Supplementary material

The association between genetically elevated telomere length and risk of cancer and non-neoplastic diseases

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SUPPLEMENTARY METHODS

Additional details on the design strategy

Identification of genetic proxies for telomere length

To identify genetic variants to serve as proxies for telomere length, we searched the GWAS catalog[13,14] on the 15 January 2015, to identify single nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with additional potential proxies, we also searched the original study reports curated by the GWAS catalog.[15–23] We included all 'telomere length' SNPs in the GWAS catalog as potential proxies, regardless of their reported P value, but used a P value threshold of $<5x10^{-8}$ (the conventional threshold for declaring association in GWAS) for SNPs identified from original study reports (if these were not already curated by the GWAS catalog). We acquired summary data for all SNPs identified by the above strategy from a meta-analysis of GWASs of telomere length, involving 9,190 participants of European ancestry.[16] SNPs initially identified as potential proxies for telomere length were subsequently excluded if they lacked strong

evidence of association with telomere length. We defined strong evidence of association as a p-value $<5x10^{-8}$ in: i) the discovery stage of at least one published GWAS of telomere length[15–22] or ii) a meta-analysis of summary data from Mangino et al[16] and other GWASs of telomere length,[15,17–22] with any overlapping studies excluded from Mangino et al.[16] We also excluded SNPs with a minor allele frequency <0.05 or showing strong evidence of between-study heterogeneity in associations with telomere length ($P \leq 0.001$).

We acquired summary data for the genetic proxies from a meta-analysis of six genome wide association studies (GWASs) of leukocyte telomere length, conducted in 9,190 participants of European ancestry.[1] Telomere length in the six studies was measured by Southern blotting. The following summary data were acquired for each genetic proxy from each of the six studies: the regression coefficient (beta) and its standard error, where the beta reflects the change in telomere length (in base pair units) per copy of the effect allele; the effect allele; the non-effect allele; and the effect allele frequency. We combined the effect estimates from the six separate studies by fixed effects meta-analysis. Associations between SNPs and telomere length were adjusted for age, sex, body mass index and smoking history. The genomic control inflation factor (λ_{GC}) ranged from 0.995 to 1.076 across the six studies, indicating little evidence for confounding by population stratification.[1]

Acquisition of summary data from disease and risk factor studies

We extracted the following summary data for each genetic proxy for telomere length from GWASs of diseases and risk factors: the regression coefficient (beta) and its standard error, the effect allele, the non-effect allele and the effect allele frequency. For binary traits, the beta corresponded to the log odds ratio per copy of the effect allele. For quantitative traits, the beta corresponded to the unit change in the trait per copy of the effect allele. We harmonized the summary data for diseases and risk factors so that the effect allele reflected the allele associated with longer telomeres. When SNPs were palindromic, i.e. A/T or G/C, we used information on allele frequency to resolve strand

ambiguity. We also requested the following metrics of SNP genotype quality: p-value for Hardy-Weinberg equilibrium (HWE), imputation quality scores and P values for between-study heterogeneity. We also estimated the percentage overlap in participants amongst the telomere length and outcome GWASs. When reported, statistics on between-study heterogeneity, Hardy–Weinberg equilibrium and imputation quality were used to exclude low quality SNPs from disease and risk factor studies, using the following criteria: strong evidence of between-study heterogeneity in the SNP-phenotype association ($P \leq 0.001$), Hardy–Weinberg disequilibrium ($P \leq 0.001$) or imputation quality metric (info or r^2) ≤ 0.90.

Power calculations

Power calculations for disease outcomes were implemented using the method described by Burgess[2] and assumed an odds ratio of ≥ 2.0 per standard deviation higher telomere length and an alpha of 0.01. Power calculations for risk factors were similar, except that a ≥ 0.5 standard deviation change in quantitative risk factors and an odds ratio of ≥ 1.5 for binary risk factors was assumed for each standard deviation change in telomere length. When more than one study was available for the same outcome trait, priority was given to the study with the higher statistical power. Power calculations took into account the variance explained in telomere length by each SNP, inferred from published reports,[3,1,4–9] and the sample size available for each analysis.

Estimating the association between genetically increased telomere length and outcome traits

We employed three general approaches for estimating the association between genetically increased telomere length and outcome traits. Our main results are based on a likelihood-approach.[10] Sensitivity analyses were based on two approaches: the weighted median[11] and MR-Egger regression.[12] The technical details of these approaches are described below.

Prior to calculating the associations of genetically increased telomere length with diseases and risk factors, we estimated the pairwise r^2 for all telomere-associated SNPs residing on the same chromosome using PLINK[13] and 1000 Genomes phase 3 data for European samples.[14] SNPs residing on separate chromosomes or separated by more than 50 megabases on the same chromosome were assumed to be in linkage equilibrium. The genetic proxies for telomere length were pruned so that no SNP pair had an $r^2>0.9$ (strong linkage disequilibrium), using the 'indep' command in PLINK.[13] The base pair position and chromosome id for each SNP, in GCRCh38 format, was extracted from Ensembl through the R biomart package.[15–17] Linkage disequilibrium between the remaining SNPs was taken into account using a variance-covariance matrix (described below). For analyses in which SNP-disease associations were derived from East Asian populations, genetic proxies were further pruned so that no SNP pair had an $r^2>0.1$ (because the variance-covariance matrix used to model the correlation between SNPs was based on a European population).

Likelihood approach

We combined summary data across SNPs into a single genetic risk score, using maximum likelihood to estimate the slope of the relationship between β_{GD} and β_{GP} and a variance-covariance matrix to make allowance for linkage disequilibrium between SNPs, where β_{GD} is the change in outcome trait per copy of the effect allele and β_{GP} is the standard deviation change in telomere length per copy of the effect allele.[10] The standard deviation of telomere length corresponds to approximately 650 base pairs.[1] The variance-covariance matrix was estimated using 1000 Genomes phase 3 data for Europeans.[10] The model that is fitted is:

$$\begin{pmatrix} \boldsymbol{\beta_{GP}} \\ \boldsymbol{\beta_{GD}} \end{pmatrix} \sim N_{2K}\left(\begin{pmatrix} \boldsymbol{\xi} \\ \beta_{IV}\boldsymbol{\xi} \end{pmatrix}, \begin{pmatrix} \Sigma_{PP} & \Sigma_{PD} \\ \Sigma_{DP} & \Sigma_{DD} \end{pmatrix}\right)$$

where $\boldsymbol{\beta_{GP}}$ is a vector of the gene-phenotype associations, $\boldsymbol{\beta_{GD}}$ is a vector of the gene-disease associations, β_{IV} is the causal effect parameter, K is the number of SNPs, Σ_{PP} is a variance-

covariance matrix with elements $(\Sigma_{PP})_{ij} = se(\beta_{GPi})se(\beta_{GPj})\rho_{ij}$ where $se(\beta_{GPi})$ is the standard error of the gene-phenotype association for the *i*th genetic variant, and ρ_{ij} is the correlation between the *i*th and *j*th variants due to linkage disequilibrium. Components of Σ_{DD} are similarly defined as $(\Sigma_{DD})_{ij} = se(\beta_{GDi})se(\beta_{GDj})\rho_{ij}$, and $\Sigma_{PD} = \Sigma_{DP} = 0$ due to the two-sample setting (sensitivity analyses in a previous study[10] suggested results were robust to some correlation between the gene-phenotype and gene-outcome associations that may arise due to sample overlap). The slope estimated by maximum likelihood can be interpreted as the log odds ratio for disease per standard deviation increase in genetically increased telomere length. The slope can further be interpreted as the causal effect of telomere length on disease if Mendelian randomization assumptions hold. The assumptions are: G is associated with telomere length (IV1); G is independent of confounders (IV2); and G is independent of disease adjusted for telomere length and confounders (IV3). See Supplementary Figure S7 for further details.

The weighted median approach[11]

Let $\hat{\beta}_{(1)},\ldots,\hat{\beta}_{(J)}$ represent the J causal effect estimates ordered from smallest ($\hat{\beta}_{(1)}$) to largest ($\hat{\beta}_{(J)}$). Now define

$$w^*_{(j)} = \frac{w_j}{S_J}, \quad \text{where} \quad S_J = \sum_j w_j ,$$

and equate $\hat{\beta}_{(j)}$ with a quantile, $p^w_{(j)}$, defined as

$$p^w_{(j)} = \frac{100}{S_J}\left(S_{(j)} - \frac{w_{(j)}}{2} \right).$$

$p^w_{(j)}$ represents the quantile from the weighted empirical distribution function of the ordered estimates $\hat{\beta}_{(1)},\ldots,\hat{\beta}_{(J)}$. The weighted median estimate, $\hat{\beta}_{WM}$ is defined as the 50th percentile of this weighted distribution. Typically the 50th percentile will lie between two estimates ($\hat{\beta}_{(l)}$ and $\hat{\beta}_{(m)}$, say), in which case $\hat{\beta}_{WM}$ is found by linear interpolation. $\hat{\beta}_{WM}$ is a consistent estimate for β provided

that at least 50% of the 'weight' making up S_J comes from genetic variants that are valid instruments. In other words, the weighted median function provides a valid estimate of the association between genetically increased telomere length and disease if at least half of the genetic information comes from valid instruments.[11] The weighted median function provides a valid estimate of the causal effect of telomere length on disease if at least half of the genetic information comes from valid instruments (assumptions illustrated in Supplementary Figure 7).[11]

The MR-Egger approach

The MR-Egger method[12] performs a weighted linear regression of the gene-outcome coefficients on the gene-exposure coefficients:

$$\frac{\hat{\Gamma}_j}{\sigma_{Yj}} = \frac{\beta_{0E}}{\sigma_{Yj}} + \beta_{1E}\frac{\hat{\gamma}_j}{\sigma_{Yj}}$$

where Γ corresponds to the gene-outcome coefficients and γ corresponds to the gene-exposure coefficients. If all genetic variants are valid instruments, then $\beta_{0E} = 0$. The value of $\hat{\beta}_{0E}$ can be interpreted as an estimate of the average pleiotropic effect across the genetic variants. An intercept term that differs from zero is indicative of overall directional pleiotropy. The MR-Egger estimate for β , $\hat{\beta}_{1E}$, is consistent even if *all* genetic variants are invalid, provided that

- Across all variants, the magnitude of the gene-exposure associations are independent of their pleiotropic effects
- The number of instruments, J, grows large.

The slope from MR-Egger regression can be interpreted as the association between genetically increased telomere length and disease corrected for pleiotropy. The intercept from MR-Egger

regression can be interpreted as a test for the presence of pleiotropy. The result from MR-Egger regression can be interpreted as a causal effect of telomere length on disease if assumptions IV1, IV2 and the InSIDE (Instrument Strength Independent of Direct Effect) assumption hold (see Supplementary Figure 7 for further details).

SUPPLEMENTARY RESULTS

In analyses of secondary cancer outcomes, genetically increased telomere length was associated with thyroid cancer, chronic lymphocytic leukemia and multiple myeloma ($P<0.05$) (Fig. S2). In analyses of secondary non-neoplastic diseases, genetically increased telomere length was associated with reduced odds of panic disorder ($P<0.05$) (Fig. S2). In secondary analyses of 44 risk factors for non-communicable diseases (Table S2), genetically increased telomere length was associated with increased pulse pressure, systolic blood pressure, diastolic blood pressure, mean arterial pressure, triglycerides, uric acid and education and with decreased HDL cholesterol, mean corpuscular haemoglobin and mean corpuscular volume ($P<0.05$) (Fig S5). There was some evidence for an association between genetically increased telomere length and ever smoking status ($P=0.03$, Fig S6) but this association is unlikely to be reliable given that the genetic proxies for telomere length were adjusted for smoking history; the association may therefore reflect collider bias.[35]

SUPPLEMENTARY DISCUSSION

Mechanisms of association between SNPs and telomere length

The mechanisms of the underlying associations between the selected SNPs and telomere length are generally unknown. Some of the SNPs were located in or near the TERC or TERT genes, suggesting that the mechanism could involve the telomerase enzyme, as well as the OBFC1 and CTC1 genes, which have known roles in regulation of telomere length biology (Table 1), OBFC1 is an enzyme involved in initiating DNA replication and is involved in the telomere-associated CST

complex.[18] CTC1 encodes a component of the CST complex, which plays a role in protecting telomeres from degradation.

Strength of the association between the selected SNPs and telomere length

The selected genetic proxies for telomere length correspond to 10 independent genomic loci and collectively account for 2-3% of the variance in leukocyte telomere length. The corresponding F statistic is around 18, which means that bias due to weak instruments is unlikely to be substantial even if there were considerable overlap amongst the various GWAS datasets.[19] The estimated overlap in participants amongst the telomere length and outcome GWASs was less than 11% for all diseases and risk factors, except for hepatic steatosis, for which overlap was around 51%, indicating that the vast majority of our results should be robust to weak instrument bias.

A common misconception about Mendelian randomization studies is that genetic proxies should explain a substantial proportion of the variation in target exposures in order to provide robust inferences about exposure-disease associations. In fact, genotype assignment in a Mendelian randomization study is analogous to treatment assignment in a randomized controlled trial, which typically also explains only a small subset of variation in target exposures.[20] Moreover, the aim of Mendelian randomization studies is to make inferences at the population level and not the individual level (for which genetic proxies of substantial explanatory power would be required).[20] On the other hand, if Mendelian randomization assumptions were violated, then the limited variation explained by our SNP proxies might not behave in similar manner to other sources of variation in telomere length, which would constrain our ability to draw causal inferences. The assumptions are: 1) the genetic proxies must be associated with telomere length; 2) the genetic proxies should not be associated with confounders; and 3) the genetic proxies must be associated with disease exclusively through their effect on telomere length.

Potential for confounding by population stratification, ancestry and age

It is unlikely that confounding by population stratification, ancestry or age (an important confounder of observational studies of telomere length) can account for our results. The 15 primary diseases showing some evidence of association with telomere length (defined as a P value<0.05) were 100% European, on the basis of self reported ancestry or genetic analyses (individuals showing genetic evidence of non-European ancestry were excluded).[3,21–38] In addition, these studies all made some allowance for population stratification in their results: 12 adjusted for principal component scores of genetic variation in their models or applied genomic control corrections to their results; and 3 concluded there was little evidence for population stratification, on the basis of visual inspection of Quantile-Quantile plots of GWAS results (i.e. lambdas for genomic inflation were close to 1). The GWAS used to defined genetic proxies for telomere length[1] also adjusted for principal component scores; and lambdas for genomic inflation from the latter GWAS were close to 1. Since our MR analyses will have inherited any adjustments made in the original analyses, it is therefore unlikely that confounding by ancestry or population stratification can explain our results.

Confounding by age is also unlikely, given the random distribution of genotypes in the general population with respect to lifestyle and other environmental factors, as well as the fixed nature of germline genotypes. Consistent with this expectation, we did not observe an association between subject age and their genetically predicted telomere length values in our previous studies.[38,39]

Associations with non-neoplastic diseases

The inverse associations observed for coronary heart disease, abdominal aortic aneurysm, celiac disease and interstitial lung disease are compatible with findings based on observational and Mendelian randomization studies of telomere length as well as dyskeratosis congenita (a congenital disease characterized by chronically short telomeres).[5,65–68]

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Supplementary Table S1. Study characteristics for included secondary non-communicable diseases

	No. cases	No. controls	No. SNPs	Statistical power	Pop.	First author /database
Cancer						
Chronic lymphocytic leukemia	2883	8350	1	0.22	EUR	Speedy/GWAS cat.[40]
Chronic myeloid leukemia	201	497	8	0.07	EA	Kim[41]
Ewing sarcoma	401	684	4	0.06	EUR	Postel-Vinay[42]
Follicular lymphoma	212	748	3	0.04	EUR	Conde[43]
Gallbladder cancer	41	866	2	0.01	EA	Cha[44]
Gastric cancer						
Cardia adenocarcinoma	1126	2111	11	0.47	EA	Abnet[45]
Noncardia adenocarcinoma	632	2111	11	0.29	EA	Abnet[45]
Multiple myeloma	4692	10990	1	0.37	EUR	Chubb/GWAS cat.[46]
Nasopharyngeal carcinoma	1583	1894	2	0.17	EA	Bei[47]
B-cell Non-Hodgkin lymphoma	253	1438	10	0.13	EA	Tan[48]
Skin squamous cell carcinoma	449	11518	13	0.34	EUR	Zhang[49]
Thyroid cancer	649	431	12	0.16	EUR	Kohler[50]
Upper gastrointestinal cancers	3523	2100	2	0.28	EA	Li/dbGAP[51]
Autoimmune/inflammatory diseases						
Inflammatory psoriatic arthritis	609	990	13	0.29	EUR	Huffmeier[52]
Kawasaki disease	405	6252	11	0.26	EUR	Khor[53]
Narcolepsy	1188	1985	9	0.46	EA	Han[54]
Psoriasis	1139	1132	9	0.34	EA	Zhang[55]
Sarcoidosis	564	1575	9	0.16	EUR	Fischer[56]
Systemic lupus erythematosus	1311	1783	4	0.20	EUR	Hom/dbGAP[57]
Vitiligo	1117	1429	2	0.12	EA	Quan[58]
Wegener's granulomatosis	459	1503	10	0.20	EUR	Xie[59]
Neurological / psychiatric diseases						
Bulimia nervosa	151	2291	8	0.07	EUR	Wade[60]
Panic disorder	718	1717	8	0.28	EA	Otowa[61]
Parkinson's disease	1713	3978	4	0.35	EUR	Simón-Sánchez/dbGAP[62]
Other						
Hirschsprung's disease	173	615	6	0.04	EA	Tang[63]
Paget's disease	741	2699	12	0.43	EUR	Albagha[64]
Vascular dementia	84	200	8	0.03	EA	Kim[65]
Independent disease studies for replication analyses						
Bladder cancer	7712	13125	1	0.56	EUR	Figueroa/GWAS cat.[66]
Colorectal cancer	728	3282	9	0.39	EA	Zhang[67]
Coronary heart disease	15399	15050	4	1.00	Mix	C4D[68]
Glioma	1854	4955	1	0.12	EUR	GliomaScan/GWAS cat.[69]
Interstitial lung disease†	542	542	11	0.15	EUR	Noth[70]
Interstitial lung disease‡	242	1469	1	0.02	EA	Mushiroda/GWAS cat.[71]
Multiple sclerosis	978	883	4	0.11	EUR	Baranzini/dbGAP[72]
Nasopharyngeal carcinoma	277	285	2	0.03	EA	Tse[73]

†≤17% cases overlapped with cases from Fingerlin et al[25] and 77% of cases had idiopathic pulmonary fibrosis; ‡all cases had idiopathic pulmonary fibrosis.
Study/database acronyms: C4D, Coronary Artery Disease Genetics Consortium; **dbGAP**, summary data downloaded from the database of Genotypes and Phenotypes; **GWAS cat.**, data downloaded from the National Human Genome Research Institute/European Bioinformatics Institute Catalogue of Genome Wide Association Studies. **Abbreviations**: EUR, European; EA, East Asian; **No.**, number; **Pop**., population; **SNP**, single nucleotide polymorphism.

Supplementary Table S2. Study characteristics for 44 disease risk factors

	Sample size	SD	Units	No. of SNPs	Stat. power	Pop.	First author / study
Anthropometric							
Birth length	22557	2.0	cm	12	1.00	EUR	EGG[74]
Birth weight	26836	547.5	g	12	1.00	EUR	EGG[75]
Body mass index	241253	4.8	kg/m^2	13	1.00	EUR	GIANT[76]
Childhood obesity	13848	NA	log_e odds	12	0.78	EUR	EGG[77]
Head circumference	10705	1.5	cm	13	1.00	EUR	EGG[78]
Height	253288	0.1	m	13	1.00	EUR	GIANT[79]
Hip circumference	224459	8.5	cm	13	1.00	EUR	GIANT[80]
Waist circumference	224459	12.5	cm	13	1.00	EUR	GIANT[80]
Waist-to-hip ratio	224459	0.1	ratio	13	1.00	EUR	GIANT[80]
Smoking behaviors							
Age of smoking initiation	47961	0.3	log_e years	13	1.00	EUR	TAG[81]
Cigarettes smoked per day	68028	11.7	CPD	13	1.00	EUR	TAG[81]
Ever smoker	74035	NA	log_e odds	13	1.00	EUR	TAG[81]
Ex smoker	41969	NA	log_e odds	13	1.00	EUR	TAG[81]
Blood pressure							
Diastolic blood pressure	66466	10.7	mm Hg	12	1.00	EUR	ICBP
Mean arterial pressure	27803	12.8	mm Hg	13	1.00	EUR	ICBP[82]
Pulse pressure	70903	13.5	mm Hg	13	1.00	EUR	ICBP[82]
Systolic blood pressure	66473	18.2	mm Hg	12	1.00	EUR	ICBP[83]
Education							
College completion	95427	NA	log_e odds	13	1.00	EUR	SSGAC[84]
Years of educational attainment	126559	1.2	years	13	1.00	EUR	SSGAC[84]
Glycemic							
2 hr glucose	15234	1.27	mmol/L	11	1.00	EUR	MAGIC[85]
Beta-cell function (HOMA-B)	46186	0.96	log_e HOMA	12	1.00	EUR	MAGIC[86]
Fasting glucose	46186	0.73	mmol/L	12	1.00	EUR	MAGIC[86]
Fasting insulin	38238	0.79	log_e pmol/L	12	1.00	EUR	MAGIC[86]
Fasting proinsulin	10701	0.81	log_e pmol/L	12	1.00	EUR	MAGIC[86]
Gycated hemoglobin (HbA1c)	46368	0.53	%	12	1.00	EUR	MAGIC[87]
Insulin resistance (HOMA-IR)	46186	0.67	log_e HOMA	12	1.00	EUR	MAGIC[86]
Hemotological							
Hemoglobin	54287	1.3	g/dL	12	1.00	EUR	van der Harst[88]
Mean cell hemoglobin	45969	1.99	pg	12	1.00	EUR	van der Harst[88]
Mean cell hemoglobin concentration	49632	1.01	g/dL	12	1.00	EUR	van der Harst[88]
Mean cell volume	51277	5.2	fl	12	1.00	EUR	van der Harst[88]
Packed cell volume	46848	5.9	%	12	1.00	EUR	van der Harst[88]
Red blood cell count	47873	0.5	$10^{12}/L$	12	1.00	EUR	van der Harst[88]
Lipids							
HDL cholesterol	103019	15.51	mg/dL	11	1.00	EUR	GLGC[89]
LDL cholesterol	97562	38.67	mg/dL	11	1.00	EUR	GLGC[89]
Total cholesterol	103266	41.75	mg/dL	11	1.00	EUR	GLGC[89]
Triglycerides	99050	90.72	mg/dL	11	1.00	EUR	GLGC[89]
Renal function							
Microalbuminuria	30482	NA	log_e odds	13	0.82	EUR	CKDGen[90]
Serum creatinine	67093	0.24	log_e ml/min/1.73m²	13	1.00	EUR	CKDGen[90]
Serum cystatin	20957	0.23	log_e ml/min/1.73m²	13	1.00	EUR	CKDGen[90]
Urinary albumin-to-creatinine ratio	31580	1.0	log_e mg/g	13	1.00	EUR	CKDGen[90]

Other							
Grade of nuclear cataract	7140	0.8	grade	11	1.00	ASN	SEEDS[91]
Hepatic steatosis	7176	5.6	Hounsfield units	12	1.00	EUR	Speliotes[92]
Percent emphysema	7914	1.4	%	12	1.00	ME	MESA[93]
Uric acid	42742	1.3	mg/dL	12	1.00	EUR	GUGC[94]

Study acronyms: **CKDGen**, chronic kidney disease genetics consortium; **EGG**, Early Growth Genetics Consortium; **GIANT**, Genetic Investigation of ANthropometric Traits; **GUGC**, Global Urate and Gout consortium; **TAG,** Tobacco and Genetics Consortium; **ICBP**, International Consortium for Blood Pressure; **SSGAC**, Social Science Genetics Association Consortium; **MAGIC**, Meta-Analyses of Glucose and Insulin-related traits Consortium; MESA, **GLGC**, Global Lipids Genetics Consortium; **SEEDS,** the Singapore Epidemiology of Eye Diseases Study. **Abbreviations**: **ASN,** Asian; **Con**., concentration; **EUR,** European population; **ME,** multi-ethnic; **SD** - standard deviation; **$\log_e$**, natural log; **Stat.,** statistical

Supplementary Table S3. Selected prospective observational studies of the association between leukocyte telomere length and disease

Cohort / first author	Disease	Year	Design	No. of controls / cohort size	No. of cases	RR (95% CI) as reported by study	Scale of RR reported by study	Conversion factor[§]	RR (95% CI) per SD increase in TL	Adjusted[‡]	Pop.	P_{het}	Search strategy†
Cancer outcomes													
NHS, HPFS[95]	Bladder cancer	2007	NCC	192	184	1.88 (1.05 to 3.36)	shortest vs. longest quartile	2.54	1.28 (1.02 to 1.61)	++	EUR	NA	2
CCHS, CGPS[96]	Breast cancer	2013	PC	24588	574	0.99 (0.95 to 1.03)	per 1000 bp (1.29 SD) decrease	-1.29	1.01 (0.98 to 1.04)	+++++	EUR		1
SWHS[97]	Breast cancer	2013	NCC	695	601	1.77 (1.02 to 3.06)	shortest vs. longest quintile	2.80	1.23 (1.01 to 1.49)	++	EA		2
Sister Study[98]	Breast cancer	2011	Case-cohort	735	342	0.93 (0.64 to 1.35)	shortest vs. longest quartile	-2.54	1.03 (0.89 to 1.19)	+	EUR (92%)	0.17	1
EPIC[99]	Breast cancer	2010	NCC	420	199	1.58 (0.75 to 3.31)	shortest vs. longest quartile	2.54	1.2 (0.89 to 1.6)	+	EUR		1
WHS[100]	Colorectal cancer	2010	NCC	357	134	0.94 (0.65 to 1.38)	per unit (1.30 SD) decrease	-1.30	1.05 (0.78 to 1.4)	+++++	EUR		3
PHS[101]	Colorectal cancer	2009	NCC	306	191	0.8 (0.55 to 1.16)	per unit (1.72 SD) decrease	-1.72	1.14 (0.92 to 1.41)	++++	EUR		3
CCHS, CGPS[96]	Colorectal cancer	2013	PC	46748	496	0.97 (0.88 to 1.07)	per 1000 bp (1.29 SD) decrease	-1.29	1.02 (0.95 to 1.1)	++++	EUR	0.47	1
SWHS[102]	Colorectal cancer	2012	NCC	549	441	1.61 (0.94 to 2.75)	longest vs. 3rd shortest quintile	1.40	1.4 (0.96 to 2.06)	+	EA		1
EPIC[99]	Colorectal cancer	2010	NCC	406	185	1.13 (0.54 to 2.36)	shortest vs. longest quartile	-2.54	0.95 (0.71 to 1.27)	+	EUR		1
NHS[103]	Endometrial cancer	2010	NCC	791	279	1.2 (0.73 to 1.96)	shortest vs. longest quartile	-2.54	0.93 (0.77 to 1.13)	+++++	EUR		2
CCHS, CGPS[96]	Endometrial cancer	2013	PC	25262	103	0.85 (0.71 to 1.02)	per 1000 bp (1.29 SD) decrease	-1.29	1.13 (0.99 to 1.31)	+++++	EUR	0.11	1

PLCO[104]	Glioma	2013	NCC	198	101	1.26 (0.69 to 2.29)	shortest vs. longest tertile	-2.18	0.9 (0.68 to 1.18)	++	EUR	NA	1
CCHS, CGPS[96]	Head & neck cancer	2013	PC	47036	76	1.17 (0.9 to 1.53)	per 1000 bp (1.29 SD) decrease	-1.29	0.89 (0.72 to 1.09)	++++	EUR	NA	1
CCHS, CGPS[96]	Kidney cancer	2013	PC	47063	59	1.04 (0.78 to 1.39)	per 1000 bp (1.29 SD) decrease	-1.29	0.97 (0.77 to 1.21)	++++	EUR	NA	1
PLCO[105]	Kidney cancer	2013	NCC	410	209	0.8 (0.5 to 1.5)	longest vs. shortest quartile	2.54	0.92 (0.74 to 1.14)	+++	EUR (89.5%)	NA	1
PLCO, ATBC, SWHS[106]	Lung adenocarcinoma	2014	NCC	288	288	2.52 (1.38 to 4.6)	longest vs. shortest quartile	2.54	1.44 (1.14 to 1.82)	++	EUR (75%)	NA	1
CCHS, CGPS[96]	Lung cancer	2013	PC	47035	522	1.08 (0.98 to 1.2)	per 1000 bp (1.29 SD) decrease	-1.29	0.94 (0.87 to 1.02)	++++	EUR		1
PLCO, ATBC, SWHS[106]	Lung cancer	2014	NCC	847	847	1.86 (1.33 to 2.62)	longest vs. shortest quartile	2.54	1.28 (1.12 to 1.46)	++	EUR (75%)	<0.001	1
PLCO, ATBC, SWHS[106]	Lung SCC	2014	NCC	163	163	1.14 (0.53 to 2.45)	longest vs. shortest quartile	2.54	1.05 (0.78 to 1.42)	++	EUR (75%)	NA	1
CCHS, CGPS[96]	Melanoma	2013	PC	46805	177	0.89 (0.77 to 1.03)	per 1000 bp (1.29 SD) decrease	-1.29	1.09 (0.98 to 1.23)	++++	EUR		1
WHI, HPFS, NHS[107]	Melanoma	2011	NCC	579	557	0.43 (0.27 to 0.7)	shortest vs. longest quartile	-2.54	1.39 (1.16 to 1.68)	+	EUR	0.03	2
CCHS, CGPS[96]	Ovarian cancer	2013	PC	25367	96	0.85 (0.7 to 1.03)	per 1000 bp (1.29 SD) decrease	-1.29	1.13 (0.98 to 1.32)	+++++	EUR	NA	1
CCHS, CGPS[96]	Pancreatic cancer	2013	PC	47091	124	1.14 (0.93 to 1.41)	per 1000 bp (1.29 SD) decrease	-1.29	0.9 (0.77 to 1.06)	++++	EUR		1
ATBC[108]	Pancreatic cancer	2013	NCC	660	193	1.58 (1.02 to 2.46)	longest vs. shortest quartile	2.54	1.2 (1.01 to 1.42)	++	EUR	0.05	1
EPIC[109]	Pancreatic cancer	2014	NCC	331	331	1.38 (0.8 to 2.41)	longest vs. shortest quartile	2.54	1.13 (0.91 to 1.41)	+	EUR		1

CCHS, CGPS[96]	Prostate cancer	2013	PC	21387	418	0.94 (0.85 to 1.04)	per 1000 bp (1.29 SD) decrease	-1.29	1.05 (0.97 to 1.13)	++++	EUR	0.37	1
HPFS[110]	Prostate cancer	2015	NCC	935	922	1.11 (1.01 to 1.22)	per SD increase	1.00	1.11 (1.01 to 1.22)	++++	EUR		1
NHS[111]	Skin BCC	2011	NCC	1683	363	0.91 (0.66 to 1.25)	longest vs. shortest quartile	2.54	0.96 (0.85 to 1.09)	+	EUR	NA	1
CCHS, CGPS[96]	Testicular cancer	2013	PC	21568	10	1.09 (0.57 to 2.09)	per 1000 bp (1.29 SD) decrease	-1.29	0.94 (0.56 to 1.55)	++++	EUR	NA	1
Non-neoplastic diseases													
Haycock[‖112]	Coronary heart disease	2014	MA	27352	2272	1.4 (1.15 to 1.7)	shortest vs. longest tertile	-2.18	0.86 (0.78 to 0.94)	*	EUR	NA	4
Haycock[#112]	Ischemic stroke	2014	MA	5300	824	1.14 (0.85 to 1.54)	shortest vs. longest tertile	-2.18	0.94 (0.82 to 1.08)	*	EUR	NA	4
Bruneck, SHFS, WHI[113]	Type 2 diabetes	2014	MA	6991	2011	1.31 (1.07 to 1.6)	shortest vs. longest quartile	-2.54	0.9 (0.83 to 0.97)	**	Mix	NA	4

†Search strategy used to identify the study (see Table S4 for details). [‖]Meta-analysis of 11 prospective studies; [#]Meta-analysis of 6 prospective studies (90% of cases were ischemic stroke, 10% were unclassified cerebrovascular disease); [$]To convert reported log RR to log RR per SD increase in telomere length; [‡]**Adjustment for confounders**: +adjusted for age and sex; ++plus smoking; +++plus body mass index; ++++plus alcohol and/or physical activity ; +++++plus hormone replacement therapy, menopause and/or parity; *most studies adjusted for age, sex and non-lipid vascular risk factors; **adjusted for age, sex and body mass index.
Acronyms/abbreviations: **BCC**, basal cell carcinoma**; bp**, base pairs; **CI**, confidence interval; **EA**, East Asian; **EUR**, European; **MA**, random-effects meta-analysis of prospective studies; **NCC**, nested case-control study; **PC**, prospective cohort; **Phet**, p value for heterogeneity between studies; **Pop.**, population; **RR**, relative risk; **SD**, standard deviation; **SCC**, squamous cell carcinoma; **vs.**, versus; **TL**, telomere length. **Study acronyms: ATBC,** Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study**; CCHS**, Copenhagen City Heart Study; **CGPS**, Copenhagen General Population Study; **EPIC**, European Prospective Investigation into Cancer and Nutrition study; **HPFS**, Health Professionals Follow-Up Study; **NHS**, Nurses Health Study; **PHS**, Physicians' Health Study; **PLCO**, Prostate, Lung, Colorectal, and Ovarian; **SHFS**, Strong Heart Family Study; the Sister Study; **SWHS**, Shanghai Women's Health Study; **WHI**, Women's Health Initiative; **WHS**, Women's Health Study

Supplementary Table S4. PubMed search strategy for prospective observational studies of association between telomere length* and disease

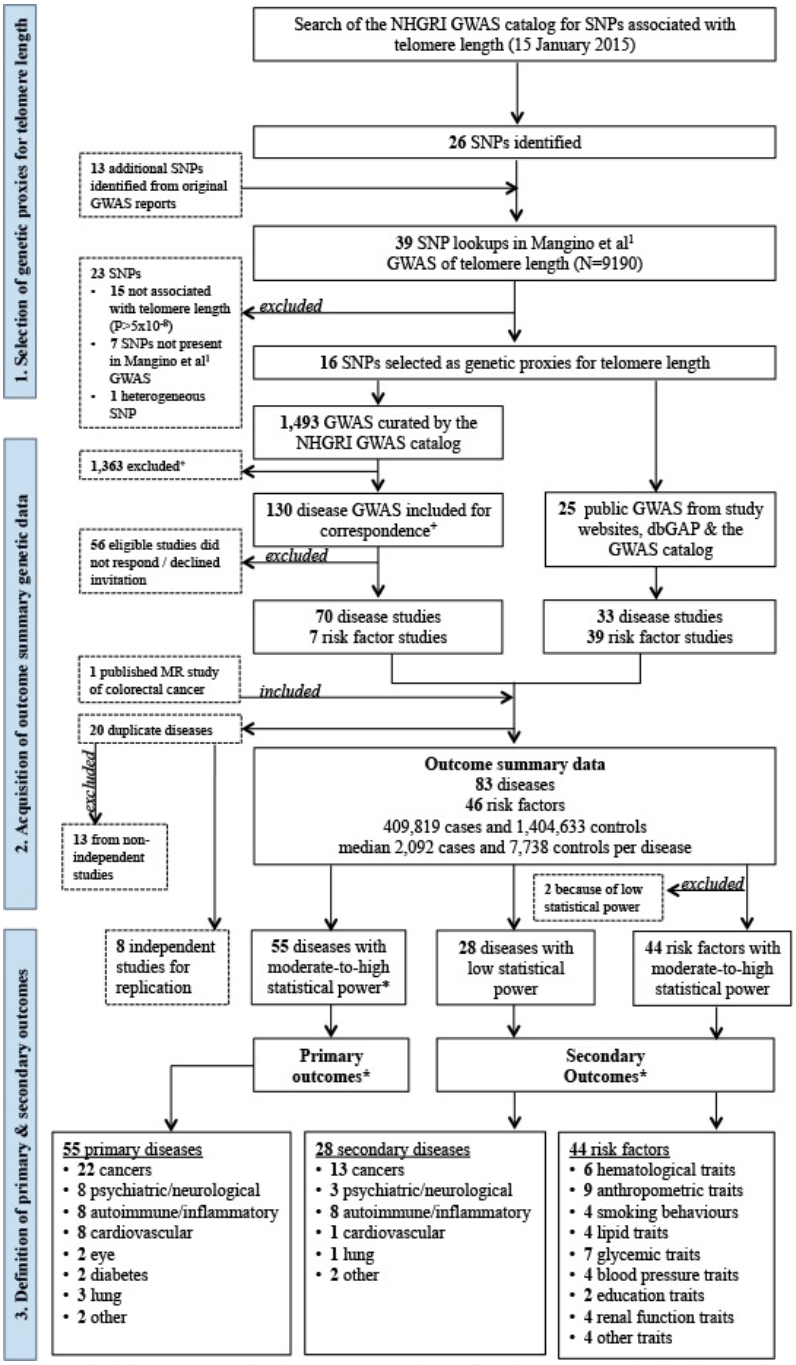
Search strategy	Search terms or meta-analysis	No. of studies identified	No. meeting inclusion criteria	Reasons for further exclusions	No. of studies included
Inclusion criteria: prospective study of primary cancer outcome and telomere length†					
Strategy 1	25 February 2015: cancer[TIAB] AND telomere length[TIAB] AND (meta analysis[TIAB] OR prospective[TIAB] OR meta-analysis[TIAB])	54	11	NA	11‡
Strategy 2	25 March 2015: telomere length[Title/Abstract] AND (retrospective[Title/Abstract] OR case-control[Title/Abstract] OR case control[Title/Abstract] OR meta-analysis[Title/Abstract] OR meta analysis[Title/Abstract] OR prospective[Title/Abstract] OR cohort[Title/Abstract] OR cross-sectional[Title/Abstract] OR cross sectional[Title/Abstract]) AND (B-cell non-Hodgkin lymphoma[Title/Abstract] OR breast cancer[Title/Abstract] OR chronic myeloid leukemia[Title/Abstract] OR esophageal adenocarcinoma[Title/Abstract] OR endometrial cancer[Title/Abstract] OR esophageal cancer[Title/Abstract] OR gastric cancer[Title/Abstract] OR gallbladder cancer[Title/Abstract] OR glioma[Title/Abstract] OR head cancer[Title/Abstract] OR neck cancer[Title/Abstract] OR oesophageal adenocarcinoma[Title/Abstract] OR kidney cancer[Title/Abstract] OR melanoma[Title/Abstract] OR nasopharyngeal carcinoma[Title/Abstract] OR neuroblastoma[Title/Abstract] OR non-melanoma skin cancer[Title/Abstract] OR basal cell carcinoma[Title/Abstract] OR squamous cell carcinoma[Title/Abstract] OR ovarian cancer[Title/Abstract] OR pancreatic cancer[Title/Abstract] OR prostate cancer[Title/Abstract] OR testicular germ cell cancer[Title/Abstract] OR Wilm's tumour[Title/Abstract] OR Bladder cancer[Title/Abstract] OR Breast cancer[Title/Abstract] OR Chronic lymphocytic leukemia[Title/Abstract] OR Colorectal cancer[Title/Abstract] OR Multiple myeloma[Title/Abstract] OR Lung adenocarcinoma[Title/Abstract] OR Lung squamous cell cancer[Title/Abstract] OR cancer[Title/Abstract] OR osteosarcoma[Title/Abstract] OR leukemia[Title/Abstract] OR leukaemia[Title/Abstract] OR Ewing sarcoma[Title/Abstract]	209	17	13 duplicates	4
Strategy 3	Ma et al[114] (2011) and Wentzensen et al[115] (2011)	48	10	8 duplicates	2
Inclusion criteria: prospective study of primary disease outcome and telomere length†					
Strategy 4	8 January 2016: (meta-analysis OR "meta analysis") AND "telomere length"	42	7	2 did not report relative risks§; 3 duplicates	2‖

*all identified eligible studies were studies of leukocyte telomere length; ‡1 study reported findings for 2 primary cancer outcomes and 1 study reported findings for 11 primary cancer outcomes; ‖1 meta-analysis reported findings for 2 primary non-neoplastic diseases; †primary outcomes were diseases where a priori statistical power was >50% to detect associations with telomere length (see supplementary text for technical details); see table S1 for a list of the primary disease outcomes; §relative risks were defined as odds ratios, hazard ratios and risk ratios

Supplementary Table S6. Glossary of terms

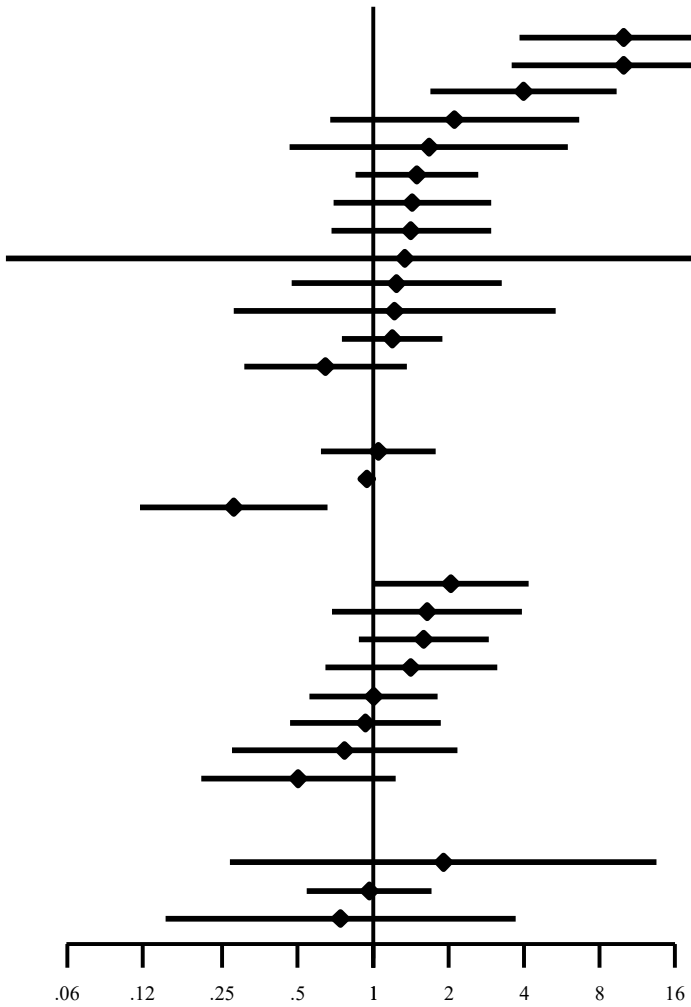
Mendelian randomization	A technique to appraise causality in observational studies using genetic variants as 'unconfounded' instruments for risk factors or modifiable exposures of interest.
Instrumental variable	A 'proxy' variable used in place of the hypothesized risk factor or exposure in a Mendelian randomization analysis. A valid instrumental variable is associated with the exposure of interest but is not associated with confounders; and is associated with the outcome (e.g. disease) exclusively via its effect on the hypothesized exposure.
Reverse causation	When the outcome causes variation in the hypothesized exposure and not *vice versa*.
Confounding	When the association between exposure and outcome is not due to a causal relationship between the two variables but arises as a result of the common correlation of the exposure and the outcome with a third factor (the confounder). Mendelian randomization studies are less susceptible to confounding in comparison to observational studies (but confounding by pleioptric pathways is possibile).
Pleiotropy	Occurs when a genetic variant is associated with multiple phenotypes. Vertical pleiotropy occurs when the phenotypes are all on the same causal pathway (and is less problematic for Mendelian randomization studies). Horizontal pleiotropy occurs if the phenotypes are associated with the genetic variant via separate pathways and can introduce confounding into a Mendelian randomization analysis. Sensitivity analyses, such as MR-Egger, the weighted median, scatter plots and funnel plots, can be used to test and, in some instances, adjust for pleiotropy.
Collider bias	The phenomenon by which statistical adjustment for a variable, M (known as the collider), that is a downstream consequence of both the exposure X and the outcome Y, induces an association between X and Y that was not previously present, and therefore leads to bias. In MR, if published genetic associations with the exposure and/or outcome are adjusted for a collider, this may lead to collider bias.
Weak instrument bias	Occurs when the instrument is only weakly associated with the exposure and can introduce confounding into a Mendelian randomization analysis when the exposure and outcome data come from the same sample. When exposure and outcome data come from separate samples, as in two-sample Mendelian randomization, bias is towards the null. An F statistic > 10, for the association between the instrument and exposure, is sometimes used as a threshold for defining strong instruments, although weak instrument bias varies continuously with the F statistic.

Supplementary Figure S1. Study design



+We searched the GWAS catalog in January 2015 for studies of non-communicable diseases that did not select controls on the basis of pre-existing conditions. Of the 1493 studies in the GWAS catalog with unique PubMed reference numbers, 773 were classified as disease studies (the excluded non-disease studies were typically studies of risk factors for disease, biomarkers or response to treatments). A further 103 studies were excluded for the following reasons: studies of infectious diseases, studies of congenital abnormalities, studies of (not-cause specific) mortality, studies nested within disease populations and studies using pooled DNA samples. Of the 670 remaining non-communicable disease studies, 130 were identified for correspondence. Our objective was to obtain the single largest available study for each non-communicable disease, so as to avoid unnecessary correspondence with duplicate studies and to avoid including studies with overlapping samples.
*Primary outcomes were diseases with sufficient cases and controls for >50% power and secondary outcomes as diseases with <50% power to detect associations with telomere length (see supplementary text for technical details). Secondary disease outcomes were reclassified as primary outcomes if the genetic association with disease could be replicated in an independent dataset. All risk factors were defined as secondary outcomes.

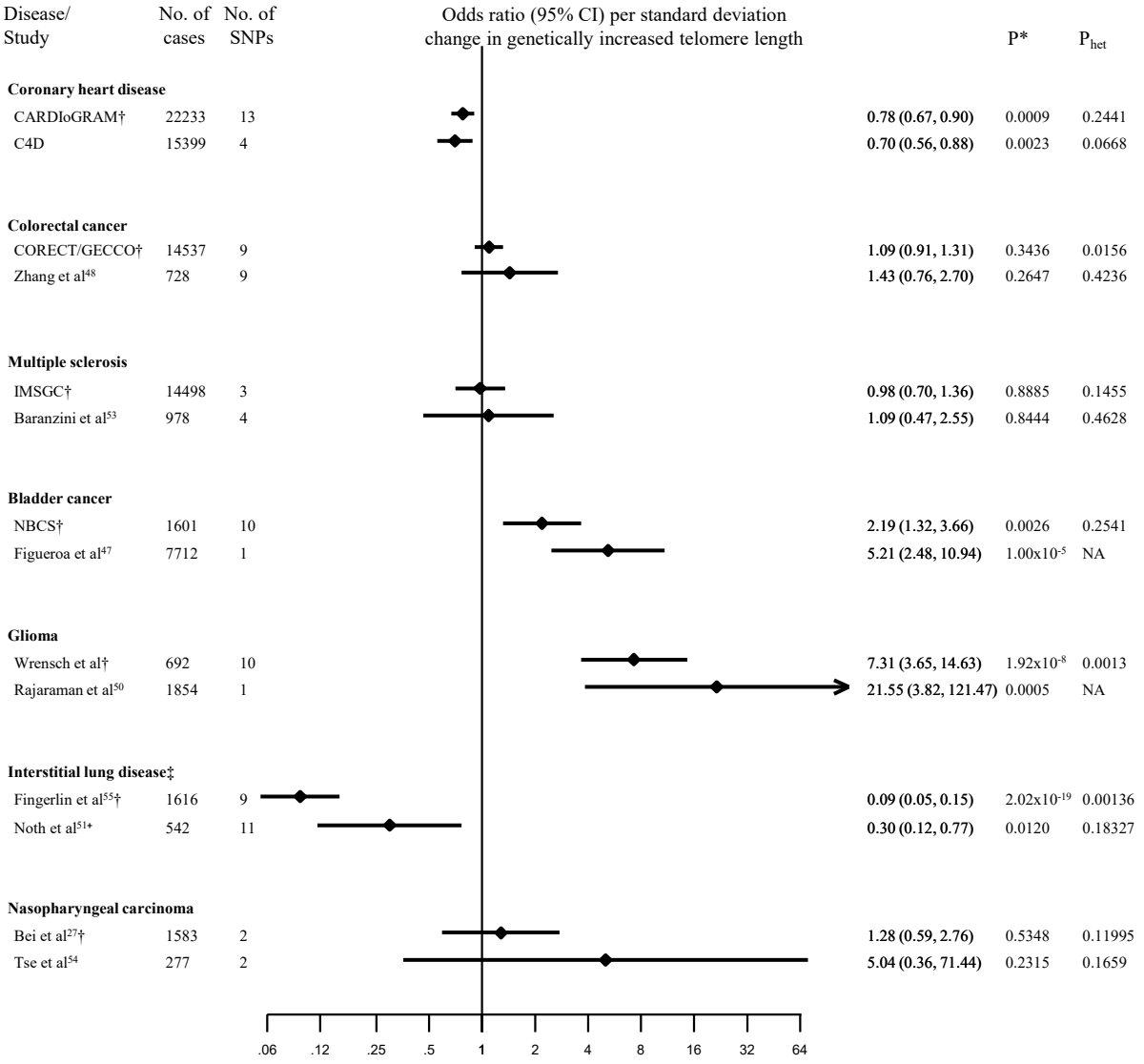
Supplementary Figure S2. Association between genetically increased telomere length and odds of secondary non-communicable diseases



	No. of cases	No. of SNPs	Odds ratio (95% CI) per standard deviation change in genetically increased telomere length	P*	P_{het}
Cancer					
Multiple myeloma	4692	1	10.02 (3.84, 26.13)	$2.46x10^{-6}$	NA
Chronic lymphocytic leukemia	2883	1	10.02 (3.56, 28.21)	$1.00x10^{-5}$	NA
Thyroid cancer	649	12	3.98 (1.69, 9.36)	0.0016	0.0623
Ewing sarcoma	401	4	2.11 (0.67, 6.62)	0.2000	0.1398
Chronic myeloid leukemia	201	8	1.67 (0.46, 5.97)	0.4334	0.1872
Gastric noncardia adenocarcinoma	632	11	1.50 (0.85, 2.63)	0.1633	0.8160
Upper gastrointestinal cancers	3523	2	1.43 (0.69, 2.96)	0.3303	0.3248
Nasopharyngeal carcinoma	1860	2	1.42 (0.68, 2.95)	0.3526	0.2794
Gallbladder cancer	41	2	1.34 (0.03, 52.74)	0.8757	0.7905
Non-Hodgkin lymphoma	253	10	1.24 (0.47, 3.27)	0.6623	0.5937
Follicular lymphoma	212	3	1.22 (0.28, 5.35)	0.7943	0.7440
Gastric cardia adenocarcinoma	1126	11	1.19 (0.75, 1.88)	0.4630	0.3249
Skin cancer (squamous cell carcinoma)	449	13	0.65 (0.31, 1.36)	0.2476	0.0288
Neurological / psychiatric diseases					
Parkinsons	1713	4	1.05 (0.62, 1.77)	0.8665	0.3926
Bulimia nervosa	151	8	0.94 (0.88, 1.01)	0.1152	0.5695
Panic disorder	718	8	0.28 (0.12, 0.66)	0.0036	0.6420
Autoimmune/inflammatory diseases					
Kawasaki disease	405	11	2.04 (1.00, 4.16)	0.0492	0.8998
Vitiligo	1117	2	1.64 (0.68, 3.93)	0.2675	0.2943
Systemic lupus erythematosus	1311	4	1.59 (0.88, 2.88)	0.1244	0.8541
Inflammatory psoriatic arthritis	609	13	1.42 (0.64, 3.12)	0.3881	0.6041
Narcolepsy	1188	9	1.01 (0.53, 1.92)	0.9850	0.4743
Psoriasis	1139	9	0.93 (0.47, 1.86)	0.8422	0.9796
Wegeners granulomatosis	492	10	0.77 (0.27, 2.17)	0.6192	<0.0001
Sarcoidosis	564	9	0.50 (0.21, 1.23)	0.1315	0.4390
Other					
Vascular dementia	84	8	1.91 (0.27, 13.50)	0.5187	0.1404
Paget's disease	741	12	0.96 (0.54, 1.71)	0.8950	0.6868
Hirschsprung disease	173	6	0.74 (0.15, 3.70)	0.7148	0.0118

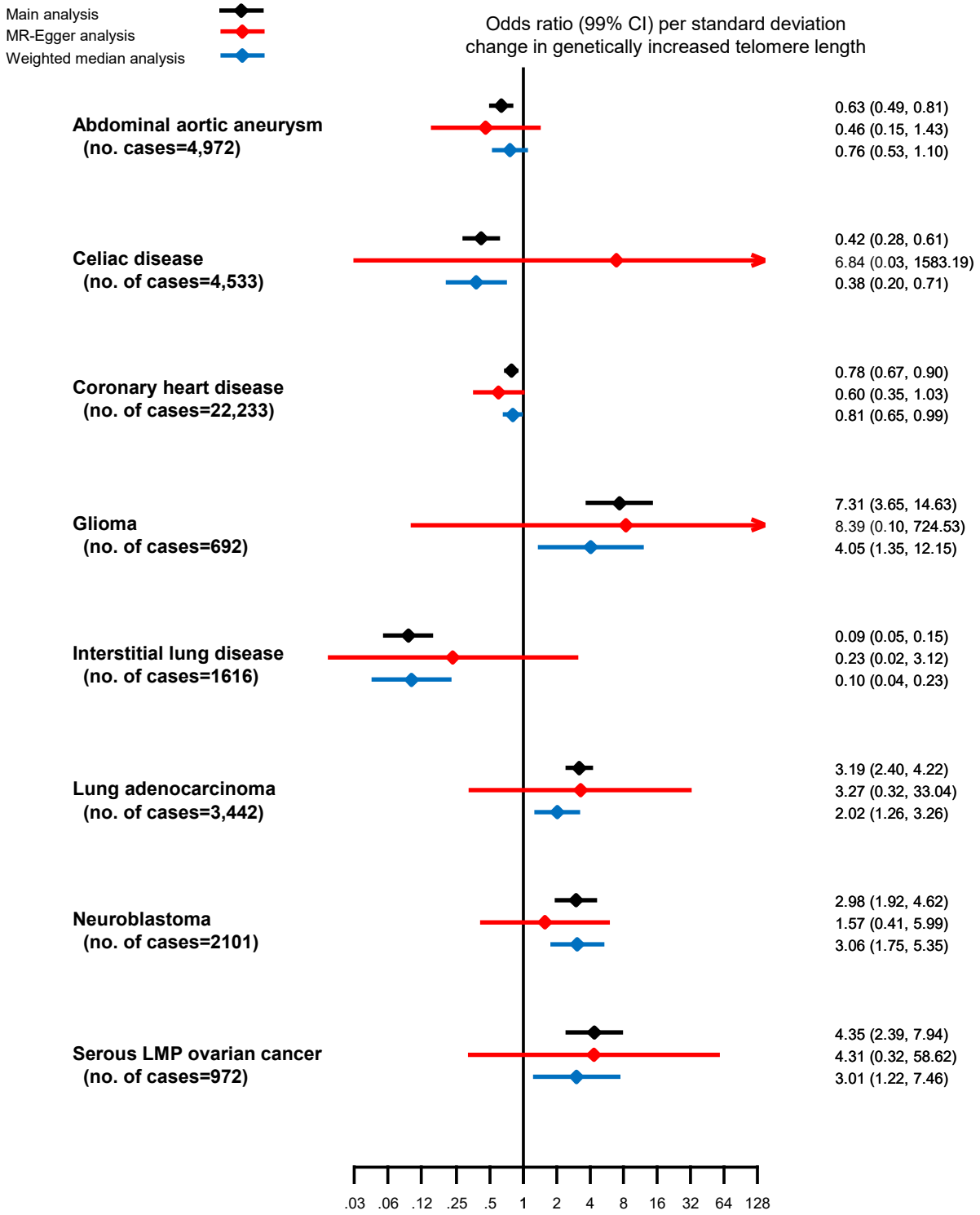
*P value for association between genetically increased telomere length and disease from maximum likelihood; P_{het}, p value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval

Supplementary Figure S3. Replication of association between genetically increased telomere length and odds of non-communicable diseases in independent datasets



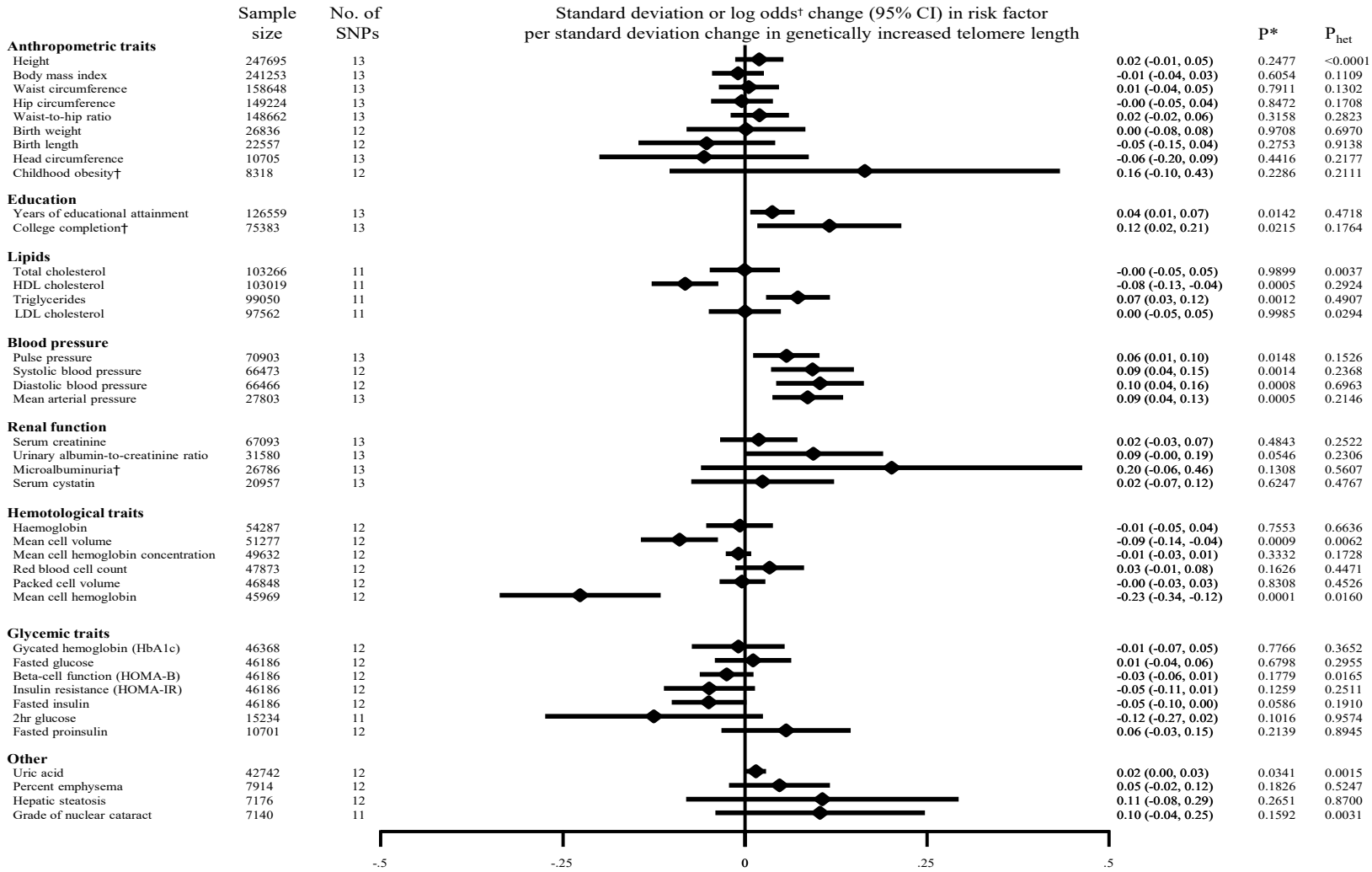
*P value for association between genetically increased telomere length and disease from maximum likelihood; †Primary or secondary study from Fig. 1 or Fig. S2. [+]Noth et al[70]: ≤17% of the cases overlapped with cases from Fingerlin et al[25] and 77% of cases had idiopathic pulmonary fibrosis; ‡An inverse association was also observed in Mushiroda et al[71]. P_{het}, p value for heterogeneity amongst SNPs in the genetic risk score (NA when only a single SNP available); SNP, single nucleotide polymorphism; CI, confidence interval. **Study abbreviations**: **C4D**, Coronary Artery Disease Genetics Consortium; **CARDIoGRAM**, Coronary ARtery DIsease Genome wide Replication and Meta-analysis; **CORECT**, ColoRectal Transdisciplinary Study; **GECCO**, Genetics and Epidemiology of Colorectal Cancer Consortium; **IMSGC**, International Multiple Sclerosis Genetic Consortium; **NBCS**, Nijmegen Bladder Cancer Study; **IMSGC**, International Multiple Sclerosis Genetic Consortium

Supplementary Figure S4. Sensitivity analyses of association between genetically increased telomere length and odds of non-communicable diseases



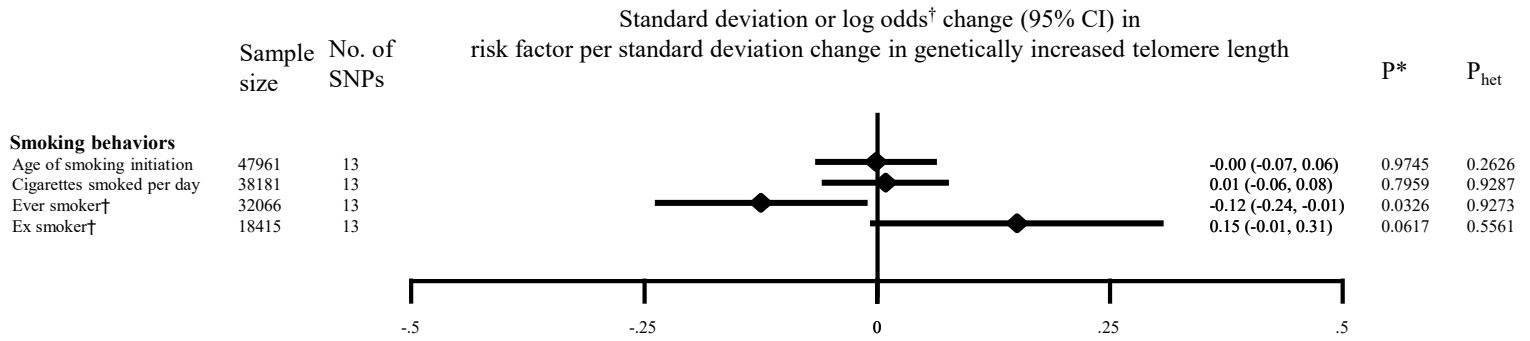
LMP, low malignancy potential; CI, confidence interval. The p-values for presence of pleiotropy from MR-Egger regression were: 0.51 for abdominal aortic aneurysm, 0.32 for celiac disease, 0.27 for coronary heart disease, 0.90 for glioma, 0.41for interstitial lung disease, 0.94 for lung adenocarcinoma, 0.38 for neuroblastoma and 0.91 for serous low malignant potential ovarian cancer.

Supplementary Figure S5. Association between genetically increased telomere length and risk factors for non-communicable diseases



*P value for association between genetically increased telomere length and risk factor from maximum likelihood; P_{het}, p value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval; HbA1c, hemoglobin A1c; HOMA-B, homeostatic model assessment β-cell function; IR, insulin resistance; †for binary risk factors results reflect the log odds ratio for the risk factor, all other results reflect the standard deviation change in the risk factor

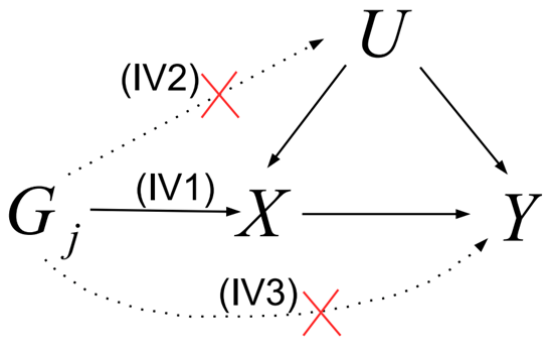
Supplementary Figure S6. Association between genetically increased telomere length and smoking



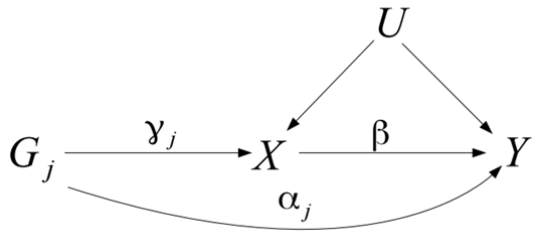
*P value for association between genetically increased telomere length and risk factor from maximum likelihood; P_{het}, p value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval; †for binary risk factors results reflect the log odds ratio for the risk factor, all other results reflect the standard deviation change in the risk factor

Supplementary Figure S7. Causal diagram illustrating the assumptions of Mendelian randomization

a)



b)



IV, instrumental variable assumption; G, genetic variant; X, telomere length; Y, outcome (disease or risk factor); U, confounder; α, G-Y association not mediated by telomere length; γ, G-X
a) Key assumptions of Mendelian randomization. G_j is associated with X (IV1); G_i is independent of confounders (IV2); G_i is independent of Y given X and U (IV3). The weighted median approach assumes that IV1-IV3 hold for genetic variants making up at least 50% of the weight in the analysis; MR-Egger relaxes assumption IV3 (see InSIDE assumption below).
b) Assumptions underlying the MR-Egger approach. IV3 is replaced with the InSIDE assumption (Instrument Strength Independent of Direct Effect): the strength of the pleiotropic effect (αj) does not correlate with the strength of the G-X association (γj)

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Amyotrophic lateral sclerosis GWAS consortia

Isabella Fogh[1], Kuang Lin[1], John F. Powell[1], the SLAGEN Consortium, Vincenzo Silani[2], the ALSGEN consortium, Orla Hardiman[3], Robert H. Brown[4], Ammar Al-Chalabi[1], Jan H. Veldink[5].

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The Aneurysm Consortium

GWAS data on abdominal aortic aneurysm (AAA) studies

All known studies with AAA genome-wide genotyping were invited to join the International Aneurysm Consortium. All studies agreed to participate in the meta-GWAS, with cohort case control descriptions and inclusion/exclusion criteria having been previously reported.[22,116,117] All AAA cases shared a common definition of infra-renal aortic diameter >30 mm.

Descriptions of AAA cohorts

In the present report, the Aneurysm Consortium consists of the original Aneurysm Consortium plus the NZ AAA Genetics Study (two separate cohorts), the Geisinger Vascular Clinic AAA study, the Iceland study and the Netherlands study.

Original Aneurysm Consortium (1846 cases and 5605 controls): The original Aneurysm Consortium recruited cases of AAA from centres across the United Kingdom and Western Australia. Cases were defined as an infra-renal aortic diameter ≥ 30 mm proven on ultrasound or computerized tomography (CT) scan. Controls were taken from the WTCCC2 common control group[22,118] and were therefore unscreened for AAA.

458 NZ AAA Genetics Study (with two separate cohorts: set 1 with 608 cases and 612 controls; set 2
459 with 397 cases and 384 controls): The Vascular Research Consortium of New Zealand recruited
460 New Zealand men and women with a proven history of AAA (infra-renal aortic diameter ≥ 30 mm
461 proven on ultrasound or CT scan). Approximately 80% had undergone surgical AAA repair
462 (typically AAA's > 50-55 mm in diameter). The vast majority of cases (>97%) were of Anglo-
463 European ancestry. The control group underwent an abdominal ultrasound scan to exclude (>25
464 mm) concurrent abdominal aortic aneurysm and Anglo-European ancestry was required for
465 inclusion. Controls were also screened for peripheral artery disease (PAD; using ankle brachial
466 index), carotid artery disease (ultrasound) and other cardiovascular risk factors.
467
468 Geisinger Vascular Clinic AAA Study, Pennsylvania, USA: AAA patients (n=724) were enrolled
469 through the Department of Vascular Surgery at Geisinger Medical Center, Danville, PA. Details of
470 this case-control set have been reported previously, and the samples have been used in previous
471 association studies.[116,119] To identify cases and controls from the electronic medical records, an
472 ePhenotyping algorithm was developed[23]. AAA cases were defined as infrarenal aortic diameter ≥
473 30 mm as revealed by abdominal imaging. Approximately 20% of individuals with AAA had a
474 family history of AAA. A control group (n=1231) was obtained through the Geisinger MyCode®
475 Project, a cohort of Geisinger Clinic patients recruited for genomic studies. The MyCode® controls
476 were matched for age distribution and sex to the Geisinger Vascular Clinic AAA cases. Based on
477 electronic medical records, controls had no ICD-9 codes for AAA in their records, but they were
478 not screened by ultrasonography for AAA. Both cases and controls from the Geisinger Clinic were
479 of European descent. The eMERGE Network Imputed GWAS for 41 Phenotypes (the dbGaP
480 eMERGE Phase 1 and 2 Merged data Submission) accession number is: phs000888.v1.p1 which
481 includes the Geisinger AAA data.
482

Iceland, deCODE Genetics: Icelandic individuals with AAA (defined as infra-renal aortic diameter ≥ 30 mm) were recruited from a registry of individuals who were admitted at Landspitali University Hospital, in Reykjavik, Iceland, 1980 – 2006. AAA patients were either followed up or treated by intervention for emergency repair of symptomatic or ruptured AAA or for an elective repair by surgery or endovascular intervention. In total, whole genome data from 557 subjects with AAA, enrolled as part of the CVD genetics program at deCODE, were included in the metaGWAS. The Icelandic controls used (n=89,235) were selected from among individuals who have participated in various GWA studies and who were recruited as part of genetic programs at deCODE. Individuals with known cardiovascular disease were excluded as controls[116] but controls were unscreened for AAA.

The Netherlands: The AAA sample set from Utrecht was recruited in 2007-2009 from eight centres in The Netherland[116], mainly when individuals visited their vascular surgeon in the polyclinic or, in rare cases, during hospital admission for elective or emergency AAA surgery. An AAA was defined as an infrarenal aorta ≥ 30 mm. The sample set (n=840) comprised 89.9% males, with a mean AAA diameter of 58.4 mm, 61.7% had received surgery, of which 8.1 % was after rupture. The Dutch controls (n=2791) used in the AAA GWAS were recruited as part of the Nijmegen Biomedical Study and the Nijmegen Bladder Cancer Study (see http://dceg.cancer.gov/icbc/membership.html).

Meta-analysis of AAA GWASs

Data from the six cohorts detailed above, comprising 4972 AAA cases and 99,858 controls, that were genotyped with a variety of genome-wide SNP arrays. All cohorts underwent quality control filtering using the manufacturers' array-specific guidelines but with consistently applied inclusion criteria of SNP or sample call rates >95% and Hardy-Weinberg equilibrium $P>5x10^{-5}$ in controls.[22,116,117,119] Each cohort then underwent imputation (Impute 2.2) to a shared reference panel from the 1000 Genomes project (Phase I integrated variant set release (v3), March 2012, NCBI

build 37(hg19 Following imputation SNPs were quality controlled by quality score (Q>0.9) and minor allele frequency (MAF>0.05 in controls) filtering, resulting in a common set of 5331120 SNPs across all discovery phase participants.

The metaGWAS analysis was conducted using the METAL software package[120] on the BCISNPmax database platform (version 3.5, BCI Platforms, Espoo, Finland). METAL was implemented using the sample size scheme with weighting for each cohort being two times the case number. The analysis was adjusted for genomic inflation (λ) in each cohort.

Acknowledgements on AAA GWAS studies:

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implemented using the sample size scheme with weighting for each cohort being two times the case number. The analysis was adjusted for genomic inflation (λ) in each cohort.

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COPDGene

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Glioma

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974 **Endometriosis GWA meta-analysis**

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European Periodontitis Genetics Group (EPG)

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The aggressive periodontitis control sample consists of three independent studies:

1. The Heinz-Nixdorff-Recall (HNR) was described in Schmermund, A., *et al.* Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk Factors, Evaluation of Coronary Calcium and Lifestyle. *Am Heart J* **144**, 212-18 (2002). The HNR study was supported by the Heinz Nixdorf Foundation (Germany). Additionally, the study was funded by the German Ministry of Education and Science and the German Research Council (DFG; Project SI 236/8-1, SI236/9-1, ER 155/6-1). The genotyping of the Illumina HumanOmni-1 Quad BeadChips of the HNR subjects was financed by the German Centre for Neurodegenerative Disorders (DZNE), Bonn. We are extremely grateful to all investigators who contributed to the generation of this dataset.

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2. The Dortmund Health Study (DOGS) is described in Berger, K. *et. al*. DHS: The Dortmund health study. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* **55**, 816-21 (2012). DOGS is supported by the German Migraine & Headache Society (DMKG) and by unrestricted grants of equal share from Almirall, Astra Zeneca, Berlin Chemie, Boehringer, Boots Health Care, Glaxo-Smith-Kline, Janssen Cilag, McNeil Pharma, MSD Sharp & Dohme and Pfizer to the University of Muenster (collection of sociodemographic and clinical data). Blood collection in the Dortmund Health Study was done through funds from the Institute of Epidemiology and Social Medicine University of Muenster.

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3. The FOCUS (Food chain plus) control sample is described in Muller, N., *et al.* IL-6 blockade by monoclonal antibodies inhibits apolipoprotein (a) expression and lipoprotein (a) synthesis in humans. *J Lipid Res* **56**, 1034-42 (2015). FOCUS was supported by the Federal Ministry of Education and Research BMBF (FKZ 0315540A). FOCUS is represented by Matthias Laudes[1]

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(http://practical.ccge.medschl.cam.ac.uk/)

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