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

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While polygenic risk scores (PRSs) are poised to be translated into clinical practice through prediction of inborn health risks[1], a strategy to utilize genetics to prioritize modifiable risk factors driving heath outcome is warranted[2]. To this end, we investigated the association of the genetic susceptibility to complex traits with human lifespan in collaboration with three worldwide biobanks (n_{total} = 675,898; BioBank Japan (n = 179,066), UK Biobank (n = 361,194) and FinnGen (n = 135,638)). In contrast to observational studies, in which discerning the cause-and-effect can be difficult, PRSs could help to identify the driver biomarkers affecting human lifespan. A high systolic blood pressure PRS was trans-ethnically associated with a shorter lifespan (hazard ratio = 1.03[1.02–1.04], $P_{meta} = 3.9 \times 10^{-13}$) and parental lifespan (hazard ratio = 1.06[1.06–1.07], $P = 2.0 \times 10^{-86}$). The obesity PRS showed distinct effects on lifespan in Japanese and European individuals ($P_{heterogeneity} = 9.5 \times 10^{-8}$ for BMI). The causal effect of blood pressure and obesity on lifespan was further supported by Mendelian randomization studies. Beyond genotype–phenotype associations, our trans-biobank study offers a new value of PRSs in prioritization of risk factors that could be potential targets of medical treatment to improve population health.

Human disease risk can be explained by the combination of genetic susceptibility, environmental exposure and lifestyle[3]. PRSs have demonstrated the predictive ability to identify those with a higher inherited risk of a disease onset[1]. An increase in statistical power and ethnic diversity in genetic studies—accelerated by nationwide biobanks—have been instrumental in the prediction accuracy[4–7]. Risk stratification based on PRSs is one way to improve population health through targeted prevention. Nevertheless, the genetic risk itself cannot be modified. The identification of risk factors that affect not only disease onset but long-term health outcomes would contribute to population health, because these factors can potentially be modified through medical treatment[8,9].

While observational studies have identified risk factors correlated with health outcomes (for example, low-density lipoprotein (LDL) cholesterol levels and myocardial infarction), the major challenge lies in inferring the cause-and-effect direction. A randomized controlled trial (RCT) is considered as the gold standard to infer the effect of the exposure on the outcome[10]. If a medical treatment to decrease LDL cholesterol leads to a decreased incidence of myocardial infarction, we could estimate that high LDL cholesterol causes myocardial infarction. RCTs, however, require a considerable amount of human and economic resources, and are not always ethically feasible.

To address this, here we utilized biomarker PRSs as an instrument to investigate the driving effect of these biomarkers on human lifespan, a health outcome of extreme importance, since genetic susceptibility is less affected by acquired confounding factors. A series of association studies of biomarker PRSs with lifespan can prioritize risk factors that drive mortality in the current generation. Furthermore, deep phenotype data, such as comorbidities and causes of deaths, can help to identify target individuals who could most benefit from the modification of these risk factors. In this context, we collaborated with three nationwide biobanks (n_{total} = 675,898) to uncover the monitorable and modifiable biomarkers affecting human lifespan across ancestries, on an unprecedented scale and without any clinical intervention.

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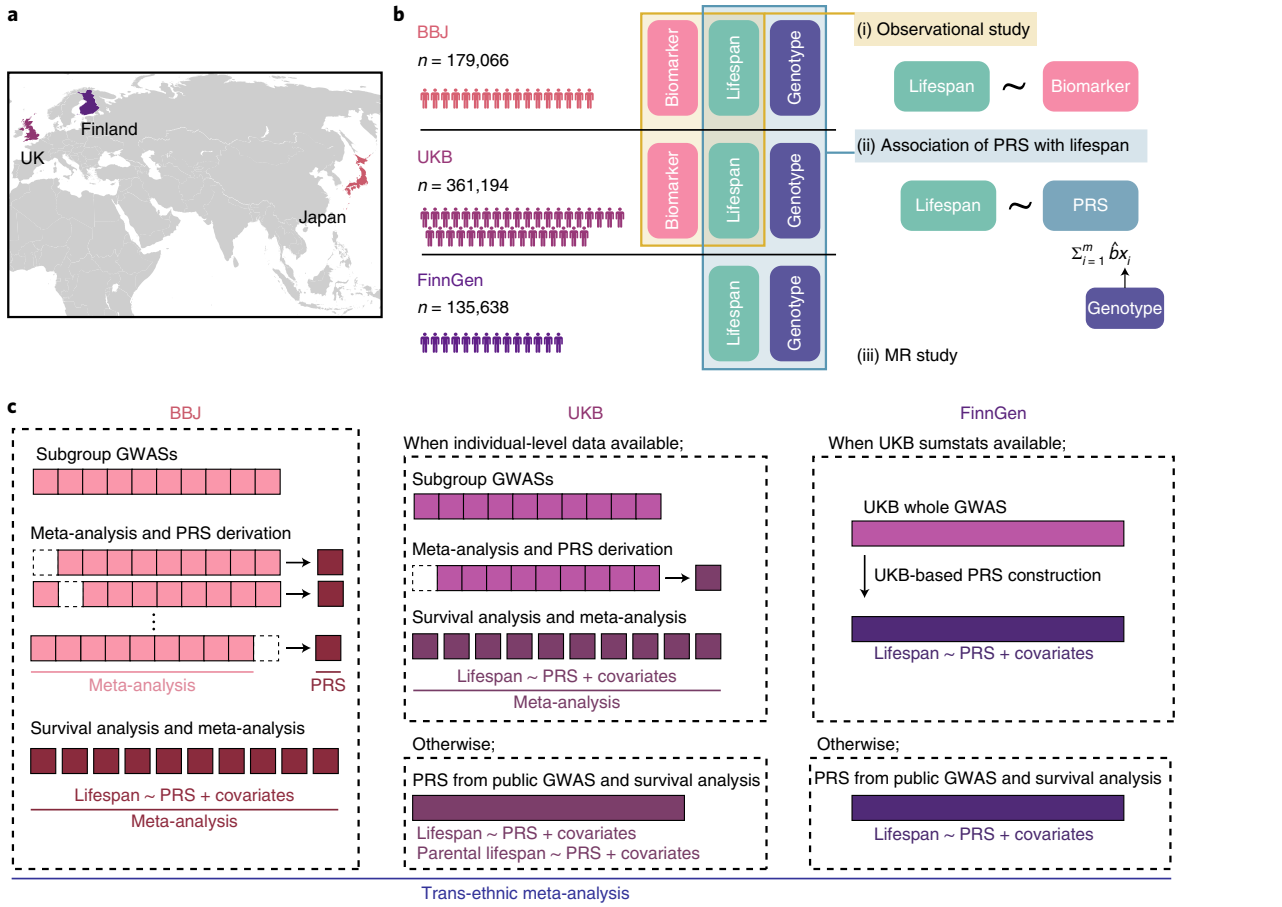
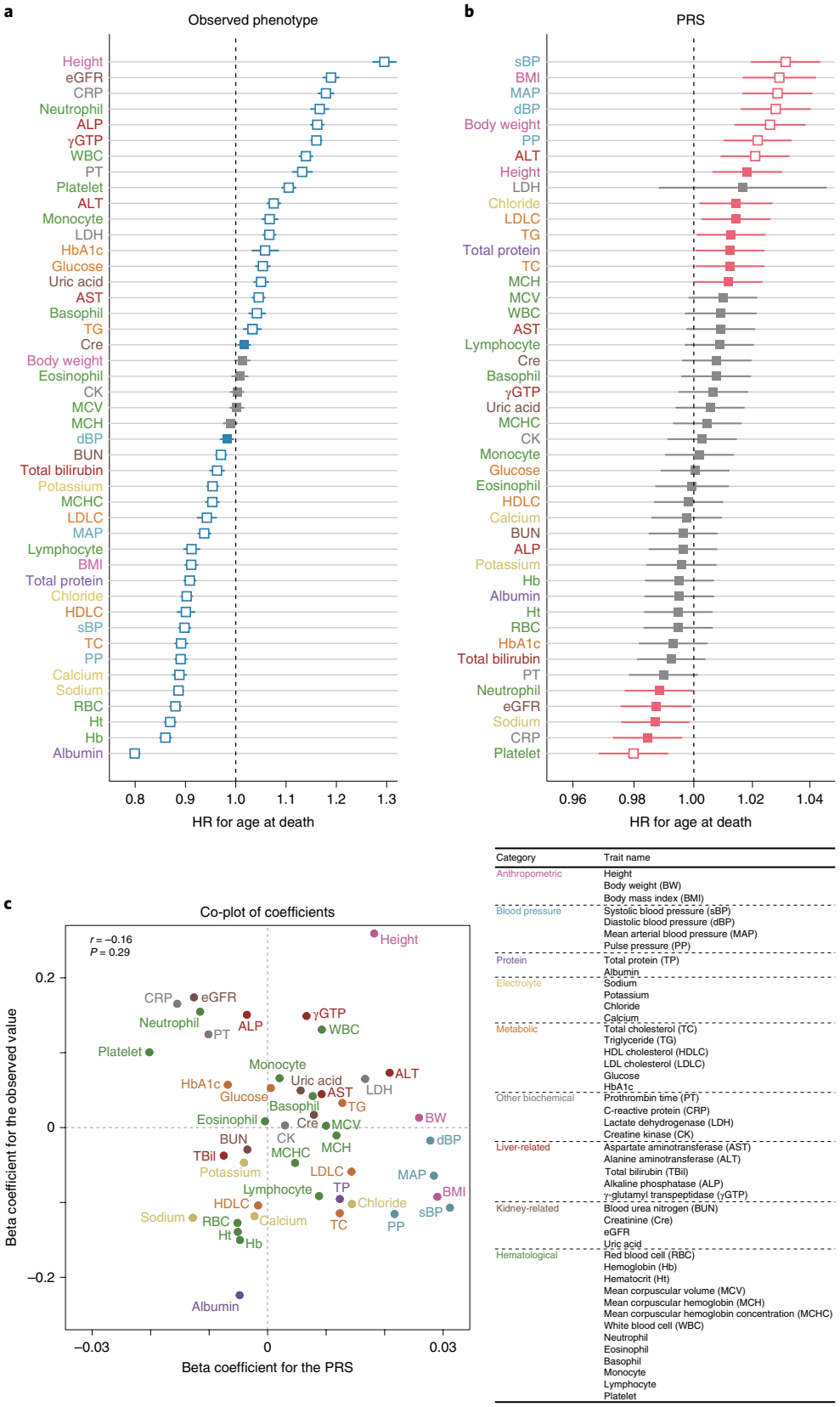


Fig. 1 | An overview of the study design. a, The geographical locations of Japan, the United Kingdom and Finland. **b**, We analyzed the biomarker, lifespan and genotype information in each cohort. We performed (i) an observational study in BBJ and UKB, where we evaluated the association of biomarkers with lifespan, (ii) an association study of biomarker PRSs (that is, genetic susceptibility) with lifespan in BBJ, UKB and FinnGen, and (iii) an MR study to validate the findings in (ii). **c**, The design of the association study of biomarker PRSs with lifespan. In BBJ, we randomly split the entire cohort into ten subgroups and performed GWASs. We then performed a tenfold LOGO meta-analysis, derived the PRSs in one remaining subgroup, and associated them with lifespan. We meta-analyzed the association statistics from the ten subgroups. In UKB, when individual-level phenotype data were available, we adopted the LOGO approach. Otherwise, we derived the PRSs by referring to public GWAS statistics, and associated the biomarker PRSs with lifespan. As a secondary analysis, we associated the PRSs with parental lifespan. In FinnGen, we derived the PRSs from UKB GWAS summary statistics or public large-scale GWAS statistics, and associated the biomarker PRSs with lifespan. Finally, we performed a trans-ethnic meta-analysis of PRS–lifespan associations.

An overview of our study is presented in Fig. 1. We analyzed three nationwide biobanks (BioBank Japan (BBJ), UK Biobank (UKB) and FinnGen; Fig. 1a) to elucidate clinical biomarkers affecting lifespan. The BBJ is a hospital-based cohort consisting of 200,000 participants in Japan, with deep clinical phenotype data[11–13] (Supplementary Table 1a). We analyzed 31,403 deaths during a mean follow-up period of 7.44 yr. The UKB is a population-based cohort consisting of ~500,000 people in the United Kingdom (Supplementary Table 1b)[14]. We analyzed 10,483 deaths during a mean follow-up period of 6.97 yr. FinnGen is a public–private partnership project combining genotype data from Finnish biobanks and health record data from health registries (Supplementary Table 1c). We analyzed 11,058 deaths among 135,638 participants in this study.

We first investigated clinical biomarkers correlated with lifespan in BBJ and UKB as an observational study (Fig. 1b). Next, we performed an association test of the PRSs of these biomarkers with lifespan in BBJ, to elucidate the drivers affecting lifespan. We replicated these associations in UKB and FinnGen, and finally meta-analyzed them across the three cohorts. The method was validated by the Mendelian randomization (MR) study.

To identify biomarkers correlated with lifespan, we associated the measured biomarker values with lifespan (that is, age at death) in BBJ. After the Bonferroni correction for multiple testing, 38/45 biomarkers showed a significant association (Fig. 2a and Supplementary Tables 2a and 3). The top traits associated with a shorter lifespan were low albumin, high γ-glutamyl transpeptidase and increased height (a hazard ratio (HR) of per s.d. increase in mortality = 0.80[0.79–0.81], 1.16[1.15–1.17] and 1.3[1.27–1.32]; $P < 1 \times 10^{-185}$), consistent with previous epidemiological studies[15–18]. To investigate whether these associations are shared between ethnicities, we performed an observational study using 20 biomarkers in UKB (Extended Data Fig. 1). We observed significant associations in 17/20 traits. Of note, 14 among the 15 traits with significant associations in BBJ showed directionally concordant associations in UKB. The only discordant trait was body mass index (BMI). While a lower BMI was associated with a shorter lifespan in BBJ, a higher BMI was associated with a shorter lifespan in UKB. This discordance could be attributed to differences in the recruitment policy (that is, hospital-based in BBJ and healthy volunteers in UKB) or differences in the health burden of obesity between ethnicities. Importantly, these observational studies could



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

Fig. 2 | The HRs for the age at death, according to clinical phenotypes and according to the PRSs and their correlations in BBJ. a,**b**, The adjusted HRs from Cox proportional hazards models for lifespan, according to clinical phenotypes (**a**) and according to the PRSs for the clinical phenotypes (**b**) in BBJ (n = 179,066). The boxes indicate the point estimates, and the horizontal bars indicate the 95% confidence interval. The blue (**a**) and red (**b**) boxes indicate the nominal significance ($P < 0.05$), and the white-filled boxes indicate the statistical significance after correcting for multiple testing by the Bonferroni method. **c**, A co-plot of the coefficients from the Cox proportional hazards models for lifespan according to the PRS (x axis) and those according to measured clinical phenotypes (y axis). Pearson's correlation, r, and the P value between them are also displayed ($n_{trait} = 45$).

not discern whether the variations in biomarkers caused the variations in lifespan.

To prioritize the drivers affecting lifespan, we utilized genetics. The PRS aims to estimate the genetic predisposition towards the investigated trait[3] and thus is less susceptible to the acquired confounders[19,20]. To determine which biomarker drives the survival outcome, we assessed the association of biomarker PRSs with lifespan. In calculating PRSs in BBJ, we adopted a tenfold leave-one-group-out (LOGO) meta-analysis method. Briefly, we split the entire cohort into ten subgroups to perform genome-wide association studies (GWASs), meta-analyzed nine GWASs (Supplementary Table 4) and constructed PRSs using a clumping and thresholding method. We then associated the biomarker PRSs with lifespan in the one withheld subgroup, and the association statistics were further meta-analyzed across the ten subgroups (Fig. 1c). Thus, we maintained the sample size in GWASs at nine-tenths of the entire cohort and validated the PRSs using all of the individuals.

Among the 45 biomarkers, high 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 (Fig. 2b and Supplementary Table 2b). In the sBP, where the PRS showed the strongest association (HR of per s.d. PRS increase in mortality = 1.03[1.02–1.04], $P = 1.4 \times 10^{-7}$), individuals with the highest PRS (the top quintile) had a 1.46-fold higher risk of hypertension when compared with those with the lowest PRS (the bottom quintile; $P = 1.4 \times 10^{-84}$), and were associated with an increased risk of mortality (Fig. 3b, top). The measured sBP showed U-shaped associations, with those with the lowest and the highest sBP both harboring an increased risk of mortality (Fig. 3a, top, and Extended Data Fig. 2). The PRS disentangled the dose-dependent association of the genetic risk of hypertension with a shorter lifespan, while the association of a low measured sBP with high mortality might have been reverse causation[21]. In contrast, although a measured low albumin level showed the strongest association with a shorter lifespan (Fig. 3a bottom), the albumin PRS was not associated with lifespan (HR = 0.99[0.98–1.00], $P = 0.40$, Fig. 3b bottom), implying that a decline in general health might have resulted in both high mortality and decreased albumin values. Overall, there was no correlation between the association coefficients of measured biomarkers with lifespan and those of biomarker PRSs with lifespan ($r = -0.16$, $P = 0.29$; Fig. 2c).

We further investigated the cause-specific mortality that propelled the association with the sBP PRS. Among the four most frequent causes of death in Japan (Methods)[12], a high sBP PRS was significantly associated with death from cardiovascular disease (HR = 1.04[1.01–1.08], $P = 0.0064$) and nominally associated with death from cerebrovascular disease (HR = 1.05[1.01–1.10], $P = 0.024$). A comorbidity-stratified analysis revealed that individuals affected by type 2 diabetes, cerebral infarction or dyslipidemia strongly drove the association of the sBP PRS with lifespan (HR = 1.05[1.03–1.07], 1.06[1.03–1.09] and 1.05[1.02–1.08]; $P = 2.6 \times 10^{-5}$, 1.9×10^{-4} and 4.0×10^{-3}). These results recapitulated epidemiological knowledge that hypertension is one of the strongest risk factors of mortality among patients with cardiovascular[22], cerebrovascular[23,24] and metabolic diseases[25].

We finally investigated the interaction between the genetic susceptibility of hypertension and lifestyle. While various lifestyles had a strong impact on lifespan (Supplementary Table 5), none of them showed a significant interaction with the sBP PRS (Supplementary Table 6). For example, the beneficial effect of smoking cessation on survival was not significantly different among those with the highest PRS (Δ10-year mortality = −0.050) or those with the lowest PRS (Δ10-year mortality = −0.049; $P_{\text{interaction}} = 0.63$).

To replicate these associations in individuals of European ancestry in UKB ($n = 361{,}194$) and FinnGen ($n = 135{,}638$), we constructed biomarker PRSs by the tenfold LOGO meta-analysis approach when the individual-level phenotype was available (20/33 traits in UKB; Supplementary Tables 7 and 8), or otherwise by using independent large-scale GWAS statistics of European ancestry (13/33 traits in UKB and 33 traits in FinnGen; Supplementary Table 9). We then associated the PRSs with lifespan, and finally performed a trans-ethnic meta-analysis across the three biobanks (Supplementary Table 10). In UKB and FinnGen, we confirmed the directional consistency of the association of a high sBP PRS with a shorter lifespan (HR = 1.02[1.00–1.04], $P = 0.083$ in UKB (Fig. 4b); HR = 1.03[1.01–1.05], $P = 0.0031$ in FinnGen (Fig. 4c)). A fixed-effect meta-analysis revealed a trans-ethnically robust effect of the sBP PRS on lifespan (HR = 1.03[1.02–1.04], $P = 3.9 \times 10^{-13}$; Fig. 4d). A secondary analysis using parental lifespan data in UKB, which offered a much larger statistical power, demonstrated that a high sBP PRS was also associated with a shorter parental lifespan (HR = 1.06[1.06–1.07], $P = 2.0 \times 10^{-86}$).

Interestingly, high PRSs of BMI and body weight (BW) were most significantly associated with a shorter lifespan in UKB and FinnGen (BMI: HR = 1.07[1.05–1.09] and 1.06[1.04–1.08]; $P = 1.7 \times 10^{-11}$ and 1.5×10^{-8}), while they showed much smaller effect sizes in BBJ (BMI: HR = 1.01[1.00–1.02], $P = 0.094$, $P_{\text{heterogeneity}} = 9.5 \times 10^{-8}$). A strong effect of obesity on mortality was shared between UKB and FinnGen, despite the different methods used for calculating PRSs (that is, LOGO in UKB and independent GWAS referral in FinnGen). The reason for the trans-ethnic heterogeneity was not attributed to the difference in heritability or the variance explained by PRSs (Supplementary Tables 4, 8, 11 and 12). The measured BMI mean and s.d. were larger in European individuals (mean = 23.3, 27.4 and 27.2; s.d. = 3.7, 4.8 and 4.1 in BBJ, UKB and FinnGen), as shown in World Health Organization data (22.8 [22.5–23.2], 27.5[27.2–27.8] and 26.6[26.1–27.1] in Japan, the United Kingdom and Finland; http://apps.who.int/gho/data/view.main.BMIMEANADULTCv?lang=en). Along with the report that the mortality in obese individuals was higher in European individuals than in East Asian individuals[26], the observed heterogeneous effect might partly explain the ethnic differences in the health burden of obesity between Japanese and European individuals, which warrants further trans-ethnic studies.

To determine what drives the association of the BMI PRS with lifespan in European individuals, we analyzed the cause-specific mortality and comorbidity data in UKB. The BMI PRS was most strongly associated with cerebrovascular death (HR = 1.12[1.08–1.17], $P = 3.1 \times 10^{-8}$). A comorbidity-stratified analysis revealed that the effect of the BMI PRS on mortality was strongest among those with unstable angina (HR = 1.17[1.05–1.30], $P = 3.1 \times 10^{-3}$). These analyses pinpointed the target individuals who would benefit most from the modification of obesity. We also investigated the interaction between the BMI PRS and lifestyle in UKB. Again, no lifestyle factors showed significant interaction ($P_{\text{interaction}} > 0.05$). Taken together with the results of the BBJ studies, this suggests that even people with a high genetic burden of hypertension or obesity could benefit from lifestyle modifications such as smoking cessation and regular exercise.

Trans-ethnic meta-analysis identified additional significant biomarker PRSs after the Bonferroni correction for multiple testing ($P_{\text{meta}} < 1.5 \times 10^{-3}$; that is, total cholesterol, LDL cholesterol, height and platelet count). The genetic burden of increased cholesterol was associated with a shorter lifespan, which supported the observational studies demonstrating the causal roles of cholesterol on worse health outcomes[27]. Increased height was indicated as a risk for cancers and cancer-related mortality[17,18]. A lower platelet count was reported as associated with increased mortality in European individuals[28].

To investigate sex-differentiated effects, we performed a sex-stratified association study of PRSs with lifespan (Extended Data Fig. 3). A sex-stratified trans-ethnic meta-analysis revealed that the

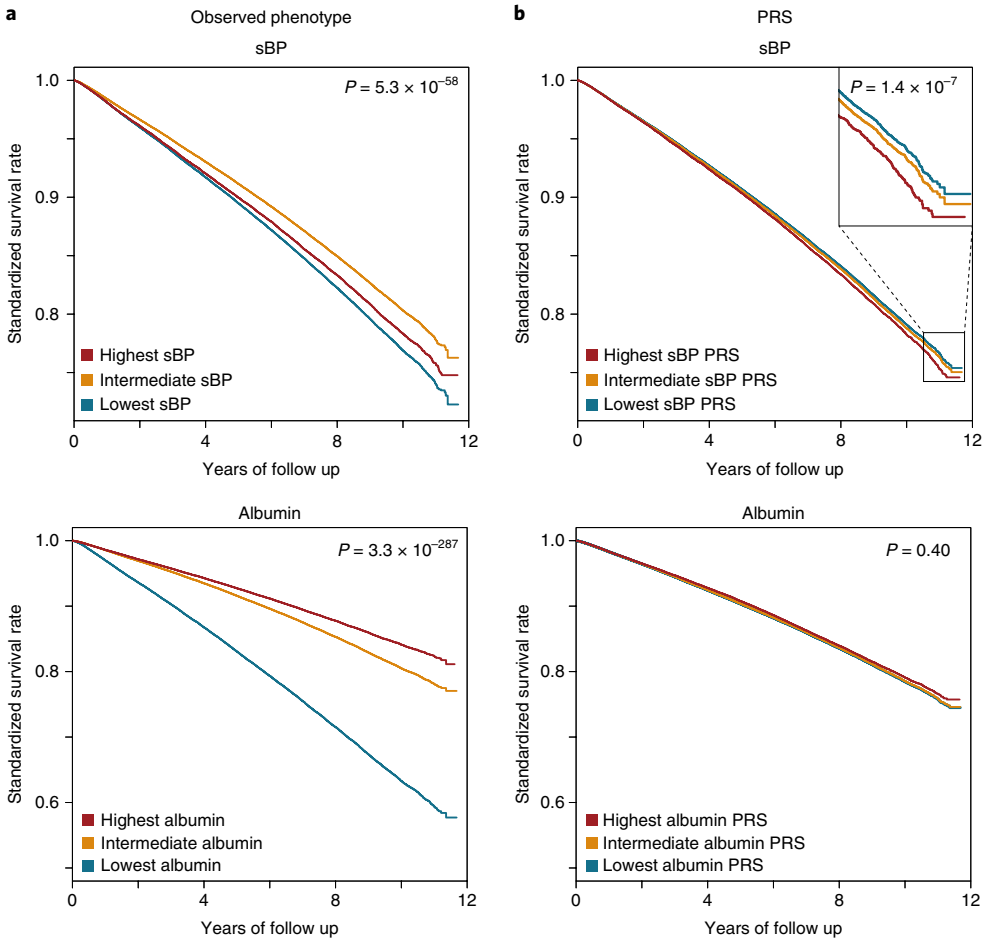


Fig. 3 | The standardized survival rate, according to sBP and albumin, and the PRS status of both traits in BBJ. In each box, the standardized and adjusted survival curves according to three bins (lowest, first quintile; intermediate, 2–4 quintiles; and highest, fifth quintile) of the investigated trait or the PRS of the investigated trait are illustrated by analyzing mortality data in BBJ (n=138,278). The standardization was performed using the mean of all the covariates. The association P values with lifespan from Cox proportional hazards models are also shown. **a**, Survival curves according to a measured sBP value (top) and according to the sBP PRS (bottom). **b**, Survival curves according to a measured serum albumin level (top) and according to the albumin PRS (bottom).

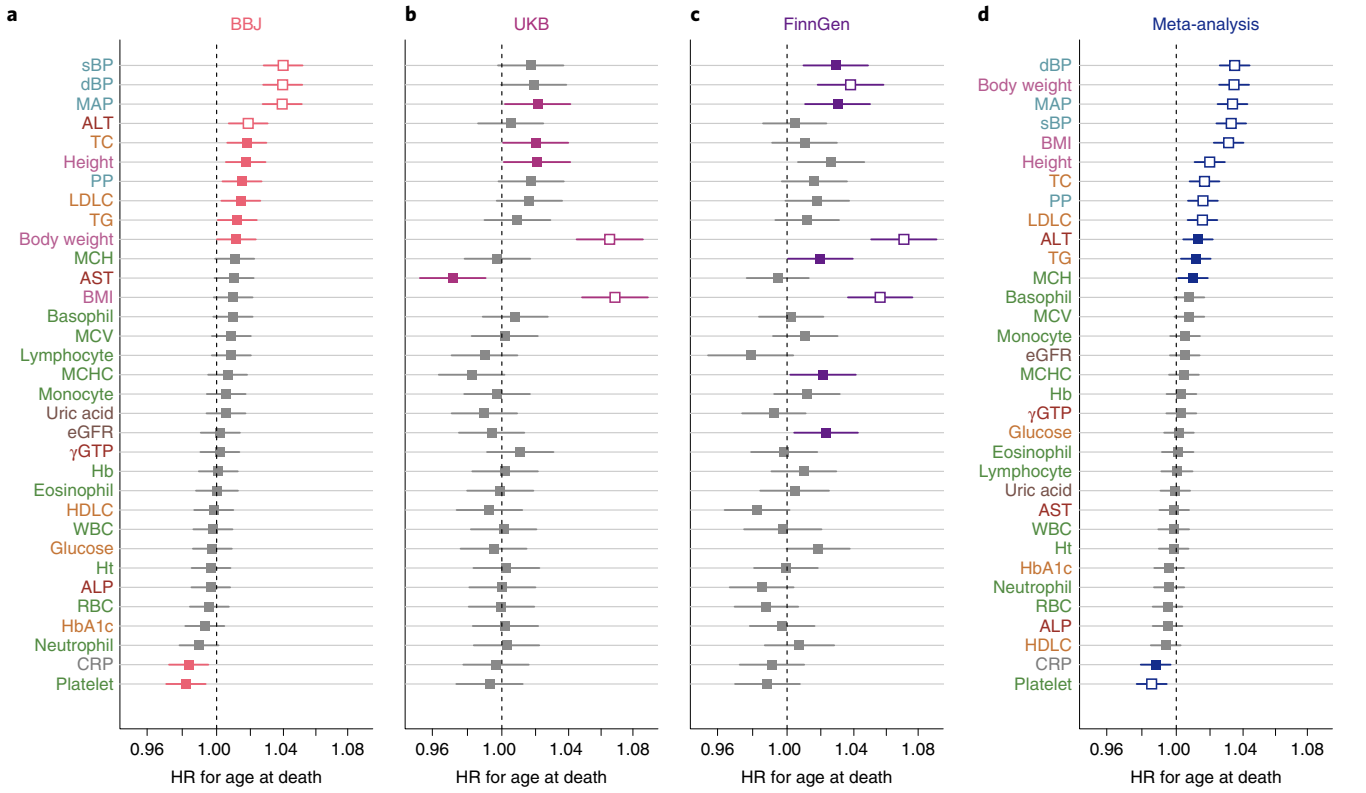
effect of the dBP PRS on lifespan, which was the largest among 33 traits in the primary meta-analysis, was significantly larger in males than in females (HR_{male} = 1.05[1.04–1.06], HR_{female} = 1.02[1.00–1.03], $P_{heterogeneity}$ = 0.0013; Extended Data Fig. 3d). This was in line with epidemiological studies showing that the mortality or cardiovascular events caused by hypertension were higher for males than for females[29,30].

Finally, we conducted a trans-ethnic MR study for validation. Two-sample MR revealed the following: significant causal effects of sBP and MAP on lifespan in BBJ; significant causal effects of BMI and BW on lifespan in UKB and FinnGen; and that a trans-ethnic meta-analysis strengthened their significance (that is, BMI, BW, sBP and MAP; β_{causal} = 0.17, 0.17, 0.15 and 0.15; P_{meta} = 1.6×10^{-11}, 9.6×10^{-11}, 1.6×10^{-4} and 8.2×10^{-4}; Extended Data Fig. 4). Despite the limitations in both methods (PRS and MR), such as pleiotropy and assumptions on instrumental variables[31,32], these consistent results complement each other and support the robustness of our findings in identifying driver biomarkers affecting lifespan.

While we agree that it is time to consider the clinical application of PRSs to accelerate health communication[33] and targeted prevention[34], the inherited genetic risks cannot be modified. Here we showed the novel value of PRSs in identifying modifiable risk factors driving health outcomes, which could be potential targets of medical treatment. We showed a global burden of hypertension and obesity as drivers of mortality. Although the magnitude of effect sizes in the association of PRSs with lifespan was relatively small, the magnitude of effect sizes in which the trait itself (for example, BP or obesity) affects lifespan, or in which the modification of the trait (for example, proper BP management or healthy diet) improves the health outcome, would be expected to be larger in terms of population health.

To improve population health, we need to prioritize the health issues. In observational studies, it is challenging to infer the cause-and-effect direction. While RCTs could provide evidence on causality, they are not always feasible, which hampers their application to diverse phenotypes. Our approach, which leverages genetic and phenotypic data already existing in biobanks, would have the potential to support the clinical evidence, especially when it is controversial, or to identify candidate risk factors to bring into RCTs. Further, in-depth analyses on cause-specific mortality and comorbidities pinpointed target individuals who could most benefit from the modification of the risk factors. These insights would be useful in designing efficient RCTs or providing individualized medical evidence.

Our genetics-driven discovery was made possible by trans-ethnic, large-scale and deep-phenotyped biobanks. The multi-biobank collaboration provided: a trans-ancestry comparison as in the example of obesity; a large sample size, which was critical in



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

Fig. 4 | Trans-ethnic association study of biomarker PRSs with lifespan. a–c, The adjusted HRs from Cox proportional hazards models for lifespan, according to the PRS of the clinical phenotypes in BBJ ($n = 179{,}066$) (**a**), UKB ($n = 361{,}194$) (**b**) and FinnGen ($n = 135{,}638$) (**c**). **d**, We further performed a trans-ethnic fixed-effect meta-analysis of the association results from the three cohorts by the inverse-variance method ($n_{total} = 675{,}898$). The boxes indicate the point estimates, and the horizontal bars indicate the 95% confidence interval. The colored boxes indicate the nominal significance ($P < 0.05$) and the white-filled boxes indicate the statistical significance after the Bonferroni correction for multiple testing ($P < 1.5 \times 10^{-3}$).

analyzing mortality data; the opportunity for replication, which suggested generalizability despite the cohort-specific characteristics; the validation of our methodology; and the integration of cohort-specific data, such as parental lifespan in UKB. Although the variants and their numbers constituting the PRSs were different among the three biobanks (Supplementary Tables 10–12), and only a small fraction was shared or tagged ($r^2 > 0.8$) (Extended Data Fig. 5), we could show consistent associations across the cohorts and ethnicities. Given an ever-expanding amount of data in biobanks, our proof-of-concept approach would discover more actionable traits driving health outcomes on a global scale.

This study has potential limitations. First, the recruitment strategy was different among the biobanks. We confirmed that the results from BBJ, a hospital-based cohort, were not confounded by the proportion of patients with a specific disease group using sensitivity analyses (Extended Data Fig. 6). The coherent results across biobanks further mitigated concerns over potential biases. Second, the small variances explained by PRSs could have caused less significant associations with lifespan. Third, the polygenic effect that partially affects other traits (that is, pleiotropy) might have coexisted with the association of the PRS of a specific trait with lifespan. Fourth, there is currently no consensus on how to harmonize the P threshold in calculating PRSs across cohorts. We set a fixed threshold of 1×10^{-6} in trans-ethnic studies, because we could not always obtain the best P, which should be optimized to maximize the explained variance using individual-level data. We confirmed that association coefficients from the threshold of 1×10^{-6} were concordant with those from the best P (Methods). Last, the statistical power in our study handling lifespan was limited due to a relatively short follow-up period, particularly in UKB, which is a recently launched population-based cohort. We complemented this point by secondarily analyzing parental lifespan in UKB. In the future, a larger number of mortality records with a longer follow-up period would provide us with an opportunity to further validate our results.

In conclusion, through trans-biobank collaboration, we identified hypertension and obesity as drivers affecting lifespan on a global scale. A comparison across different populations and the integration with deep phenotype data pinpointed target

individuals who would be expected to benefit most from the modification of these traits through adherence to a healthy lifestyle or medical treatment. With global biobanks' efforts—enrolling individuals from diverse backgrounds and collecting granular phenotype data along with health outcomes—we have shown a potential application of genetics to improve population health by providing information on modifiable risk factors driving our health outcomes.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-0785-8.

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Methods

Study populations, genotyping and imputation. *BBJ.* Clinical information and genotype data were obtained from the BBJ Project[11,13], 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 a diagnosis of at least 1 of 47 diseases. 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. All of the participants provided written informed consent approved by the ethics committees of the RIKEN Center for Integrative Medical Sciences, and the Institute of Medical Sciences at 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 of participants and genotypes was described elsewhere[35]. 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 were further imputed with 1000 Genomes Project Phase 3 version 5 genotype data ($n=2,504$) and Japanese whole-genome sequencing data ($n=1,037$)[35] 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%.

UKB. The UKB project is a population-based prospective cohort that recruited approximately 500,000 people aged between 40 and 69 yr from 2006 to 2010 from across the United Kingdom (summary in Supplementary Table 1b; http://www.ukbiobank.ac.uk). Deep phenotype data, such as electronic medical records, lifestyle indicators and bioassays, and genotype data were available for most of the participants. The participants are linked to a death registry, which provides the age and cause of death when they die. The genotyping was performed using either the Applied Biosystems UK BiLEVE Axiom Array or the Applied Biosystems UKB 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 extensively described elsewhere[14]. In this project, we analyzed 361,194 individuals of white British genetic ancestry as determined by the PCA-based sample selection criteria (https://github.com/Nealelab/UK_Biobank_GWAS/blob/master/ukb31063_eur_selection.R). We excluded variants with: INFO score ≤ 0.8; MAF ≤ 0.0001 (except for missense and protein-truncating variants annotated by the Variant Effect Predictor[36], which were excluded if MAF ≤ 1×10^{-6}); and Hardy–Weinberg equilibrium P value ≤ 1×10^{-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 (https://www.finngen.fi/en). A list of FinnGen contributors is presented in Supplementary Notes. 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 FinnGen release 3 data in this project, which consists of the genotype and phenotype data of 135,638 participants, excluding population outliers via PCA (summary in Supplementary Table 1c). The death information was retrieved from the national death registry. The study participants were genotyped with the FinnGen1 ThermoFisher array and previous cohorts were genotyped with various genotyping arrays. The genotype data were imputed using whole-genome sequencing data from 3,775 Finnish individuals by beagle4.1 software (https://faculty.washington.edu/browning/beagle/b4_1.html)[37]. After the imputation, we excluded variants with an imputation INFO score < 0.8 or MAF < 0.0001.

Observational study on the association of clinical biomarkers with lifespan. We used Cox proportional hazard models to test the association of clinical phenotypes with lifespan (that is, age at death) in BBJ as described elsewhere[38]. To obtain and compare the HRs across the traits, we scaled each trait to have zero mean and unit variance by Z-score transformation. The primary analyses included adjustment for sex, the 47-disease status and the top 20 principal components, which were supposed to account for possible confounders and population stratification. Additional summaries of clinical phenotypes and the number of samples without missing values are described in Supplementary Table 3. We next performed the same survival analyses in 20 clinical phenotypes, where individual-level phenotype data were available in UKB (Supplementary Table 7). We used Cox proportional hazards models to test the association of these clinical phenotypes with lifespan with an adjustment for sex and the top 20 principal components as covariates.

GWASs. *BBJ.* In BBJ, an independent reference GWAS of East Asian ancestry was not publicly available. Conventionally, when independent GWAS statistics with matched population and sufficient sample size are not available, a strategy to split the cohort into two groups (that is, a discovery group to conduct GWASs and a validation group to derive PRSs) has been used. This strategy either reduces the accuracy of GWAS statistics or lowers the statistical power in PRS validations, depending on how the cohort is split. To address this, we adopted a tenfold LOGO meta-analysis. We first randomly split the entire cohort into ten subgroups. We then conducted GWASs for 45 quantitative traits within each of the 10 subgroups. We performed the linear regression assuming the additive effect of the imputed dosage of each variant by PLINK[39]. 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 using the adjusted sBP and dBP. We also added smoking status as a covariate for BP-related traits. Other trait-specific covariates, adjustment for medications and sample exclusion criteria are described in Supplementary Table 13 and elsewhere[40]. We next meta-analyzed the statistics from nine subgroups by the inverse-variance method assuming the fixed-effect ten times, keeping one subgroup away from the meta-analysis for PRS derivation and validation each time (a tenfold 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 adopted this strategy to obtain precise estimates of the HR, not to maximize the R^2 value, which will be maximized when we have the largest GWAS samples. We applied linkage disequilibrium (LD) score regression (LDSC)[41] to the meta-analyzed summary statistics to estimate the heritability and potential population stratification. We also performed cross-trait LDSC[42] to compare the statistics from the LOGO GWAS (meta-analysis of nine subgroup GWASs) and those from the conventional GWAS (using all individuals in the cohort). The summary results of the GWASs are described in Supplementary Table 4.

UKB. We applied the tenfold LOGO approach to 20 clinical phenotypes for which individual-level phenotype data in UKB were available (Supplementary Table 7). We performed GWASs using the linear regression model in Hail v0.2 (https://hail.is) with covariates including age, age^2, sex and the top 20 principal components. For BP-related traits, we added 15 mmHg and 10 mmHg to sBP and dBP, respectively, if individuals are taking anti-hypertensive medication, and derived the MAP and pulse pressure using the adjusted sBP and dBP. We also added smoking status as a covariate for BP-related traits. We performed cross-trait LDSC[42] to compare the statistics from the LOGO GWAS and those from the whole-cohort GWAS, for which we used summary statistics from B. M. Neale's laboratory (http://www.nealelab.is/uk-biobank). The summary results of the meta-analyzed GWASs are described in Supplementary Table 8. For the additional 13 traits among the remaining 25 traits investigated in BBJ, we were able to collect independent large-scale GWAS summary statistics of European ancestry, either from publicly available websites or on request to the authors. The information on these 13 GWASs is described in Supplementary Table 9. We note that although we exhaustively checked for cohort-level overlap between the biobanks and previous GWASs, we could not completely exclude the possibility of an individual-level overlap, which would be technically difficult to detect in large-scale genetic studies.

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 UKB, we referred to UKB GWAS summary statistics from all of the 361,194 white British individuals. With the exception of C-reactive protein (CRP), for 12 traits among the 13 traits where we used independent previous GWAS summary statistics in UKB, we utilized the same GWAS summary statistics, as we confirmed that there was no apparent cohort-level overlap with FinnGen (Supplementary Table 9). For CRP, since the GWAS of Ligthart et al.[43] included the FINRISK Study, which was also involved in FinnGen, we additionally performed GWAS in UKB individuals ($n=353,466$), and used these summary statistics in the calculation of PRSs. When performing CRP GWAS in UKB, we excluded individuals with autoimmune or inflammatory diseases.

Construction of PRSs. *BBJ.* By referring to the effect sizes and P values of ten summary results from meta-analyzed GWASs of nine subgroup GWASs, we derived the PRSs of individuals in the one withheld subgroup using a clumping and thresholding method. First, we performed LD clumping on the meta-analyzed GWAS summary statistics with PLINK software using 5,000 randomly selected BBJ participants as an LD reference. Briefly, we first used PLINK to clump all of the variants using the following flags: --clump-p1 1 --clump-p2 1 --clump-r2 0.1 --clump-kb 1000. We then computed PRSs for variants meeting the following P-value 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 one withheld subgroup, we derived PRSs by multiplying the dosage of risk alleles for each variant by the effect size in the GWAS and summing the scores across all of the selected variants. We quantified the trait variance explained by the derived PRSs in individuals within the withheld subgroup, by calculating the adjusted R^2 attributable to the PRSs from nested models, in which the full linear model was the trait value ~ PRS + all covariates and the nested model dropped only the PRS term (Supplementary Table 11). For sBP, we also assessed the association of the PRS status (the highest quintile versus the lowest quintile) and the status of hypertension, which was defined as either being hypertensive (sBP > 130 mmHg or dBP > 80 mmHg) or being treated with anti-hypertensive medications, by using a generalized linear model.

UKB and FinnGen. For the clinical phenotypes where the individual clinical data were available (20 traits in UKB), we derived the PRSs in the same manner as described above for BBJ (the tenfold LOGO approach and deriving the PRSs in the one withheld group using the weights from the meta-analyzed summary statistics of nine subgroup GWASs by a clumping and thresholding approach). The variance explained by the derived PRSs is described in Supplementary Table 12. 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. We basically followed the original quality-control policy that had been adopted within each of the cohorts, and thus the PRSs of UKB and FinnGen could have included the rarer variants when compared with those for BBJ (MAF > 0.0001 versus MAF ≥ 0.01). We confirmed that both the performance of the PRSs and the result of downstream analyses did not substantially change (that is, the correlation r of these statistics exceeded 0.97), even when we restricted the variants used for calculating the PRSs to those with MAF ≥ 0.01 in UKB and FinnGen.

Survival analysis using PRSs. *BBJ.* We used Cox proportional hazards models to test the association of the derived PRSs of clinical phenotypes with lifespan (that is, age at death) in the withheld subgroups. For the within-BBJ analysis, we selected PRSs from the P-value threshold of the best predictive capacity that had the largest variance explained by the PRS (the best P value). We note that the threshold selection was based on the predictive capacity of the trait under investigation and not based on the result of the association of PRSs with lifespan. For the trans-biobank analysis, since individual-level data were not always available for some of the traits, optimization of the P-value thresholds was technically challenging. We thus selected PRSs from a fixed P-value threshold of 1.0×10^{-6}, which was supposed to account for the polygenic architecture of complex traits while avoiding potential biases in PRS predictions induced by the large number of non-significant variants[44].

The PRSs for each trait in each subgroup were scaled to have zero mean and unit variance by Z-score transformation to obtain and compare the effect sizes across the investigated phenotypes. We used Cox proportional hazards models to test the association of the scaled PRS of each trait in each subgroup with lifespan, with adjustment for sex, the 47-disease status and the top 20 principal components. We performed Schoenfeld residual tests[45] to examine the proportional hazards assumption for the Cox regression. No apparent correlation between the Schoenfeld residuals and time was statistically or visually confirmed. We further meta-analyzed the association statistics from each of the ten subgroups by the inverse variance method. We confirmed that association statistics (that is, coefficients) from the fixed threshold of 1×10^{-6} were concordant with those from the best P values (Pearson's $r=0.85$ and $P=2.5\times10^{-13}$). Nevertheless, we consider that further implementation of the methodology for optimally harmonizing PRSs across different cohorts is still warranted. In addition, here we note that spouse pairs in LOGO analyses might potentially cause a subtle bias in GWASs and PRS–lifespan associations if assortative mating exists[46].

To conduct the association test of the PRSs with cause-specific mortality, we categorized the individual cause of death defined by the International Classification of Diseases 10 into the four most frequent causes of death in Japan as described elsewhere[12]. Briefly, we defined the deaths from malignant diseases as C00-C97, the deaths from cardiovascular diseases as I01–I02, I05–I09, I20–I25, I27, and I30–I52, the deaths from pneumonia as J12-J18, and the deaths from cerebrovascular diseases as I60-69. We then performed the survival analyses to investigate the association of the biomarker PRS with each of the four mortality outcomes. A sex-stratified association study (Extended Data Fig. 3a) was conducted by using the same Cox proportional hazards models within male and female participants, except that we excluded sex from the covariates.

To describe a standardized survival curve, we compared HRs for participants at the highest genetic risk (fifth quintile of PRSs) with those at an intermediate risk (quintiles 2 to 4) or the lowest risk (first quintile) as described previously[47], which were standardized to the mean of all the covariates (Extended Data Fig. 7). For the sBP PRS, we also analyzed the interaction effects with lifestyle factors recorded in the cohort. The lifestyle factors were obtained from the questionnaire to the participants, which asked them about their usual frequency of consumption or exercise of an investigated trait by selecting one from four categorical values. The answered values were converted to the quantitative values so that they represented the mean value of each category, except for the two binary lifestyle traits (whether a participant has ever smoked cigarettes and whether a participant currently drinks alcohol) (Supplementary Table 5). All the survival analyses were performed using the survival package in R software, version 3.3.0 (https://cran.r-project.org/package=survival).

UKB and FinnGen. For the clinical biomarkers where the individual level-data was available (20 traits in UKB), we performed the same 10-fold survival analyses followed by meta-analysis as explained above in BBJ. We included the same covariates used in the GWASs for each cohort, except for age and age squared, in the Cox proportional hazard models. For the remaining traits, we performed the survival analyses in the entire cohort to test the association of the public GWAS-based PRS of each trait with lifespan. As described above, we adopted the fixed P value threshold of 1×10^{-6} for the derivation of PRSs for the cross-biobank comparison. We confirmed that association coefficients from the fixed threshold of 1×10^{-6} was concordant with those from the best P values in the 20 traits in UKB (Pearson's $r=0.93$ and $P=1.3\times10^{-9}$). To conduct the association test of the PRSs with cause-specific mortality, we again categorized the individual cause of death defined by the International Classification of Diseases 10 into the four causes of death as described above. A sex-stratified association study (Extended Data Fig. 3b,c) was conducted by using the same Cox proportional hazards models within male and female participants, except that we excluded sex from the covariates.

As a secondary analysis, we performed an association test of the sBP PRS with parental lifespan in UKB to validate the result of the primary analysis with a much larger statistical power. To perform an association test of individuals' genotype 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[48].

For the BMI PRS, we also analyzed the interaction effects with lifestyle factors recorded in UKB. We collected the individual-level data of smoking status (ever smoked and smoking cessation), alcohol intake, coffee intake and regular physical activity. We tested the effect of an 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 BBJ, UKB and FinnGen, by the 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 previously[38,48]

$$\text{Years gained} = 10\times\left\{-\log_e(\text{CoxHR})\right\}$$

The association results of the trans-ethnic PRS meta-analysis including the years of life gained/lost are described in Supplementary Table 10.

Trans-ethnic MR study. We conducted a two-sample MR study to investigate the effect of each of the 33 biomarkers investigated in the trans-ethnic study on the outcome (that is, lifespan).

For the traits where we performed LOGO in the PRS calculation (that is, 33 traits in BBJ and 20 traits in UKB), we randomly split the cohort in half, with one group for performing GWAS and the other group for performing MR. For the selection of variants to be used as instrumental variables, we performed GWASs within the GWAS group with the same covariates described earlier, and selected independent genetic variants with $P_{GWAS}<1.0\times10^{-6}$ for each trait (lead variants at significant loci at least ±500 kilobases distant from each other). We next performed an association study of these genetic variants with lifespan within the MR group, by using the same Cox proportional hazards model as described earlier. By using these genetic variants and the association estimates, we obtained the effect estimate of the exposure (biomarker) on the outcome (lifespan) by pooling all MR estimates using the fixed-effects inverse-variance-weighted method[49].

For the traits where we used independent previous GWAS summary statistics in the PRS calculation (that is, 13 traits in UKB and 33 traits in FinnGen), we selected independent genetic variants with $P_{GWAS}<1.0\times10^{-6}$ from these statistics. We next performed an association study of these genetic variants with lifespan in the whole cohort, by using the same Cox proportional hazards model. These estimates are used to obtain the MR effect estimate by the inverse-variance-weighted method.

We finally performed a fixed-effect meta-analysis of the MR effect estimates from each of the three cohorts.

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

Data availability

The genotype data of BBJ used in this study are available from the Japanese Genotype-phenotype Archive (http://trace.ddbj.nig.ac.jp/jga/index_e.html) with the accession code JGAD00000000123. The GWAS summary statistics for BBJ are available at the National Bioscience Database Center Human Database with the accession code hum0014. The UKB analysis was conducted via the application 31063, and its GWAS summary statistics are available at http://www.nealelab.is/uk-biobank. This study used the FinnGen release 3 data. Summary statistics from FinnGen are available on request from the FinnGen project and are being prepared for public release in May 2020.

Code availability

We used publicly available software for the analyses. The software programs used are listed and described in the Methods.

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Author contributions

S.S., Y.K. and Y.O. conceived the study. M.H., M.Kubo, K.M. and Y.M. collected and managed the BBJ 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 BBJ. M.Kanai performed statistical analysis on UKB. 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 interests

The authors declare no competing interests.

Additional information

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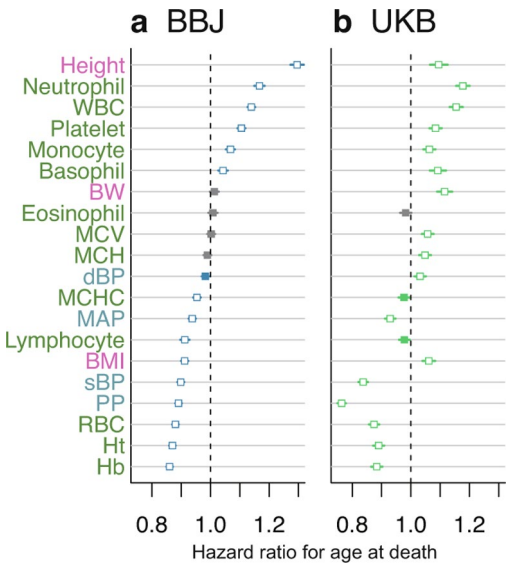
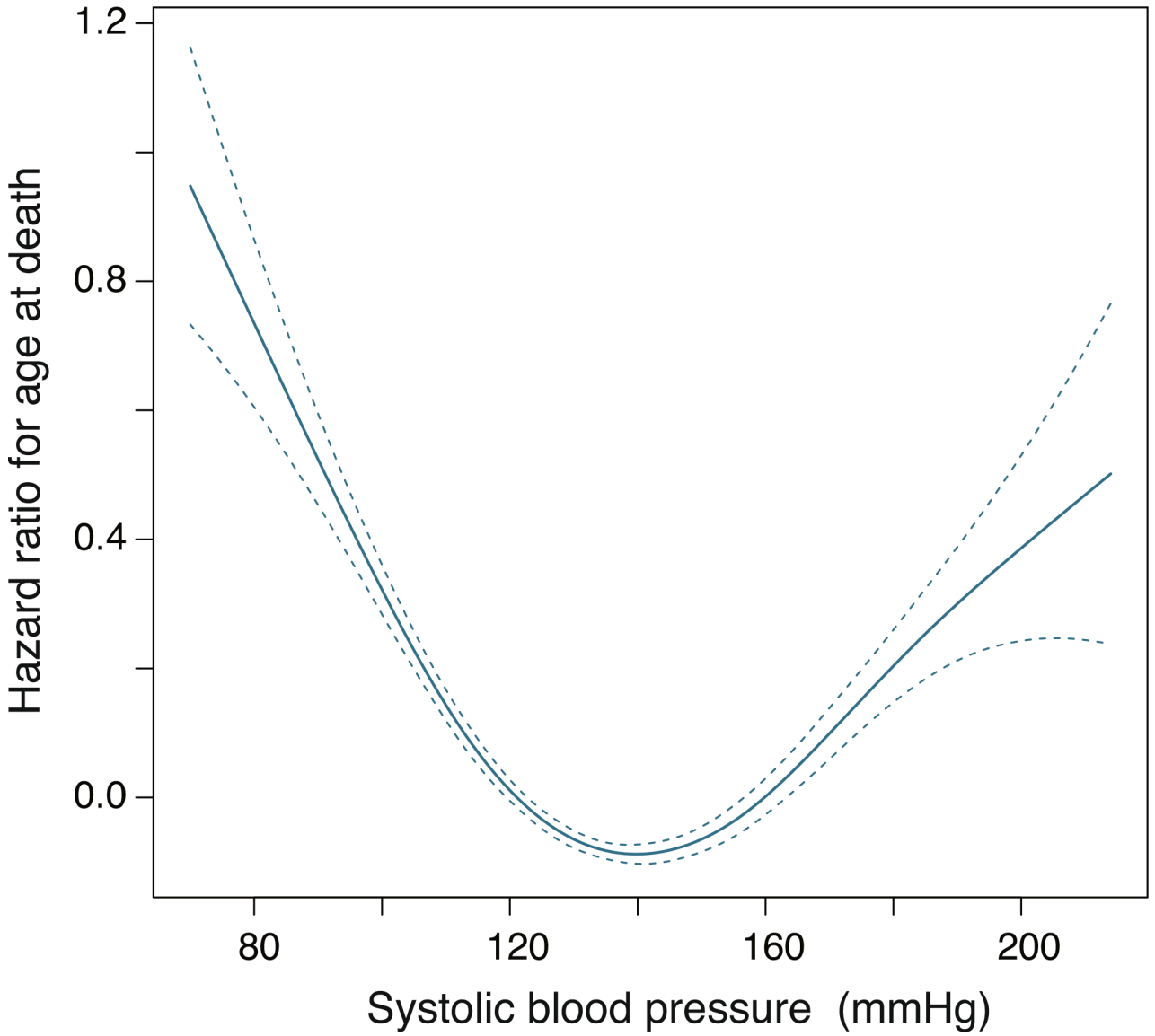
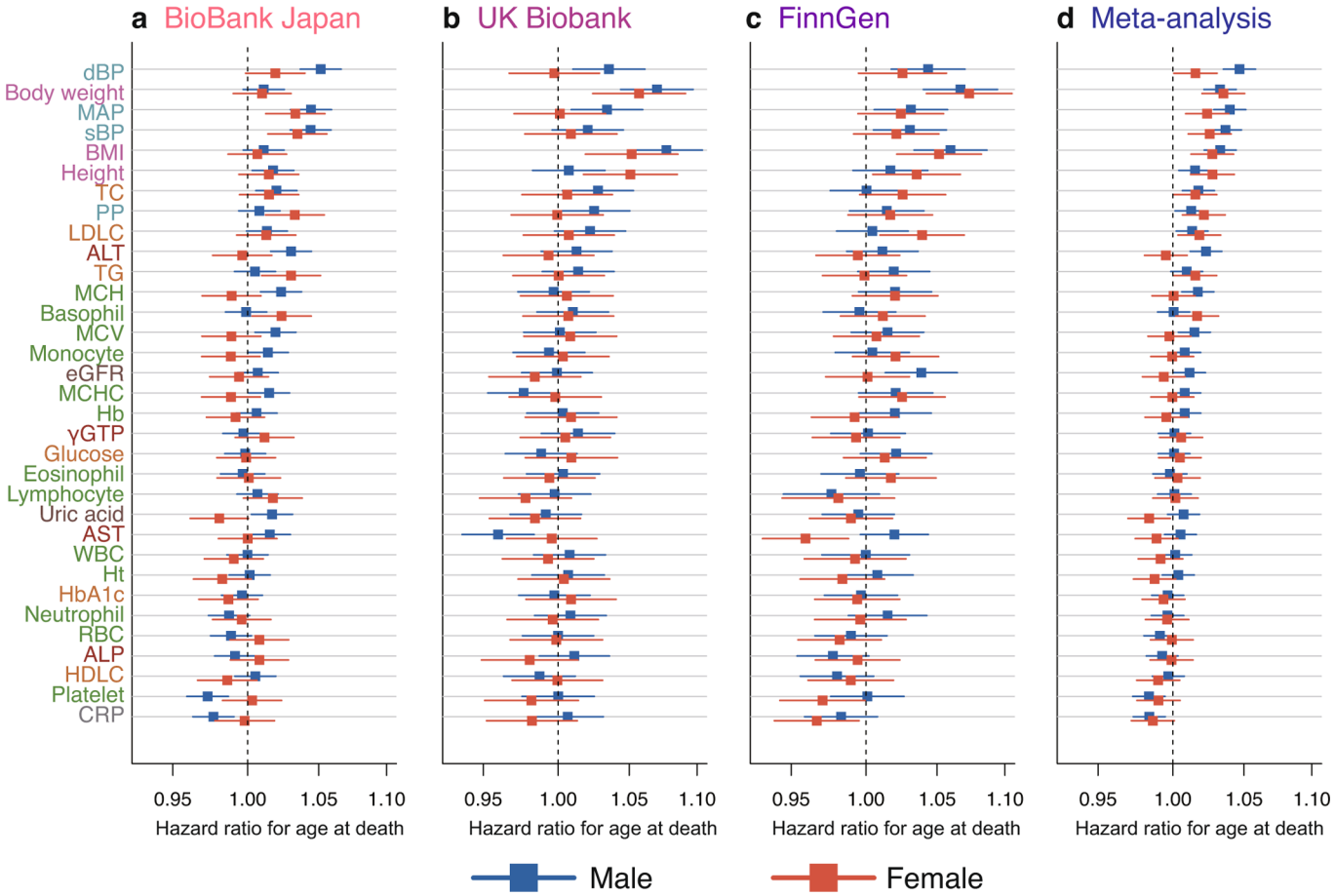


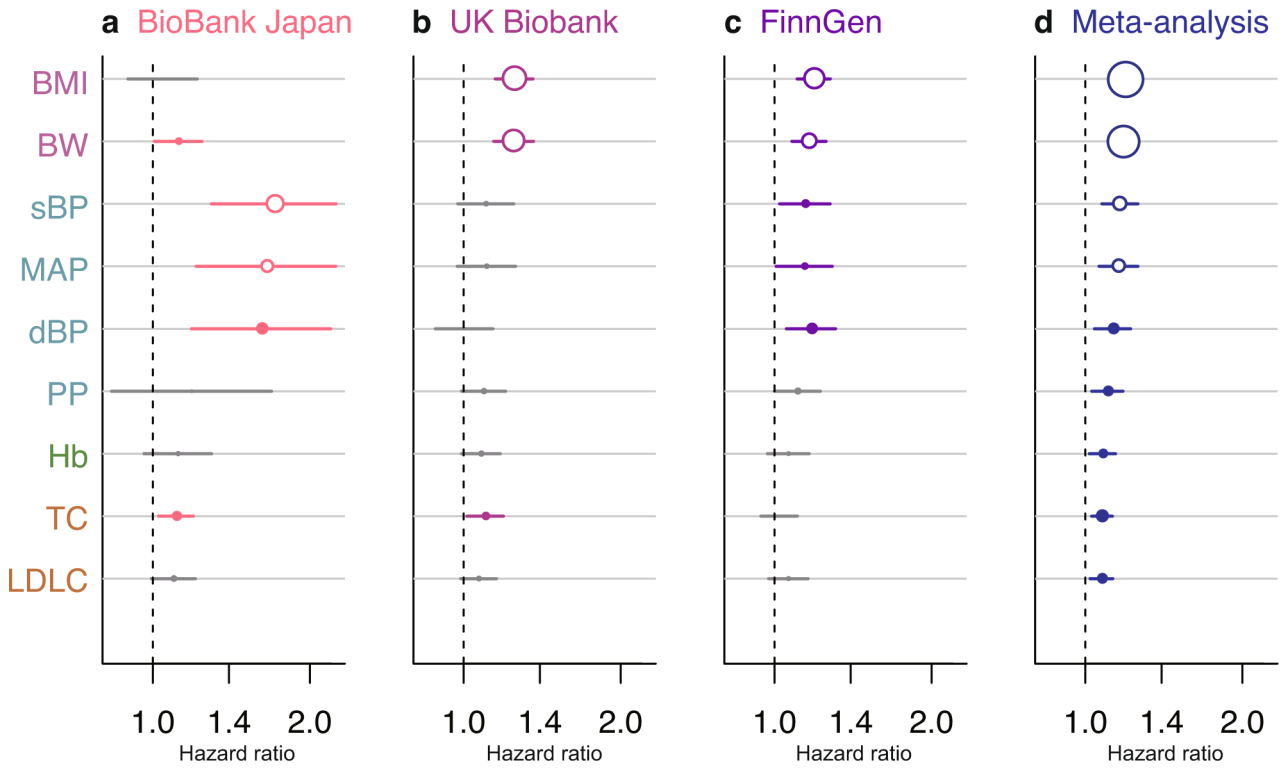
Extended Data Fig. 1 | A comparison between observational studies in BioBank Japan and UK Biobank. Hazard ratios (HRs) from Cox proportional-hazard models for lifespan according to observed phenotypes in BioBank Japan (BBJ [*n*=179,066]; **a**) and UK Biobank (UKB [*n*=361,194]; **b**) are shown and compared. The boxes indicate the point estimates, and the horizontal bars indicate the 95% confidence interval. Boxes colored in blue (**a**) or green (**b**) indicate the nominal significance ($P < 0.05$) and the white-filled boxes indicate the statistical significance after correcting for multiple testing by the Bonferroni method. All the acronyms are described in Fig. 2.



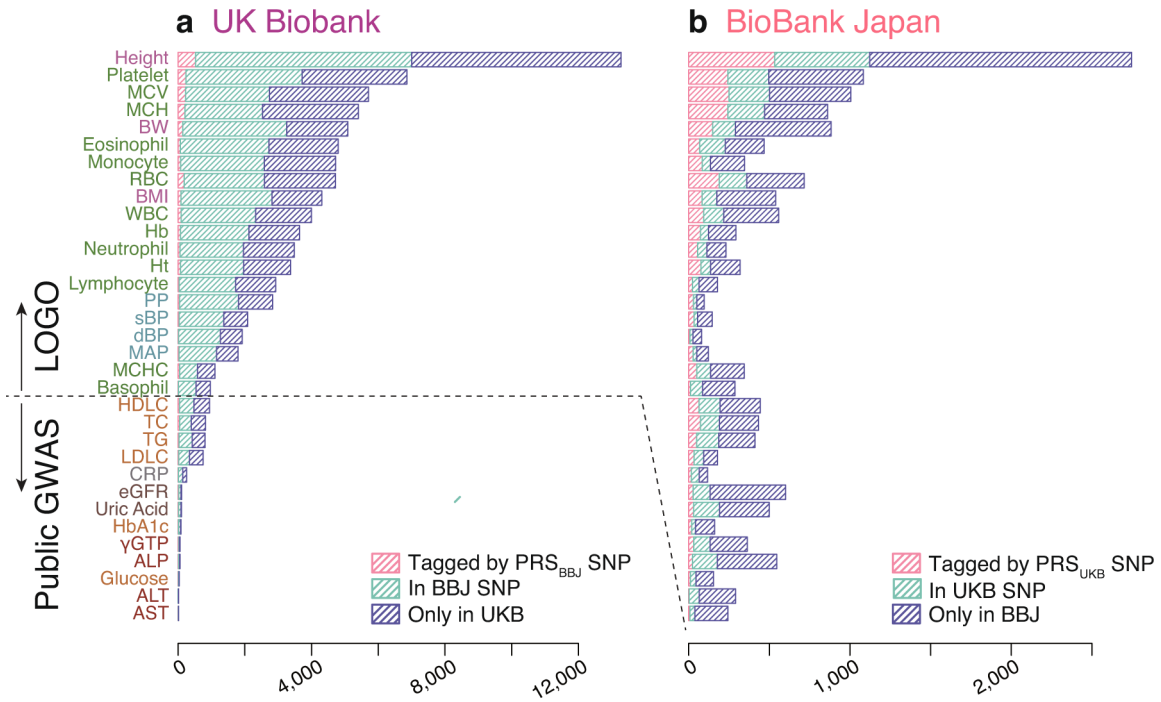
Extended Data Fig. 2 | The relationship between systolic blood pressure and HR for age at death in BioBank Japan. The HR for age at death according to the observed systolic blood pressure in BBJ (*n*=179,066) is shown. The dotted lines represent the 95% confidence interval.



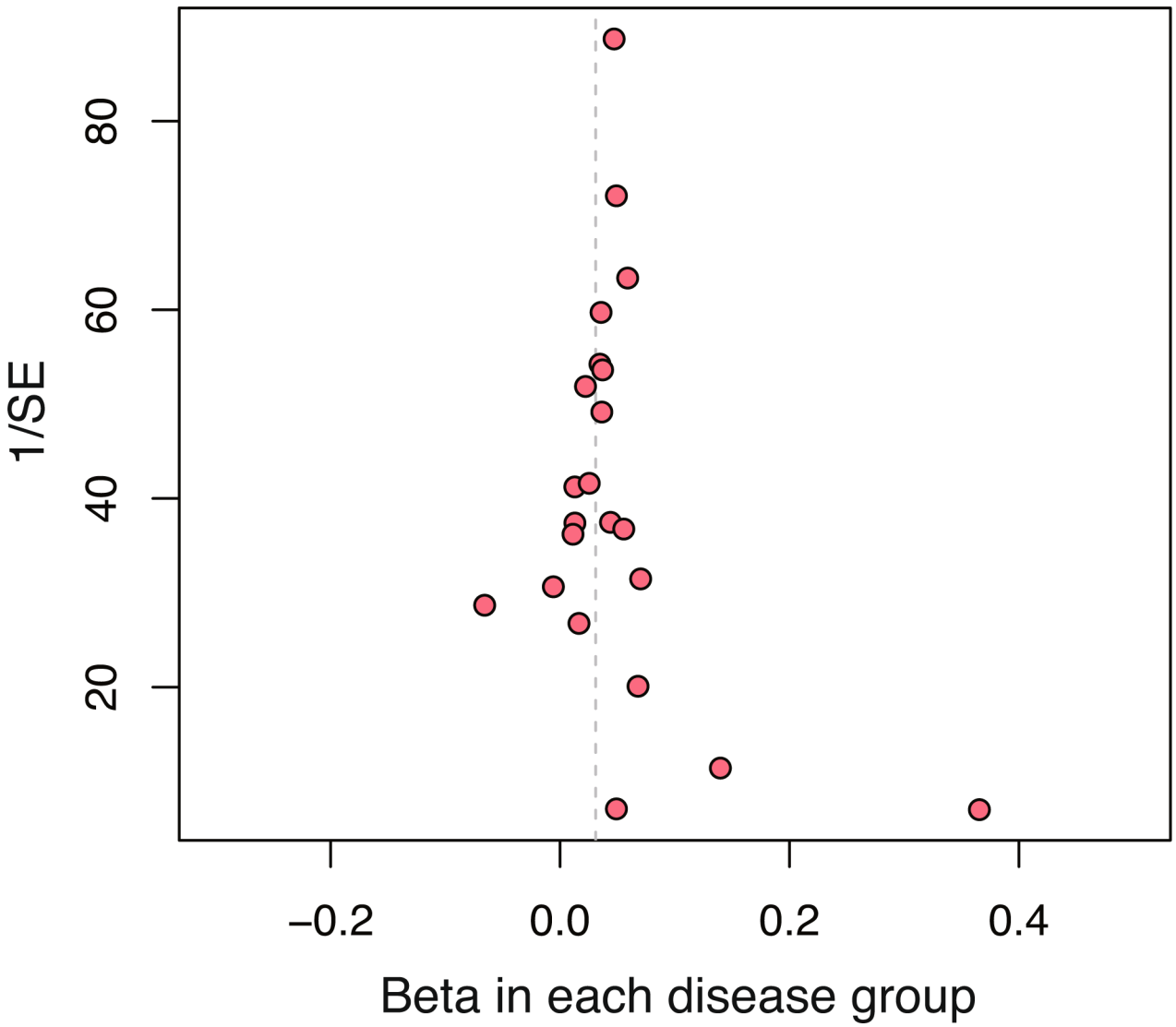
Extended Data Fig. 3 | Sex-stratified association studies of PRS with lifespan across three cohorts. The results of hazard ratios from sex-stratified Cox proportional-hazard models for lifespan, according to the PRS of the clinical phenotypes in (**a**) BioBank Japan (*n*=179,066), (**b**) UK Biobank (*n*=361,194), and (**c**) FinnGen (*n*=135,638) are shown. The boxes in blue indicate the point estimates in males, and those in red indicate the point estimates in females. The horizontal bars are the 95% confidence interval. For both sexes, we separately performed the fixed-effect meta-analyses of the association results from the three cohorts (**d**) by the inverse-variance method.



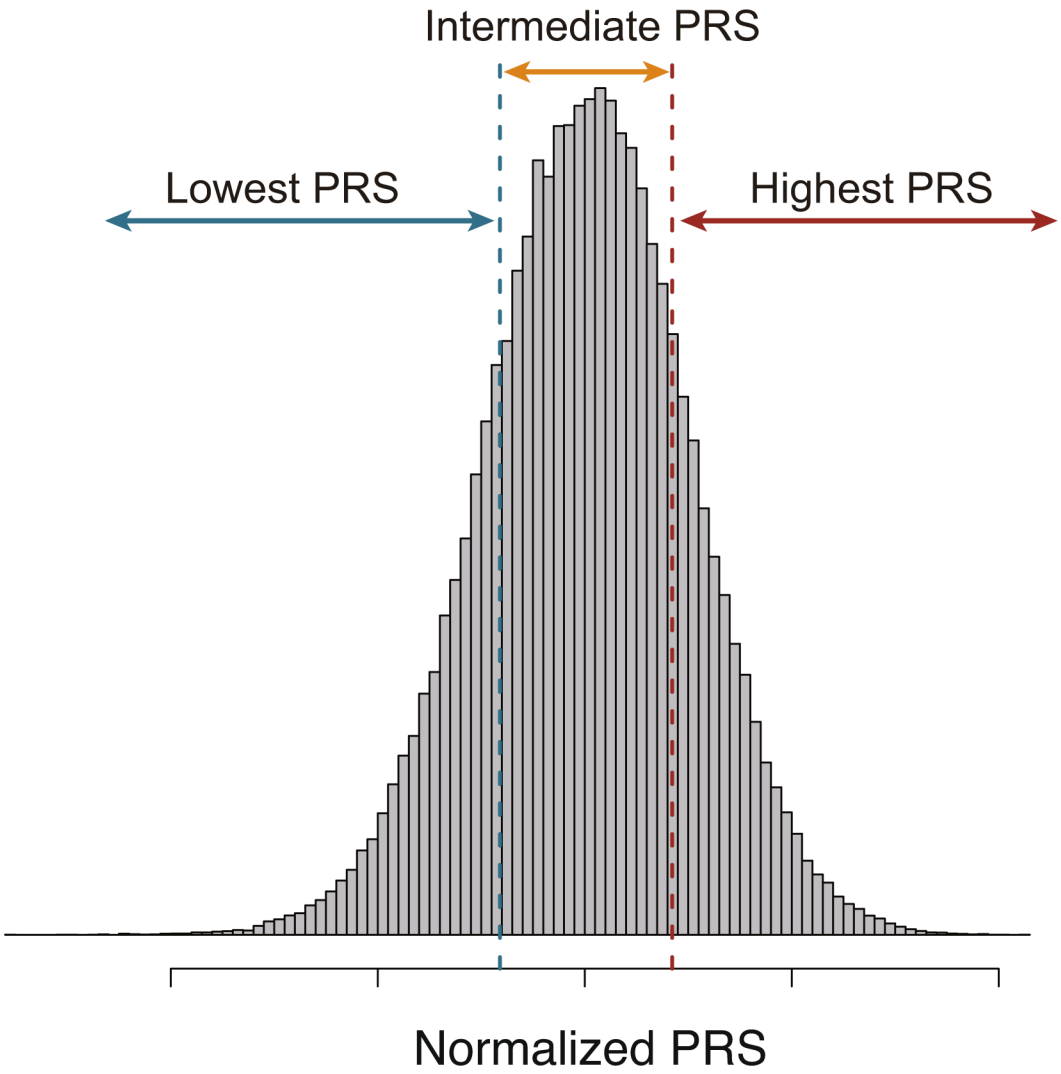
Extended Data Fig. 4 | Trans-ethnic Mendelian randomization studies. Shown are the results of two-sample Mendelian randomization studies with an inverse-variance weighted method to estimate the causal effect of biomarkers on lifespan in (**a**) BioBank Japan (n=179,066), (**b**) UK Biobank (n=361,194), and (**c**) FinnGen (n=135,638). We performed a fixed-effect meta-analysis of the association results from the three cohorts (**d**) by the inverse-variance method (n_{total}=675,898), and displayed only nominally significant traits (9 out of 33 investigated traits). The circles indicate the point estimates, and the horizontal bars are the 95% confidence interval. Circles in colors indicate the nominal significance ($P < 0.05$) and the white-filled circles indicate the statistical significance after the Bonferroni correction for multiple testing. The size of the circles reflects the statistical significance in $-\log_{10}(P)$.



Extended Data Fig. 5 | The overlap of the variants constituting the PRSs between UK Biobank and BioBank Japan. a, Among the variants constituting UK Biobank PRSs, the variants in blue did not exist in BioBank Japan variant dataset, those in green existed in BioBank Japan variant dataset, and those in pink were shared with or tagged ($r^2 > 0.8$) by the variants constituting BioBank Japan PRSs of the same trait. To calculate r^2 of LD, we used the LD reference panel from 5,000 randomly selected BioBank Japan individuals. Please note that the variants constituting PRSs from all the 10 sub-groups were concatenated in 20 traits with LOGO analysis. **b**, Among the variants constituting BioBank Japan PRSs, the variants in blue did not exist in UK Biobank variant dataset, those in green existed in UK Biobank variant dataset, and those in pink were shared with or tagged by the variants constituting UK Biobank PRSs of the same trait. To calculate r^2 of LD, we again used the LD reference panel from 5,000 randomly selected BioBank Japan individuals. Please note that the variants constituting PRSs from all the 10 sub-groups were concatenated in all 33 traits with LOGO analysis.



Extended Data Fig. 6 | A funnel plot for the effects of systolic blood pressure (sBP) PRS on lifespan, according to disease groups. Sensitivity analyses of the effect of sBP PRS on the age at death. A funnel plot of the effects of sBP PRS on the age at death is shown by stratifying study participants into disease groups with at least 3,000 case samples (n_{trait}=22). The effect sizes from Cox proportional-hazard models are on x axis, and inverse standard errors (precision) are on y axis. A dotted line indicates the effect size from overall participants (n=179,066).



Extended Data Fig. 7 | A definition of the three bins according to the PRSs. A distribution of normalized sBP PRS and the stratification according to the quintiles. We defined the lowest, intermediate, and highest PRS bins according to the quintiles of PRS (first, 2-4th, and fifth, respectively). Each quintile bin was defined so as to have the same number of participants.

nature research

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☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	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.
Data analysis	We used publicly available software for the data analysis (R 3.3.0, plink 1.9 and 2.0, Minimac3, IMPUTE4, Hail 0.2, Beagle 4.1, LDSC v1.0.1).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The genotype data of BioBank Japan used in this study are available from the Japanese Genotype-phenotype Archive (JGA; http://trace.ddbj.nig.ac.jp/jga/index_e.html) with accession code JGAD00000000123. The GWAS summary statistics of BioBank Japan are available at the National Bioscience Database Center (NBDC) Human Database with the accession code hum0014. UK Biobank analysis was conducted via the application 31063, and its GWAS summary statistics is available at http://www.nealelab.is/uk-biobank. This study used the FinnGen release 3 data. Summary statistics from FinnGen are available on request from FinnGen project and being prepared for a public release in May 2020.

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Life sciences study design

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

Sample size	Clinical information and genotype data were obtained from BioBank Japan (BBJ) project, which is a biobank that collaboratively collected DNA and serum samples from 12 medical institutions in Japan and recruited approximately 200,000 participants. Of them, we included individuals with genotype and basic phenotype data. The UK Biobank project is a population-based prospective cohort that recruited approximately 500,000 people. FinnGen is a public-private partnership project combining genotype data from Finnish biobanks and digital health record data from Finnish health registries. Of them, we used the genotype and phenotype data of 135,638 participants in this project.
Data exclusions	In BBJ, we excluded individuals with the age under 18, low call rate in genotyping (< 98%), closely related (PI_HAT < 0.125), and ancestry other than Japanese (based on PCA plot) for quality control and to avoid potential confounders as described in Akiyama et al. Nat Commun 2019, and Kanai et al. Nat Genet 2018.
Replication	We replicated our findings on survival analyses by conducting the same analysis with the same pipeline in UK Biobank cohort (n = 361,194) and FinnGen cohort (n = 135,638).
Randomization	In the newly developed method called LOGO, we assigned a random number to each participant and randomly split the whole participants into 10 groups.
Blinding	We did not apply blinding of the samples because no intervention was conducted in our study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	The detailed information of participants such as age and sex distributions is summarized in Supplementary Table 1a. BioBank Japan is a hospital-based cohort, and participants have the diagnosis of at least one of 47 common diseases. UK Biobank is a population-based cohort, enrolling healthy volunteers. Since it is a recently-launched cohort, mean age at death is younger than the other two cohorts. FinnGen is a mixture of population-based and disease-based cohorts.
Recruitment	BioBank Japan (BBJ) project recruited approximately 200,000 participants from 12 medical institutions with the diagnosis of at least one of 47 diseases, mainly of Japanese ancestry. Participants have the diagnosis of at least one of 47 common diseases. We confirmed that the main conclusion of our manuscript was not confounded by the proportion of patients with a specific disease group by the sensitivity analyses. The coherent results with the other two biobanks further mitigated concerns over potential biases.
Ethics oversight	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.

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