blood Pressure	Systolic blood pressure (sBP)
	Diastolic blood pressure (dBP)
	Mean arterial blood pressure (MAP)
	Pulse pressure (PP)
Kidney-related	eGFR
	Uric acid

Category	Trait name
Metabolic	Total cholesterol (TC)
	Triglyceride (TG)
	HDL cholesterol (HDLC)
	LDL cholesterol (LDLC)
	Glucose
	HbA1c
Other biochemical	C-reactive protein (CRP)
Liver-related	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Alkaline phosphatase (ALP)
	γ-glutamyl transpeptidase (γGTP)

Category	Trait name
Hematological	Red blood cell (RBC)
	Hemoglobin (Hb)
	Hematocrit (Ht)
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
	White blood cell (WBC)
	Neutrophil
	Eosinophil
	Basophil
	Monocyte
	Lymphocyte
	Platelet

Figure 4. Trans-ethnic association study of PRS with lifespan.

Shown are the adjusted HRs from Cox proportional-hazard models for lifespan, according to the PRS of the clinical phenotypes in **(a)** BioBank Japan, **(b)** UK Biobank and **(c)** FinnGen. The threshold of significance for the derivation of PRS was set $P = 1.0\times10^{-6}$. We further performed a trans-ethnic fixed-effect meta-analysis of the association results from the three cohorts **(d)** by the inverse-variance method. The boxes indicate the point estimates, and the horizontal bars indicate the 95% confidence interval. Boxes in colors indicate the nominal significance ($P < 0.05$) and the white-out boxes indicate the statistical significance after the Bonferroni correction for multiple testing ($P < 1.5\text{x}10^{-3}$).

381 ***No evidence of an interaction effect of PRSs of complex traits and lifestyle factors on***
382 ***lifespan***

383 Motivated by the identification of biomarkers genetically affecting lifespan, we finally
384 investigated whether there existed any interaction between the PRS of these biomarkers and
385 various lifestyles. As blood pressure PRSs were most strongly associated with lifespan in the
386 Japanese population, we tested the interaction effect between sBP PRS and lifestyle on
387 lifespan in BioBank Japan (**Supplementary Table 11**). While various lifestyle factors had a
388 strong impact on lifespan (**Supplementary Table 12**), none of them showed significantly
389 heterogeneous effects on survival according to the sBP PRS status. For example, the
390 beneficial effect of smoking cessation on survival was not significantly different among those
391 with the highest risk of increased blood pressure (Δ10-year mortality = -0.050) or those with
392 the lowest risk of increased blood pressure (Δ10-year mortality = -0.049, interaction $P = 0.63$)
393 inBioBank Japan. In Europeans, as we found the strongest association between the obesity
394 PRS and lifespan, we investigated the interaction between BMI PRS and lifestyle in UK
395 Biobank. Again, no significant interaction effect on lifespan was observed ($P_{interaction} > 0.05$).

396 Taken together, even people with the high genetic burden of increased blood pressure or
397 obesity could benefit from the modifiable lifestyles such as abstinence from smoking and
398 regular exercise, which could lead to a better survival.
399

Discussion

Harnessing a global effort to expand genetic studies in both sample size and the scope of phenotypes, with the additional notion of the importance of population diversity[5], PRS is expected to identify individuals with inborn health risks in clinics. While early detection and appropriate health communication should contribute to the improvement of health care[33], the inherited genetic risks of disease onset cannot be modified.

We here showed the novel value of PRS study to identify the monitorable phenotypes that genetically affect health outcomes. Our approach has the potential to contribute to the improvement of healthcare because the identified factors can be modified by medical intervention. We showed a global burden of increased blood pressure and obesity as drivers of mortality from genetics. Our study also revealed that those with a genetic burden to cause high blood pressure or obesity could benefit from healthy lifestyles to the same degree as those without. If those with high-risk alleles are to be notified about their own risks, the early lifestyle modification and medical attention should prevent their premature death. Of note, the magnitude of the effect size in which the PRS of the trait was associated with lifespan was relatively small. However, the magnitude of effect size in which the trait itself (e.g., blood pressure or obesity) affects lifespan, or in which the modification of the trait (e.g., proper blood pressure management or healthy diet) would improve health outcomes, would be expected to be larger in terms of population health.

In order to improve population health, we need to decide on how to prioritize the numerous health issues. The observational studies could partly address this point, but the biggest challenge has been that we cannot infer the cause-and-effect direction. While RCTs have been the gold standard to provide robust evidence of the effect of risk factors on health

423 outcomes, they are not always feasible because conducting RCTs (i.e. recruitment, random
424 allocation, treatment, and follow-up etc.) takes a huge amount of resources, which hampers
425 the application to diverse phenotypes. Our approach, which leverages genetic and
426 phenotypic information already existing in biobanks, would have the potential to support the
427 clinical evidence, or to identify candidate risk factors to bring into RCTs. We also note that
428 in-depth analyses, such as those leveraging cause-specific mortality and comorbidity data,
429 could pinpoint target individuals who could most likely benefit from medical attention and
430 intervention. These insights would also be useful in designing efficient RCTs or providing
431 individualized medical evidence.

432 Notably, the genetics-driven identification of critical factors for health outcomes was made
433 possible by trans-ethnic, large-scale, and deep-phenotyped biobanks. The trans-biobank
434 collaboration provided (i) a large sample size, which was critical in analyzing mortality data,
435 (ii) the opportunity for replication, which made our findings robust to cohort-specific
436 confounders, (iii) a trans-ethnic comparison as in the example of obesity, (iv) the validation
437 of our methodology (i.e., we confirmed the coherent result between LOGO and independent
438 GWAS), and (v) the integration of cohort-specific data, such as parental lifespan data in UK
439 Biobank. Nation-wide biobanks, such as those in this study, are prospectively collecting
440 deep phenotype and health outcomes of genotyped individuals, and our proof-of-concept
441 approach would be expected to discover the actionable traits driving health outcomes on a
442 global scale if further applied to diverse and larger populations.

443 This study has potential limitations. First, as BioBank Japan is a hospital-based cohort, it
444 does not represent the Japanese population as a whole. However, since we performed the
445 survival analyses with an adjustment for the disease status and principal components

446 followed by sensitivity analyses, our main result was not confounded by the proportion of
447 patients with a specific disease group (**Supplementary Figure 6**) or population stratification.
448 Of note, UK Biobank generally enrolls healthy-volunteers[34]. The directional concordance of
449 statistics in BioBank Japan with those in UK Biobank should further support the robustness
450 of the results and mitigates the concern on potential biases due to the differences in genetic
451 structure and environmental interactions. Second, it is unclear whether the PRSs of the traits
452 that showed less significant results in our study were not associated with lifespan because
453 there is truly no relationship, because the PRS did not sufficiently explain the variance of the
454 investigated phenotype, or because there was a strong effect of rare variants, which were
455 not captured in our study. Third, the polygenic effect of the variants constituting the PRSs
456 which also partially affect other traits (pleiotropy), might have coexisted with the association
457 of the PRS of a specific trait with lifespan. Further integration with novel statistical methods
458 to handle and disentangle pleiotropy and desirably RCTs, if feasible, are warranted to obtain
459 clearer insights into the true effect of the complex trait on human lifespan. Fourth, there is
460 currently no consensus on how to optimize and harmonize the *P* value threshold in calculating
461 PRSs across different cohorts. Our strategy was to set a fixed *P* value threshold of 1×10^{-6} in
462 the trans-ethnic meta-analysis, because we could not obtain trait-specific best *P* values for
463 every trait which should be optimized to maximize the variance explained by using individual-
464 level phenotype data. We confirmed that association statistics (i.e. coefficients) from the fixed
465 threshold of 1×10^{-6} was fairly concordant with those from best *P* values (Pearson's $r = 0.85$
466 and $P = 2.5\times10^{-13}$ in BioBank Japan, and $r = 0.93$ and $P = 1.3\times10^{-9}$ in UK Biobank).
467 Nevertheless, we consider that further implementation of the methodology for optimally
468 harmonizing PRSs across different cohorts is still warranted. Fifth, it is possible that spouse-

pairs in biobanks might have caused a subtle bias the GWAS and PRSs-lifespan association if assortative mating exists[35]. Sixth, although we exhaustively checked the cohort-level overlap across biobanks and previous GWASs used in this study, we could not completely exclude the possibility of individual-level overlap, which would be technically difficult to detect as a general point in large-scale genetic studies. Last, the statistical power in the association study with lifespan was limited, partly due to a relatively short follow-up period. This was particularly the case in UK Biobank, which is a recently launched population-based cohort, and only a small number of people have died during the follow-up period. We complemented this point by utilizing parental lifespan data in UK Biobank as a secondary analysis. Since the participants of the biobanks in this study are ongoingly followed-up, the larger number of mortality records in the future would provide us with an opportunity to further validate the robustness of our results.

In conclusion, through trans-ethnic biobank collaboration, we demonstrated that blood pressure and obesity were genetically associated with the lifespan of the current generation on a global scale. A comparison across different populations and the integration with deep phenotype data further pinpointed a group of individuals who would be expected to benefit most from the intervention of these traits. With global biobanks' ongoing efforts—enrolling individuals from diverse background and collecting granular phenotype along with health outcomes—we have shown a potential application of genetics to improve population health by providing information of common and modifiable risk factors driving our health outcomes.

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Author Contributions

S.S., Y.K., and Y.O. conceived the study. M.H., M. Kubo, K.M., Y.M. collected and managed the BioBank Japan samples. S.S., M. Kanai, M.A., N.M., A.T., M. Kubo., Y.K. and Y.O. performed data cleaning and statistical analysis on Biobank Japan. M. Kanai performed statistical analysis on UK Biobank. J.K., M. Kurki and M. Kanai performed data cleaning and statistical analysis on FinnGen. M. J. D. contributed to the overall study design and the FinnGen analysis. Y.O. supervised the study. S.S., M. Kanai, J.K., Y.K., and Y.O wrote the manuscript.

Competing Financial Interests

The authors declare that no conflicts of interest exist.

Methods

Study Populations, genotyping and imputation

BioBank Japan

Clinical information and genotype data were obtained from BioBank Japan (BBJ) project[10,12], which is a prospective biobank that collaboratively collected DNA and serum samples from 12 medical institutions in Japan and recruited approximately 200,000 participants, mainly of Japanese ancestry, with the diagnosis of at least one of 47 diseases. All the participants provided written informed consent approved from ethics committees of RIKEN Center for Integrative Medical Sciences, and the Institute of Medical Sciences, the University of Tokyo. Detailed participant information is summarized in **Supplementary Table 1a**.

We genotyped participants with the Illumina HumanOmniExpressExome BeadChip or a combination of the Illumina HumanOmniExpress and HumanExome BeadChips. The quality control (QC) of participants and genotypes was described elsewhere[36]. In this project, we analyzed 179,066 participants of Japanese ancestry as determined by the principal component analysis (PCA)-based sample selection criteria. The genotype data was further imputed with 1000 Genomes Project Phase 3 version 5 genotype (n = 2,504) and Japanese whole-genome sequencing data (n = 1,037)[36] using Minimac3 software. After the imputation, we excluded variants with an imputation quality of Rsq < 0.7 or those with a minor allele frequency (MAF) < 1%.

UK Biobank

The UK Biobank project is a population-based prospective cohort that recruited approximately 500,000 people aged between 40–69 years from 2006 to 2010 from across

the United Kingdom (summary in **Supplementary Table 1b**; see **URLs**). Deep phenotype data, such as electronic medical records, lifestyle indicators and bioassays, and genotype data were available for most of the participants. The genotyping was performed using either the Applied Biosystems UK BiLEVE Axiom Array or the Applied Biosystems UK Biobank Axiom Array. The genotypes were further imputed using a combination of the Haplotype Reference Consortium, UK10K, and 1000 Genomes Phase 3 reference panels by IMPUTE4 software. The detailed characteristics of the cohort were previously extensively described[34].

In this project, we analyzed 361,194 individuals of white British genetic ancestry as determined by the PCA-based sample selection criteria (see **URLs**). We excluded the variants with (i) INFO score ≤ 0.8, (ii) MAF ≤ 0.0001 (except for missense and protein-truncating variants annotated by VEP[37], which were excluded if MAF ≤ 1×10^{-6}), and (iii) HWE $P \leq 1 \times 10^{-10}$. All of the analyses were conducted via application 31063.

FinnGen

FinnGen is a public-private partnership project combining genotype data from Finnish biobanks and digital health record data from Finnish health registries (see **URLs**). Six regional and three country-wide Finnish biobanks participate in FinnGen. Additionally, data from previously established population and disease-based cohorts are utilized. Participants' health outcomes are followed up by linking to the national health registries (1969–2016), which collect information from birth to death. We used the genotype and phenotype data of 135,638 participants in this study, excluding population outliers via PCA (summary in **Supplementary Table 1c**). These individuals were genotyped with the FinnGen1 ThermoFisher array and previous cohorts were genotyped with various genotyping arrays.

555 The genotype data was imputed using whole genome sequencing data from 3,775 Finnish
556 individuals by beagle4.1 software (see **URLs**)[38]. After the imputation, we excluded variants
557 with an imputation INFO score < 0.8 or MAF < 0.0001.
558
559
560 ***Survival analysis of clinical phenotypes***
561 We used Cox proportional hazard models to test the association of clinical phenotypes with
562 lifespan (age at death) in BioBank Japan as described elsewhere[39]. In order to obtain and
563 compare the HRs for the all-cause mortality across the traits, we scaled each trait to have
564 zero mean and unit variance by Z-score transformation. The primary analyses included
565 adjustment for sex, the 47-disease status and the top 20 principal components, which were
566 supposed to account for possible confounders and population stratification. Additional
567 summaries of clinical phenotypes and the number of samples without missing values are
568 described in **Supplementary Table 3**. We next performed the same survival analyses in 20
569 clinical phenotypes where individual-level phenotype data was available in UK Biobank
570 (**Supplementary Table 7**). We used Cox proportional-hazard models to test the association
571 of these clinical phenotypes with lifespan (age at death) with an adjustment for sex and the
572 top 20 principal components as covariates.
573
574
575 ***Genome-wide association studies***
576 *BioBank Japan*

In order to derive population-specific PRSs of BioBank Japan, we first split the cohort into ten sub-groups. We then conducted GWASs for 45 quantitative traits within each of the ten sub-groups. We performed the linear regression assuming the additive effect of the imputed dosage of each variant by PLINK[40]. For individuals taking anti-hypertensive medications, we added 15 mmHg to their sBP and 10 mmHg to their dBP and derived their MAP and pulse pressure (PP) using the adjusted sBP and dBP. We also added smoking status as a covariate for blood pressure-related traits. Other trait-specific covariates, adjustment for medications, and sample exclusion criteria are described in **Supplementary Table 13** and elsewhere[41]. We next meta-analyzed the statistics from nine sub-groups by the inverse-variance method assuming the fixed-effect ten times, with keeping one sub-group away from the meta-analysis for PRS derivation and validation each time (a 10-fold leave-one-group-out [LOGO] meta-analysis approach). Before performing LOGO, we excluded genetically related individuals from the cohort, based on PI_HAT > 0.125, as calculated by PLINK software. We note that we adopted this strategy to obtain precise estimates of the HR, not to maximize R^2 value, which will be maximized when we have the largest GWAS samples. We applied LD Score Regression (LDSC)[42] to the meta-analyzed summary statistics to estimate the heritability and potential population stratification. We also performed cross-trait LDSC[43] to compare the statistics from the LOGO GWAS (meta-analysis of 9 subgroup GWASs) and those from the conventional GWAS (using all the individuals in the cohort). The summary results of the GWASs are described in **Supplementary Table 4**.

UK Biobank

We applied the ten-fold LOGO approach to 20 clinical phenotypes for which individual-level phenotype data in UK Biobank was available (**Supplementary Table 7**). We performed GWASs using the linear regression model in Hail v0.2 (see **URLs**) with covariates including age, age^2, sex, and the top 20 principal components. For blood pressure traits, we added 15 mmHg and 10 mmHg to sBP or dBP, respectively, if individuals are taking anti-hypertensive medication and derived the MAP and PP using the adjusted sBP and dBP. We also added smoking status as a covariate for blood pressure-related traits. We again performed cross-trait LDSC[43] to compare the statistics from the LOGO GWAS and those from the conventional GWAS, for which we used summary statistics from Dr. Benjamin Neale's lab (see **URLs**). The summary results of the meta-analyzed GWASs are described in **Supplementary Table 8**. For the additional 13 traits among the remainder of the 25 traits investigated in BioBank Japan, we were able to collect independent large-scale GWAS summary statistics of European ancestry, either from publicly available websites or upon request to the authors. The information of these 13 GWASs is described in **Supplementary Table 6**.

FinnGen

We did not perform within-cohort GWASs for the FinnGen cohort because the availability of individual-level phenotype data was limited. For the 20 traits where we performed LOGO in UK Biobank, we referred to UK Biobank GWAS summary statistics from all 361,194 white British individuals. With the exception of C-reactive protein (CRP), for 12 traits among the 13 traits where we used independent GWAS summary statistics in UK Biobank, we utilized the same GWAS summary statistics, as we confirmed that there was no apparent cohort overlap with FinnGen (**Supplementary Table 6)**. For CRP, since the GWAS of Ligthart et al. included

622 the FINRISK Study, which was also involved in FinnGen, we additionally performed GWAS
623 in UK Biobank individuals (*n* = 353,466). When performing CRP GWAS in UK Biobank, we
624 excluded the individuals with autoimmune or inflammatory diseases.
625
626
627 ***Construction of Polygenic Risk Scores***
628 *BioBank Japan*
629 By referring to the effect sizes and *P* values of ten summary results from meta-analyzed
630 GWASs of nine sub-group GWASs, we derived the PRSs of individuals in the one withheld
631 sub-group using a clumping and thresholding method. First, we performed LD clumping on
632 the meta-analyzed GWAS summary statistics with PLINK software using 5,000 randomly
633 selected BioBank Japan participants as the LD reference. Briefly, we first used PLINK to
634 clump all the variants using the following flags: --clump-p1 1 --clump-p2 1 --clump-r2 0.1 --
635 clump-kb 1000. We then computed PRSs for variants meeting the following *P* value
636 thresholds: 5×10^{-8}, 5×10^{-7}, 1×10^{-6}, 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 5×10^{-2}, 0.1, 0.2, 0.5, and 1. In the
637 one withheld sub-group, we derived PRSs by multiplying the dosage of risk alleles for each
638 variant by the effect size in the GWAS and summing the scores across all the selected
639 variants. We quantified the trait variance explained by the derived PRSs in individuals within
640 the withheld sub-group, by calculating the adjusted R^2 attributable to the PRSs from nested
641 models, in which the full linear model was the trait value ~ PRS + all covariates and the
642 nested model dropped only the PRS term (**Supplementary Table 5**).
643
644 *UK Biobank and FinnGen*

For the clinical phenotypes for which the individual clinical data was available (20 traits in UK Biobank), we derived the PRSs in the same manner as described above for BioBank Japan (the ten-fold LOGO approach and deriving the PRSs in the one withheld group using the weights from the meta-analyzed summary statistics of nine sub-group GWASs by a clumping and thresholding approach). The variance explained by the derived PRSs is described in **Supplementary Table 10**. For the remaining 13 traits, we used a clumping and thresholding method on the collected large-scale GWAS summary statistics. Then, we derived the PRSs in the entire cohort referring to the weights and selected variants from the clumping and thresholding results. As noted above, we basically followed the original QC policy that had been adopted within each of the cohorts, and thus PRSs of UK Biobank and FinnGen could have included the rarer variants when compared with those of BioBank Japan (MAF > 0.0001 vs. MAF ≥ 0.01). We confirmed that both the performance of the PRSs and the result of downstream analyses did not substantially change, even when we restricted the variants used for calculating the PRSs to those with MAF ≥ 0.01 (i.e. the correlation *r* of these statistics exceeded 0.97) in UK Biobank and FinnGen.

Survival Analysis using PRSs

BioBank Japan

We used Cox proportional-hazard models to test the association of the derived PRSs of clinical phenotypes with the length of lifespan (age at death) in the withheld sub-group. For the within-BioBank Japan analysis, we selected PRSs from the *P* value threshold of the best predictive capacity that had the largest variance explained by the PRS. We note that the

668 threshold selection was based on the predictive capacity of the trait under investigation and
669 not based on the result of the association of PRSs with lifespan. For the trans-biobank
670 analysis, since there were no individual-level data available for some of the traits, optimization
671 of the *P* value thresholds for all the traits was technically challenging. We thus selected PRSs
672 from the *P* value threshold of 1.0×10^{-6}, which was supposed to account for the polygenic
673 architecture of complex traits while avoiding potential biases in PRS predictions induced by
674 the large number of non-significant variants[44]. The PRSs for each trait in each sub-group
675 were scaled to have zero mean and unit variance by Z-score transformation so as to obtain
676 and compare the effect sizes across the investigated phenotypes. We used Cox proportional-
677 hazard models to test the association of the scaled PRS of each trait in each sub-group with
678 lifespan, with adjustment for sex, the 47-disease status and the top 20 principal components.
679 We performed Schoenfeld residual tests[45] to examine the proportional hazards assumption
680 for the Cox regression. No apparent correlation between the Schoenfeld residuals and time
681 was statistically and visually confirmed. We further meta-analyzed the association statistics
682 from each of the ten sub-groups by the inverse variance method. A sex-stratified association
683 study (**Supplementary Figure 4a**) was conducted by using the same Cox proportional-
684 hazard models within male and female participants, except that we excluded sex from
685 covariates.

686 To describe a standardized survival curve, we compared HRs for participants at the
687 highest genetic risk (fifth quintile of PRSs) with those at an intermediate risk (quintiles 2 to 4)
688 or the lowest risk (first quintile) as described previously[46], which were standardized to the
689 mean of all the covariates (**Supplementary Figure 7**). For the PRS of systolic blood pressure
690 (sBP), we also analyzed the interaction effects with lifestyle factors recorded in the cohort.

691 The lifestyle factors were obtained from the questionnaire to the participants, which asked
692 them about their usual frequency of consumption or exercise of an investigated trait by
693 selecting one from four categorical values. The answered values were converted to the
694 quantitative values so that they represented the mean value of each category, except for the
695 two binary lifestyle traits (whether the participant has ever smoked cigarettes and whether
696 the participant currently drinks alcohol) (**Supplementary Table 12**). All the survival analyses
697 were performed using the survival package in R software, version 3.3.0 (see **URLs**).
698
699 *UK Biobank and FinnGen*
700 For the quantitative traits where the individual level-data was available (20 traits in UK
701 Biobank), we performed the same 10-fold survival analyses followed by meta-analysis as
702 explained above in BioBank Japan. For the remaining traits, we performed the survival
703 analyses on the entire cohort to test the association of the public GWAS-based PRS of each
704 trait with lifespan. As described above, we adopted the *P* value threshold of 1×10^{-6} for the
705 derivation of PRSs for the cross-biobank comparison. We included the same covariates used
706 in the GWASs for each cohort, except for age and age^2, in the Cox proportional hazard
707 models. A sex-stratified association study (**Supplementary Figure 4b** and **c**) was conducted
708 by using the same Cox proportional-hazard models within male and female participants,
709 except that we excluded sex from the covariates.
710 As a secondary analysis, we performed a replication study of the association of sBP PRS
711 on lifespan by using parental lifespan data in UK Biobank to validate the result of primary
712 analysis with larger statistical power. To perform an association test of individuals' genotype
713 with their father's and mother's survival, we separately calculated Martingale residuals of

the Cox model under a null model, scaled up to give a residual trait with a 1:1 correspondence with the HR, and tested its association with genotype dosage as described previously[47].

For the PRS of BMI, we also analyzed the interaction effects with lifestyle factors recorded in UK Biobank. We collected the individual-level data of smoking status (ever smoked and smoking cessation), alcohol intake, coffee intake, and regular physical activity, and tested the effect of the interaction term between the BMI PRS and each of the lifestyle factors on lifespan.

We finally performed a fixed-effect meta-analysis of the PRS-lifespan association studies from BioBank Japan, UK Biobank, and FinnGen, by inverse variance method. To estimate the years of life gained or lost from PRS-lifespan associations, we converted the effect size from the Cox proportional hazard models into the years gained based on the following equation as described preciously[39,47];

$$\text{Years gained} = 10 \times \{-log_e(cox\ hazard\ ratio)\}$$

The association results of the trans-ethnic PRS meta-analysis including the years of life gained/lost are described them in **Supplementary Table 9**.

Trans-ethnic Mendelian Randomization study

We conducted two-sample Mendelian randomization (MR) study to see the effect of each of 33 biomarkers on the outcome (i.e. lifespan) across three cohorts.

For the traits where we performed LOGO in PRS calculation (i.e. 33 traits in BioBank Japan and 20 traits in UK Biobank), we randomly split the cohort into half, and assigned them to the GWAS group (discovery) and the MR group (validation). For the selection of variants

737 to be used as instrumental variables, we performed GWASs within the GWAS group for these
738 traits with the same covariates described earlier, and selected independent genetic variants
739 with $P_{GWAS} < 1.0\times10^{-6}$ for each trait (lead variants at significant loci at least +- 500 kb distant
740 from each other). We next performed association study of these genetic variants with lifespan
741 within the MR group, by using the same Cox proportional-hazard model described earlier. By
742 using these genetic variants and association estimates, we obtained the effect estimate of
743 the exposure (biomarker) on the outcome (lifespan) by pooling all MR estimates using the
744 fixed-effects inverse-variance weighted method[48].

745 For the traits where we used independent GWAS summary statistics in PRS calculation
746 (i.e. 13 traits in UK Biobank and 33 traits in FinnGen), we selected independent genetic
747 variants with $P_{GWAS} < 1.0\times10^{-6}$ from these statistics. We next performed association study of
748 these genetic variants with lifespan in a whole cohort, by using the same Cox proportional-
749 hazard model. These estimates are used to obtain the MR effect estimate by inverse-variance
750 weighted method.

751 We finally performed the fixed-effect meta-analysis of these effect estimate in MR from
752 each of the three cohorts.

753

754

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872 **URLs**

873 - Mean body mass index trends among adults estimates by country from Global Health
874 Observatory data repository by WHO;
875 http://apps.who.int/gho/data/view.main.BMIMEANADULTCv?lang=en
876 - UK Biobank; http://www.ukbiobank.ac.uk
877 - FinnGen; https://www.finngen.fi
878 - Source code for selecting individuals of white British ancestry;
879 https://github.com/Nealelab/UK_Biobank_GWAS/blob/master/ukb31063_eur_selection.
880 R
881 - Beagle4.1: https://faculty.washington.edu/browning/beagle/b4_1.html
882 - Hail software; https://hail.is
883 - Survival package in R software; https://cran.r-project.org/package=survival
884 - UK Biobank GWAS results from Dr. Benjamin Neale's lab; http://www.nealelab.is/uk-
885 biobank