Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases

Mendelian randomization study of the association between telomere length and risk of cancer and non-neoplastic diseases

The Telomeres Mendelian Randomization Collaboration

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2995 words [word limit 3000]

3 figures, 2 tables, 132 references; 7 supplementary figures / 6 supplementary tables

ABSTRACT 349 WORDS

Importance The causal direction and magnitude of the association between telomere length and incidence of cancer and non-neoplastic diseases is uncertain, due to the susceptibility of observational studies to confounding and reverse causation.

Objective To conduct a Mendelian randomization study, using germline genetic variants as instrumental variables, to appraise the causal relevance of telomere length for risk of cancer and non-neoplastic diseases.

Data Sources Genome-wide association studies (GWAS) published up to January 15 2015.

Study Selection GWAS of non-communicable diseases that assayed germline genetic variation and did not select cohort or control participants on the basis of pre-existing diseases. Of 163 GWAS of non-communicable diseases identified, summary data from 103 were available.

Data Extraction Summary association statistics for single nucleotide polymorphisms (SNPs) that are strongly associated with telomere length in the general population.

Main Outcomes Odds ratios (ORs) for disease per standard deviation (SD) higher telomere length due to germline genetic variation.

Results Summary data were available for 35 cancers and 48 non-neoplastic diseases, corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median 6,789 per disease). Increased telomere length due to germline genetic variation was generally associated with increased risk for site-specific cancers. The strongest associations were observed for (ORs per 1-SD change in genetically increased telomere length): glioma 5.27 (3.15-8.81), serous low-malignant-potential ovarian cancer 4.35 (2.39-7.94), lung adenocarcinoma 3.19 (2.40-4.22), neuroblastoma 2.98 (1.92-4.62), bladder cancer 2.19 (1.32-3.66), melanoma 1.87 (1.55-2.26), testicular cancer 1.76 (1.02-3.04), kidney cancer 1.55

(1.08-2.23) and endometrial cancer 1.31 (1.07-1.61). Associations were stronger for rarer cancers and at tissue sites with lower rates of stem cell division ($P<0.05$). There was generally little evidence of association between genetically increased telomere length and risk of psychiatric, autoimmune, inflammatory, diabetic and other non-neoplastic diseases, except for coronary heart disease (0.78 [0.67-0.90]), abdominal aortic aneurysm (0.63 [0.49-0.81]), celiac disease (0.42 [0.28-0.61]) and interstitial lung disease (0.09 [0.05- 0.15]).

Conclusions It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases.

INTRODUCTION

At the ends of chromosomes, telomeres are DNA-protein structures that protect the genome from damage, shorten progressively over time in most somatic tissues[1] and are proposed physiological markers of ageing.[2,3] Shorter leukocyte telomeres are correlated with older age, male sex and other known risk factors for non-communicable diseases[4–6] and are generally associated with higher risk for cardiovascular diseases[7,8], type 2 diabetes[9] and non-vascular non-neoplastic causes of mortality.[8] Whether these associations are causal, however, is unknown. Telomere length has also been implicated in risk of cancer but the direction and magnitude of the association is uncertain and contradictory across observational studies.[10–14] The uncertainty reflects the considerable difficulty of designing observational studies of telomere length and cancer incidence that are robust to reverse causation, confounding and measurement error.

The aim of the present report was to conduct a Mendelian randomization study, using germline genetic variants as instrumental variables for telomere length, to help clarify the nature of the association between telomere length and risk of cancer and non-neoplastic diseases. The approach, which mimics the random allocation of individuals to the placebo and intervention arms of a randomized controlled trial, allowed us to: (1) estimate the direction and broad magnitude of the association of telomere length with risk of multiple cancer and non-neoplastic diseases; (2) appraise the evidence for causality in the estimated etiological associations; (3) investigate potential sources of heterogeneity in findings for site-specific cancers; and (4) compare genetic estimates to findings based on directly measured telomere length in prospective observational studies.

METHODS

Study design

The design of our study, illustrated in Figure S1, had three key components: 1) the identification of genetic variants to serve as instruments for telomere length; 2) the acquisition of summary data for the genetic instruments from genome wide association studies (GWASs) of diseases and risk factors for non-communicable diseases; and 3) the classification of diseases and risk factors into primary or secondary outcomes based on *a priori* statistical power. As a first step, we searched the GWAS catalog[15,16] on the 15 January 2015, to identify single nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with additional potential instruments, we also searched the original study reports curated by the GWAS catalog (using a P-value threshold of $5x10^{-8}$).[17–25] We acquired summary data for all SNPs identified by our search from a meta-analysis of GWASs of telomere length, involving 9,190 participants of European ancestry.[18]

The second key component of our design strategy involved the acquisition of summary data, corresponding to the selected genetic instruments for telomere length, from GWASs of non-communicable diseases and risk factors (Fig. S1). As part of this step, we invited principal investigators of non-communicable disease studies curated by the GWAS catalog[15,26] to share summary data for our study (see Fig. S1 for further details). We also downloaded summary data for diseases and risk factors from publically available sources, including study-specific websites, dbGAP, ImmunoBase and the GWAS catalog (Fig. S1).

The third key component of our design strategy was the classification of diseases and risk factors into either primary or secondary outcomes, which we defined on the basis of *a priori* statistical power to detect associations with telomere length. Primary outcomes were defined

as diseases with sufficient cases and controls for >50% statistical power and secondary outcomes defined as diseases with <50% statistical power to detect odds ratios ≥2.0 per standard deviation (SD) change in genetically increased telomere length (alpha assumed to be 0.01). All risk factors were defined as secondary outcomes. Risk factors with <50% statistical power were excluded.

Further details on our design strategy can be found in the supplement.

Comparison with prospective observational studies

We searched PubMed for prospective observational studies of the association between telomere length and disease (see Tables S3 and S4 for details of the search strategy and inclusion criteria). Study-specific relative risks for disease per unit change or quantile comparison of telomere length were transformed to a SD scale using previously described methods.[27] Hazard ratios, risk ratios and odds ratios were assumed to approximate the same measure of relative risk. Where multiple independent studies of the same disease were identified, these were combined by fixed effects meta-analysis, unless there was strong evidence of between-study heterogeneity ($P_{Cochran's\ Q}<0.001$), in which case they were kept separate.

Statistical analysis

We combined summary data across SNPs into a single instrument, 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,[28] where β_{GD} is the change in disease log odds or risk factor levels per copy of the effect allele and β_{GP} is the SD change in telomere length per copy of the effect allele (see supplementary methods

144 for technical details). The slope from this approach can be interpreted as the log odds ratio for
145 binary outcomes, or the unit change for continuous risk factors, per SD change in genetically
146 increased telomere length. P-values for heterogeneity amongst SNPs, in the estimated
147 associations of genetically increased telomere length with disease and risk factors, were
148 estimated by likelihood ratio tests.[28] Associations between genetically increased telomere
149 length and continuous risk factors were transformed into SD units. For five secondary disease
150 outcomes where only a single SNP was available for analysis, we estimated associations
151 using the Wald ratio: $\beta_{GD}/\beta_{GP,}$ with standard errors approximated by the delta method.[29]

152 Inference of causality in the estimated etiological associations between telomere length and
153 disease depends on satisfaction of Mendelian randomization assumptions (Fig. S7; see Table
154 S6 for a glossary of terms).[30,31] The assumptions are: 1) the selected SNPs are associated with
155 telomere length; 2) the selected SNPs are not associated with confounders; and 3) the selected
156 SNPs are associated with disease exclusively through their effect on telomere length. If these
157 assumptions are satisfied, the selected SNPs are valid instrumental variables and their
158 association with disease can be interpreted as a causal effect of telomere length. We modeled
159 the impact of violations of these assumptions through two sets of sensitivity analyses: a
160 weighted median function[32] and MR-Egger regression[30] (see supplementary methods for
161 technical details). We restricted our sensitivity analyses to diseases showing the strongest
162 evidence of association with genetically increased telomere length (defined as
163 $P_{Bonferroni} \leq 0.05$).
164
165 We used meta-regression to appraise potential sources of heterogeneity in our findings for
166 cancer. The association of genetically increased telomere length with the log odds of cancer
167 was regressed on cancer incidence, survival time and median age-at-diagnosis, downloaded
168 from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)

Program,[33] and tissue-specific rates of stem cell division from Tomasetti and Vogelstein.[34] As the downloaded cancer characteristics from SEER correspond to the United States population, 77% of which was of white ancestry in 2015[35], the meta-regression analyses excluded genetic studies conducted in East Asian populations.

All analyses were performed in R version 3.1.2[36] and Stata release 13.1 (StataCorp, College Station, TX). P-values were two-sided and evidence of association was declared at $P<0.05$. Where indicated, Bonferroni corrections were used to make allowance for multiple testing, although this is likely to be overly conservative given the non-independence of many of the outcomes tested.

RESULTS

We selected 16 SNPs as instruments for telomere length (Fig. S1 & Table 1). The selected SNPs correspond to 10 independent genomic regions that collectively account for 2-3% of the variance in leukocyte telomere length, which is equivalent to an F statistic of ~18. This indicates that the genetic instrument, constructed from these 10 independent genomic regions, is strongly associated with telomere length (details in supplementary discussion).[37] Summary data for the genetic instruments were available for 83 non-communicable diseases, corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median 6,789 per disease), and 44 risk factors (Fig. S1, Table 2 and Table S1). The median number of SNPs available across diseases was 11 (min=1, max=13) and across risk factors was 12 (min=11, max=13). Of the 83 diseases, 56 were classified as primary outcomes and 27 as secondary outcomes (Table 2, Fig. S1 and Table S1). For 9 of the 83 non-communicable diseases, additional summary data were available from 10 independent studies for replication

194 analyses, corresponding to 40,465 cases (median 1,416 per disease) and 52,306 controls
195 (median 3,537 per disease) (Table S1).

196 The results from primary analyses of non-communicable diseases are presented in Figure 1;
197 results from secondary analyses of risk factors and diseases with low *a priori* power are
198 presented in the supplement (Fig. S2, S5 and S6). Genetically increased telomere length was
199 associated with higher odds of disease for 9 of 22 primary cancers ($P<0.05$), including (odds
200 ratio [95% confidence interval]): glioma (5.27 [3.15-8.81]), endometrial cancer (1.31 [1.07-
201 1.61]), kidney cancer (1.55 [1.08-2.23]), testicular germ cell cancer (1.76 [1.02-3.04]),
202 melanoma (1.87 [1.55-2.26]), bladder cancer (2.19 [1.32-3.66]), neuroblastoma (2.98 [1.92-
203 4.62]), lung adenocarcinoma (3.19 [2.40-4.22]) and serous low-malignancy-potential (LMP)
204 ovarian cancer (4.35 [2.39-7.94]) (Fig. 1). The associations were, however, highly variable
205 across cancer types, varying from an odds ratio of 0.86 (0.50-1.48) for head and neck cancer
206 to 5.27 (3.15-8.81) for glioma. Substantial variability was also observed within tissue sites.
207 For example, the odds ratio for lung adenocarcinoma was 3.19 (2.40-4.22) compared to 1.07
208 (0.82-1.39) for squamous cell lung cancer. For serous LMP ovarian cancer the odds ratio was
209 4.35 (2.39-7.94) compared to odds ratios of 1.21 (0.87-1.68) for endometrioid ovarian cancer,
210 1.12 (0.94-1.34) for serous invasive ovarian cancer, 1.04 (0.66-1.63) for clear cell ovarian
211 cancer and 1.04 (0.73-1.47) for mucinous ovarian cancer. The strongest evidence of
212 association was observed for glioma, lung adenocarcinoma, neuroblastoma and serous LMP
213 ovarian cancer ($P_{Bonferroni}<0.05$). Results for glioma and bladder cancer showed evidence for
214 replication in independent datasets (independent datasets were not available for other
215 cancers) (Fig. S3).

216 Genetically increased telomere length was associated with reduced odds of disease for 6 of 32
217 primary non-neoplastic diseases ($P<0.05$), including coronary heart disease (0.78 [0.67-0.9]),
218 abdominal aortic aneurysm (0.63 [0.49-0.81]), Alzheimer's disease (0.84 [0.71-0.98]), celiac

disease (0.42 [0.28-0.61]), interstitial lung disease (0.09 [0.05-0.15]) and type 1 diabetes (0.71 [0.51-0.98]) ($P<0.05$) (Figure 1). The strongest evidence of association was observed for coronary heart disease ($P_{Bonferroni}=0.05$) and abdominal aortic aneurysm, celiac disease and interstitial lung disease ($P_{Bonferroni}<0.05$). The associations with coronary heart disease and interstitial lung disease showed evidence for replication in independent datasets (Fig. S3).

Our genetic findings were generally similar in direction and magnitude to estimates based on observational prospective studies of leukocyte telomere length and disease (Figure 3). Our genetic estimates for lung adenocarcinoma, melanoma, kidney cancer and glioma, were, however, stronger in comparison to observational estimates.

In sensitivity analyses, we appraised the potential impact of confounding by pleiotropic pathways on our results. Associations estimated by the weighted median and MR-Egger were broadly similar to the main results for glioma, lung adenocarcinoma, serous LMP ovarian cancer, neuroblastoma, abdominal aortic aneurysm, coronary heart disease and interstitial lung disease (Fig. S4). In the second set of sensitivity analyses, implemented by MR-Egger regression, we found little evidence for the presence of pleiotropy ($P_{intercept}\geq0.27$) (Fig. S4). The MR-Egger analyses were, however, generally underpowered, as reflected by the wide confidence intervals in the estimated odds ratios.

In meta-regression analyses, we observed that genetically increased telomere length tended to be more strongly associated with rarer cancers ($P=0.02$) and cancers at tissue-sites with lower rates of stem cell division ($P=0.02$) (Figure 2). The associations showed little evidence of varying by percentage survival five years after diagnosis or median age-at-diagnosis ($P\geq37$).

DISCUSSION

In this report we show that genetically increased telomere length is associated with increased risk of several cancers and with reduced risk of some non-neoplastic diseases. 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, these results should be less susceptible to confounding and reverse causation in comparison to observational studies. Our results are therefore compatible with causality. On the other hand, our results could reflect violations of Mendelian randomization assumptions, such as confounding by pleiotropy, population stratification or ancestry.[38] Although we cannot entirely rule out this possibility, the majority of our results persisted in sensitivity analyses that made allowance for violations of Mendelian randomization assumptions. Confounding by population stratification or ancestry is also unlikely, given the adjustments made for ancestry in the disease GWASs (see supplementary discussion).

Comparison with previous studies

Our findings for cancer are generally contradictory to those based on retrospective studies, which tend to report increased risk for cancer in individuals with shorter telomeres.[11,12,39–42] The contradictory findings may reflect reverse causation in the retrospective studies, whereby shorter telomeres arise as a result of disease, or of confounding effects, e.g. due to cases being slightly older than controls even in age-matched analyses. Our findings for cancer are generally more consistent with those based on prospective observational studies, which tend to report weak or null associations of longer leukocyte telomeres with overall and site-specific risk of cancer,[10–13,41,43–62] with some exceptions.[63] Our results are also similar to previously reported Mendelian randomization studies of telomere length and risk of

melanoma, lung cancer, chronic lymphocytic leukemia and glioma.[64–67] The shape of the association with cancer may not, however, be linear over the entire telomere length distribution. For example, individuals with dyskeratosis congenita, a disease caused by germline loss-of-function mutations in the telomerase component genes *TERC* and *TERT,* have chronically short telomeres and are at increased risk of some cancers, particularly acute myeloid leukemia and squamous cell carcinomas arising at sites of leukoplakia,[68,69] presumably due to increased susceptibility to genome instability and chromosomal end-to-end fusions.[70] Our results should therefore be interpreted as reflecting the average association at the population level and may not be generalizable to the extreme ends of the telomere length distribution.

Mechanisms of association

Our cancer findings are compatible with known biology.[70] By limiting the proliferative potential of cells, telomere shortening may serve as a tumour suppressor; and individuals with longer telomeres may be more likely to acquire somatic mutations owing to increased proliferative potential.[70] Rates of cell division are, however, highly variable amongst tissues[34] and thus the relative gain in cell proliferative potential, conferred by having longer telomeres, may also be highly variable across tissues. This could explain the ~6-fold variation in odds ratios observed across cancer types in the present study, as well as the tendency of our results to be stronger at tissue sites with lower rates of stem cell division. For example, the association was strongest for glioma (OR=5.27) and comparatively weak for colorectal cancer (OR=1.09) and the rates of stem cell division in the tissues giving rise to these cancers differ by several orders of magnitude. In neural stem cells, which give rise to gliomas, the number of divisions is ~270 million and for colorectal stem cells is ~1.2 trillion over the average lifetime of an individual.[34] The observation that genetically increased telomere

length was more strongly associated with rarer cancers potentially reflects the same mechanism, since rarer cancers also tend to show lower rates of stem cell division.[34] For example, the incidence of glioma is 0.4 and for colorectal cancer is 42.4 per 100,000 per year in the United States.[33]

The inverse associations observed for some non-neoplastic diseases may reflect the impact of telomere shortening on tissue degeneration and an evolutionary trade-off for greater resistance to cancer at the cost of greater susceptibility to degenerative diseases, particularly cardiovascular diseases.[71,72]

Study limitations

Our study is subject to some limitations, in addition to the Mendelian randomization assumptions already considered above. First, our method assumes that the magnitude of the association between SNPs and telomere length is consistent across tissues. Second, our study assumed a linear shape of association between telomere length and disease risk, whereas the shape could be "J" or "U" shaped.[44,57,68] Third, our results assume that the samples used to define the genetic instrument for telomere length[18] and the various samples used to estimate the SNP-disease associations are representative of the same general population, practically defined as being of similar ethnicity, age and sex distribution.[73] This assumption would, for example, not apply in the case of the SNP-disease associations derived from East Asian or pediatric populations. Generally speaking, violation of the aforementioned assumptions could bias the magnitude of the association between genetically increased telomere length and disease; but would be unlikely to increase the likelihood of false positives (i.e. incorrectly inferring an association when none exists).[74] Our results should therefore remain informative for the direction and broad magnitude of the average association at the population level, even

in the presence of such violations. Fourth, we cannot rule out chance in explaining some of the weaker findings. Fifth, our results may not be fully representative of non-communicable diseases (since not all studies shared data and our analyses were underpowered for the secondary disease outcomes). The diseases represented in our primary analyses probably account for >60% of all causes of death in American adults.[75]

Clinical relevance of findings

Our findings suggest that potential clinical applications of telomere length, e.g. as a tool for risk prediction or as an intervention target for disease prevention, may have to consider a trade-off in risk between cancer and non-neoplastic diseases. For example, a number of companies have been established that offer telomere length measurement services to the public (via a requesting physician), under the claim that shorter telomeres are a general indicator of poorer health status and older biological age and that such information can be used to motivate healthy lifestyle choices in individuals. However, the conflicting direction of association between telomere length and risk of cancer and non-neoplastic diseases, indicated by our findings, suggests that such services to the general public may be premature.

Conclusion

It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases. Further research is required to resolve whether telomere length is a useful predictor of risk that can help guide therapeutic interventions, to clarify the shape of any dose-response relationships and to characterise the nature of the association in population subgroups.

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350 Melanoma meta-analysis consortium; Qiong Yang[17], Bradford B. Worrall[18] and Hugh
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352 and Chris I Amos[22] on behalf of the ILCCO consortium; Amanda Spurdle[23], Deborah J
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357 Ulrika Svenson[42] on behalf of EPIC; Andre van Rij[43], Annette F Baas[44], Matthew J Bown[45],
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360 Consortium; Mattias Johansson[49]; James Mckay[49]; Ghislaine Scelo[49]; Robert Carreras-
361 Torres[49]; Valerie Gaborieau[49]; Paul Brennan[49]; Paige M. Bracci[50], Rachel E Neale[15], Sara H
362 Olson[51], Steven Gallinger[20], Donghui Li[52], Gloria M. Petersen[54], Harvey Risch[55], and Alison
363 P. Klein[56] on behalf of PanC[4]; Jiali Han[57,58]; Christian C. Abnet[59]; Neal D. Freedman[59]; Philip
364 R. Taylor[59]; John M Maris[60]; Katja K Aben[61,62]; Lambertus A Kiemeney[61]; Sita H
365 Vermeulen[61]; John K Wiencke[63,64]; Kyle M Walsh[63,64]; Margaret Wrensch[63,64]; Terri Rice[63];
366 Clare Turnbull[65]; Kevin Litchfield[66]; Lavinia Paternoster[1] and Marie Standl[67] on behalf of the
367 EAGLE consortium; Gonçalo R Abecasis[68]; John Paul SanGiovanni[69]; Lars G Fritsche[68];
368 Yong Li[70] and Vladan Mijatovic[71] on behalf of the CKDGen consortium; Yadav Sapkota[15];
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Morrison[90], Janine F Felix[91] and Nicholas L Smith[92] on behalf of the CHARGE-Heart Failure Working Group; Angela M Christiano[93]; Lynn Petukhova[94]; Regina C. Betz[95]; Xing Fan[96]; Xuejun Zhang[96]; Caihong Zhu[96]; Carl Langefeld[97]; Susan D. Thompson[98]; Feijie Wang[99]; Xu Lin[99,100]; David A. Schwartz[101]; Tasha Fingerlin[102]; Jerome I. Rotter[103,104], Mary Frances Cotch[105] and Richard A Jensen on behalf of the CHARGE-Eye Working Group[106,107]; Matthias Munz[108], Henrik Dommisch[108] and Arne S Schaefer[108] on behalf of the European Periodontitis Genetics Group; Fang Han[109]; Hanna M Ollila[110]; Ryan P. Hillary[110]; Omar Albagha[111]; Stuart H. Ralston[112]; Chenjie Zeng[113]; Wei Zheng[113]; Xiao-Ou Shu[113]; Andre Reis[114]; Steffen Uebe[114]; Ulrike Hüffmeier[114]; Yoshiya Kawamura[115], Takeshi Otowa[116,117] and Tsukasa Sasaki[118] on behalf of the Japanese Collaboration Team for GWAS of Panic Disorder; Martin Lloyd Hibberd[119]; Michael Levin[120]; Sonia Davila[121]; Gang Xie1[22,20]; Katherine Siminovitch[122,20]; Jin-Xin Bei[123]; Yi-Xin Zeng[123,124]; Asta Försti[125,126]; Bowang Chen[125]; Stefano Landi[127]; Andre Franke[128]; Annegret Fischer[128,129]; David Ellinghaus[128]; Carlos Flores[130,131]; Imre Noth[132]; Shwu-Fan Ma[132]; Jia Nee Foo[133]; Jianjun Liu[133]; Jong-Won Kim[134]; David G. Cox[135]; Olivier Delattre[136]; Olivier Mirabeau[136]; Christine F. Skibola[137]; Clara S. Tang[138]; Merce Garcia-Barcelo[138]; Kai-Ping Chang[139]; Wen-Hui Su[140]; Yu-Sun Chang[141]; Nicholas G Martin[15]; Scott Gordon[15]; Tracey Wade[142]; Chaeyoung Lee[143]; Michiaki Kubo[144]; Pei-Chieng Cha[145]; Yusuke Nakamura[146]; Daniel Levy[147]; Masayuki Kimura[7]; Shih-Jen Hwang[147]; Steven Hunt[148]; Tim Spector[8]; Nicole Soranzo[149]; Ani W Manichaikul[150]; R Graham Barr[151]; Bratati Kahali[152], Elizabeth Speliotes[152] and Laura M Yerges-Armstrong[153] on behalf of the GOLD Consortium; Ching-Yu Cheng[154,155,156], Jost B. Jonas[157,158] and Tien Yin Wong[154,155,156] on behalf of the SEED consortium; Isabella Fogh[159], Kuang Lin[159] and John F. Powell[159] on behalf of the SLAGEN and ALSGEN consortia; Kenneth Rice[160] on behalf of the ICBP; Caroline Relton[1]; Richard M Martin[1,3,161]; George Davey Smith[1]

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Affiliations of the Telomeres Mendelian Randomization Collaboration

Acknowledgements

This work was supported by CRUK grant number C18281/A19169 (the Integrative Cancer Epidemiology Programme). Dr Haycock is supported by CRUK Population Research Postdoctoral Fellowship C52724/A20138. The MRC Integrative Epidemiology Unit is supported by grants MC_UU_12013/1 and MC_UU_12013/2. Dr Martin is supported by the

National Institute for Health Research (NIHR), the Bristol Nutritional Biomedical Research Unit and the University of Bristol.

We gratefully acknowledge all the studies and databases that made GWAS summary data available (see supplementary materials for detailed acknowledgements): **AC** (the aneurysm consortium), **ALSGEN (**the International Consortium on Amyotrophic Lateral Sclerosis Genetics), **AMD Gene (**Age-related Macular Degeneration Gene Consortium), **BCAC** (Breast Cancer Association Consortium), **C4D** (Coronary Artery Disease Genetics Consortium), **CARDIoGRAM** (Coronary ARtery DIsease Genome wide Replication and Meta-analysis), **CHARGE-HF** (Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium – Heart Failure Working Group), **COPDGene** (The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease), **CORECT** (ColoRectal Transdisciplinary Study), **CKDGen** (Chronic Kidney Disease Genetics consortium), **dbGAP** (database of Genotypes and Phenotypes), **DIAGRAM** (DIAbetes Genetics Replication And Meta-analysis), **EAGLE** (EArly Genetics & Lifecourse Epidemiology Eczema Consortium, excluding 23andMe), **ECAC** (Endometrial Cancer Association Consortium), **EGG** (Early Growth Genetics Consortium), **EPG** (European Periodontitis Genetics Group), **GABRIEL** (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community), **GCAN** (Genetic Consortium for Anorexia Nervosa), **GECCO** (Genetics and Epidemiology of Colorectal Cancer Consortium), **GIANT** (Genetic Investigation of ANthropometric Traits), **GLGC** (Global Lipids Genetics Consortium), **GUGC** (Global Urate and Gout consortium), **ICBP** (International Consortium for Blood Pressure), **IGAP** (International Genomics of Alzheimer's Project), **HPFS** (Health Professionals Follow-Up Study), **JCTGPD** (Japanese Collaboration Team for GWAS of Panic Disorder), **ILCCO** (International Lung Cancer Consortium), **ImmunoBase** (genetic

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434 Sclerosis Genetic Consortium), **IIBDGC** (International Inflammatory Bowel Disease
435 Genetics Consortium); **KIDRISK** (Kidney cancer consortium), **MAGIC** (Meta-Analyses of
436 Glucose and Insulin-related traits Consortium), **MC** (the melanoma meta-analysis
437 consortium), **MESA** (Multi-Ethnic Study of Atherosclerosis), **METASTROKE/ISGC**
438 (METASTROKE project of the International Stroke Genetics Consortium), **NBCS** (Nijmegen
439 Bladder Cancer Study), **NHGRI-EBI GWAS catalog** (National Human Genome Research
440 Institute and European Bioinformatics Institute Catalog of published genome-wide
441 association studies), **NHS** (Nurses' Health Study), **OCAC** (Ovarian Cancer Association
442 Consortium), **PanScan** (Pancreatic Cancer Cohort Consortium), **PGC** (Psychiatric Genomics
443 Consortium), **PRACTICAL** (Prostate Cancer Association Group to Investigate Cancer
444 Associated Alterations in the Genome), **SEEDS** (the Singapore Epidemiology of Eye
445 Diseases Study), **SLAGEN** (Italian Consortium for the Genetics of Ayotrophic Lateral
446 Sclerosis), **SSGAC (**Social Science Genetics Association Consortium), **TAG** (Tobacco and
447 Genetics Consortium), **T1Dbase** (type 1 diabetes database), **TICG** (Tourette International
448 Collaborative-Genetics); **TSAICG** (Tourette Syndrome Association International Consortium
449 for Genetics).

450 We gratefully acknowledge the assistance and contributions of Dr Julia Gumy, Ms Lisa
451 Wright, Dr Georg B. Ehret (ICBP), Dr Louise V. Wain (ICBP), Dr Caroline Fox (CKDGen),
452 Dr Stephan Ripke (IIBDGC), Dr Jimmy Liu (IIBDGC), Dr Carl Anderson (IIBDGC) and Dr
453 Jeremiah Scharf (TSAICG and TICG).

Table 1. Single nucleotide polymorphisms associated with telomere length

SNPs	Chr	Pos	Gene	EA	OA	EAF*	Beta*	SE*	P-value*	Phet*	No. studies*	Sample size*	Discovery p-value	% variance explained	Discovery study
rs11125529	2	54248729	*ACYP2*	A	C	0.16	0.065	0.012	0.000606	0.313	6	9177	8.00E-10	0.080	Codd[21]
rs6772228	3	58390292	*PXK*	T	A	0.87	0.041	0.014	0.049721	0.77	6	8630	3.91E-10	0.200	Pooley[17]
rs12696304	3	169763483	*TERC*	C	G	0.74	0.090	0.011	5.41E-08	0.651	6	9012	4.00E-14	0.319	Codd[22]
rs10936599	3	169774313	*TERC*	C	T	0.76	0.100	0.011	1.76E-09	0.087	6	9190	3.00E-31	0.319	Codd[21]
rs1317082	3	169779797	*TERC*	A	G	0.71	0.097	0.011	4.57E-09	0.029	6	9176	1.00E-08	0.319	Mangino[18]
rs10936601	3	169810661	*TERC*	C	T	0.74	0.087	0.011	8.64E-08	0.433	6	9150	4.00E-15	0.319	Pooley[17]
rs7675998	4	163086668	*NAF1*	G	A	0.80	0.048	0.012	0.008912	0.077	6	9161	4.35E-16	0.190	Codd[21]
rs2736100	5	1286401	*TERT*	C	A	0.52	0.085	0.013	2.14E-05	0.54	4	5756	4.38E-19	0.310	Codd[21]
rs9419958	10	103916188	*OBFC1*	T	C	0.13	0.129	0.013	5.26E-11	0.028	6	9190	9.00E-11	0.171	Mangino[18]
rs9420907	10	103916707	*OBFC1*	C	A	0.14	0.142	0.014	1.14E-11	0.181	6	9190	7.00E-11	0.171	Codd[21]
rs4387287	10	103918139	*OBFC1*	A	C	0.14	0.120	0.013	1.40E-09	0.044	6	8541	2.00E-11	0.171	Levy[25]
rs3027234	17	8232774	*CTC1*	C	T	0.83	0.103	0.012	2.75E-08	0.266	6	9108	2.00E-08	0.292	Mangino[18]
rs8105767	19	22032639	*ZNF208*	G	A	0.25	0.064	0.011	0.000169	0.412	6	9096	1.11E-09	0.090	Codd[21]
rs412658	19	22176638	*ZNF676*	T	C	0.35	0.086	0.010	1.83E-08	0.568	6	9156	1.00E-08	0.484	Mangino[18]
rs6028466	20	39500359	*DHX35*	A	G	0.17	0.058	0.013	0.003972	0.533	6	9190	2.57E-08†	0.041	Mangino[18] & Gu
rs755017	20	63790269	*ZBTB46*	G	A	0.17	0.019	0.0129	0.339611	0.757	5	8026	6.71E-09	0.090	Codd[21]

*Summary data from Mangino et al[18]; Chr, chromosome; pos, base-pair position (GRCh38.p3); EA, effect allele, OA, other allele, Beta, standard deviation change in telomere length per copy of the effect allele; SE, standard error; EAF - effect allele frequency; Phet - p value for between-study heterogeneity in association between SNP and telomere length; †from a meta-analysis of Mangino[18] and Gu[20] performed in the present study.

Table 2. Study characteristics for primary non-communicable diseases

	No. cases	No. controls	No. SNPs	Statistical power	Pop.	Study / First author
Cancer						
Bladder cancer	1601	1819	10	0.62	EUR	NBCS[76]
Breast cancer	48155	43612	13	1.00	EUR	BCAC[17,77]
Estrogen receptor –ve	7465	42175	13	1.00	EUR	BCAC[17,77]
Estrogen receptor +ve	27074	41749	13	1.00	EUR	BCAC[17,77]
Colorectal cancer	14537	16922	9	1.00	EUR	CORECT/GECCO[64,78]
Endometrial cancer	6608	37925	12	1.00	EUR	ECAC[79,80]
Esophageal SCC	1942	2111	11	0.64	EA	Abnet[81]
Glioma	1130	6300	12	0.72	EUR	Wrensch[82] & Walsh[66]
Head & neck cancer	2082	3477	12	1.00	EUR	McKay et al[83]
Kidney cancer	2461	5081	12	0.99	EUR	KIDRISK[84]
Lung cancer	11348	15861	13	1.00	EUR	ILCCO[85]
Adenocarcinoma	3442	14894	13	1.00	EUR	ILCCO[85]
Squamous cell carcinoma	3275	15038	13	1.00	EUR	ILCCO[85]
Skin cancer						
Melanoma	12814	23203	13	1.00	EUR	MC[86]
Basal cell carcinoma	3361	11518	13	1.00	EUR	NHS/HPFS[87]
Neuroblastoma	2101	4202	12	0.87	EUR	Diskin[88]
Ovarian cancer	15397	30816	13	1.00	EUR	OCAC[17,89]
Clear cell	1016	30816	13	0.76	EUR	OCAC[17,89]
Endometriod	2154	30816	13	0.98	EUR	OCAC[17,89]
Mucinous	1643	30816	13	0.94	EUR	OCAC[17,89]
Serous invasive	9608	30816	13	1.00	EUR	OCAC[17,89]
Serous LMP	972	30816	13	0.73	EUR	OCAC[17,89]
Pancreatic cancer	5105	8739	12	1.00	EUR	PanScan (incl. EPIC)[90]
Prostate cancer	22297	22323	11	1.00	EUR	PRACTICAL[91,92]
Testicular germ cell cancer	986	4946	11	0.52	EUR	Turnbull[93] & Rapley[94]
Autoimmune/inflammatory diseases						
Alopecia areata	2332	5233	7	0.60	EUR	Betz[95]
Atopic dermatitis	10788	30047	13	1.00	EUR	EAGLE[96]
Celiac disease	4533	10750	3	0.82	EUR	Dubois[97]
Inflammatory bowel disease						
Crohn's disease	5956	14927	11	1.00	EUR	IIBDGC[98]
Ulcerative colitis	6968	20464	12	1.00	EUR	IIBDGC[98]
Juvenile idiopathic arthritis	1866	14786	11	0.87	EUR	Thompson[99]†
Multiple sclerosis	14498	24091	3	1.00	EUR	IMSGC[100]
Aggressive periodontitis	888	6789	13	0.63	EUR	Schaefer[101]
Rheumatoid arthritis	5538	20163	11	1.00	EUR	Stahl[102]
Cardiovascular diseases						
Abdominal aortic aneurysm	4972	99858	13	1.00	EUR	AC[103–108]
Coronary heart disease	22233	64762	13	1.00	EUR	CARDIoGRAM[109]
Heart failure	2526	20926	13	0.99	EUR	CHARGE-HF[110]
Hemorrhagic stroke	2963	5503	12	0.96	EUR	METASTROKE/ISGC[111]
Ischemic stroke	12389	62004	13	1.00	EUR	METASTROKE/ISGC[112,113]
large vessel disease	2167	62004	13	0.99	EUR	METASTROKE/ISGC[112,113]
small vessel disease	1894	62004	13	0.97	EUR	METASTROKE/ISGC[112]
cardioembolic	2365	62004	13	0.99	EUR	METASTROKE/ISGC[112]
Sudden cardiac arrest	3954	21200	13	1.00	EUR	Unpublished
Diabetes						
Type 1 diabetes	7514	9045	6	0.95	EUR	T1DBase[114115]
Type 2 diabetes	10415	53655	11	1.00	EUR	DIAGRAM[116]
Eye disease						

AMD	7473	51177	13	1.00	EUR	AMD Gene[117]
Retinopathy	1122	18289	12	0.75	EUR	Jensen[118]
Lung diseases						
Asthma	13034	20638	4	1.00	EUR	Ferreira/GABRIEL[119,120]
COPD	2812	2534	12	0.85	EUR	COPDGene[121]
Interstitial lung disease	1616	4683	9	0.60	EUR	Fingerlin[122]
Neurological / psychiatric diseases						
ALS	6100	7125	12	1.00	EUR	SLAGEN/ALSGEN[123]
Alzheimer's disease	17008	37154	12	1.00	EUR	IGAP[124]
Anorexia nervosa	2907	14860	9	0.93	EUR	GCAN[125]
Autism	4949	5314	7	0.82	EUR	PGC[126]
Bipolar disorder	7481	9250	9	1.00	EUR	PGC[127]
Major depressive disorder	9240	9519	8	0.99	EUR	PGC[128]
Schizophrenia	35476	46839	12	1.00	EUR	PGC[129]
Tourette syndrome	1177	4955	13	0.74	EUR	TICG/TSAICG[130]
Other						
Chronic kidney disease	5807	56430	13	1.00	EUR	CKDGen[131]
Endometriosis	4604	9393	11	1.00	Mix	Nyholt[132]

Study acronyms: AC, the aneurysm consortium; **ALSGEN,** the International Consortium on Amyotrophic Lateral Sclerosis Genetics**; AMD Gene**, Age-related Macular Degeneration Gene Consortium; **BCAC**, Breast Cancer Association Consortium; **CARDIoGRAM**, Coronary ARtery DIsease Genome wide Replication and Meta-analysis; **CHARGE-HF**, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium – Heart Failure Working Group; **COPDGene**, The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease; **CKDGen**, Chronic Kidney Disease Genetics consortium; **CORECT**, ColoRectal Transdisciplinary Study; **DIAGRAM**, DIAbetes Genetics Replication And Meta-analysis; **EAGLE**, EArly Genetics & Lifecourse Epidemiology Eczema Consortium (excluding 23andMe); **ECAC**, Endometrial Cancer Association Consortium; **EPIC**, European Prospective Investigation into Cancer and Nutrition study; **GABRIEL**, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community; **GCAN**, Genetic Consortium for Anorexia Nervosa; **GECCO**, Genetics and Epidemiology of Colorectal Cancer Consortium; **IGAP**, International Genomics of Alzheimer's Project; **HPFS**, Health Professionals Follow-Up Study; **ILCCO**, International Lung Cancer Consortium; **IMSGC**, International Multiple Sclerosis Genetic Consortium; **IIBDGC**, International Inflammatory Bowel Disease Genetics Consortium; **KIDRISK**, Kidney cancer consortium; **MC**, the melanoma meta-analysis consortium; **METASTROKE/ISGC**, METASTROKE project of the International Stroke Genetics Consortium; **NBCS**, Nijmegen Bladder Cancer Study; **NHS**, Nurses' Health Study; **OCAC**, Ovarian Cancer Association Consortium; **PanScan**, Pancreatic Cancer Cohort Consortium; **PGC**, Psychiatric Genomics Consortium; **PRACTICAL**, Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; **SLAGEN**, Italian Consortium for the Genetics of Ayotrophic Lateral Sclerosis; **T1DBase**, type 1 diabetes database; **TICG** (Tourette International Collaborative-Genetics); **TSAICG** (Tourette Syndrome Association International Consortium for Genetics);. **Abbreviations**: **ALS**, amyotrophic lateral sclerosis; **AMD**, age-related macular degeneration; **COPD**, chronic obstructive pulmonary disease; **EUR**, European; **EA**, East Asian; **LMP**, low malignant potential; **No.**, number; **Pop**., population; **SCC**, squamous cell carcinoma; **SNP**, single nucleotide polymorphism; **-ve**, negative; **+ve**, positive; †plus previously unpublished data.

Figure 1. The association between genetically increased telomere length and odds of primary non-communicable diseases

Legend to Figure 1

*P value for association between genetically increased telomere length and disease from maximum likelihood; the effect estimate for heart failure is a hazard ratio (all others are odds ratios); P_{het}, P-value for heterogeneity amongst SNPs within the instrument; COPD, chronic obstructive pulmonary disease; SNP, single nucleotide polymorphism; CI, confidence interval; LMP, low malignancy potential; ER, estrogen receptor; -VE, negative; +VE, positive.

Figure 2. The association between genetically increased telomere length and odds of cancer as a function of selected characteristics

Legend to Figure 2

The plotted data show how the strength of the relationship between genetically increased telomere length and cancer varies by the selected characteristic. The R^2 statistic indicates how much of the variation between cancers can be explained by the selected characteristic. P-values are from meta-regression models. Circle sizes are proportional to the inverse of the variance of the log odds ratio. The hashed line indicates the null of no association between telomere length and cancer (i.e. an odds ratio of 1). Data for percentage survival 5 years after diagnosis, cancer incidence and median age-at-diagnosis was downloaded from the Surveillance, Epidemiology, and End Results Program.[33] Data for average lifetime number of stem cell divisions was downloaded from Tomasetti and Vogelstein.[34] Not all cancers had information available for the selected characteristics (hence the number of cancers varies across the subplots). Information was available for 9 cancers for tissue-specific rates of stem cell division, 13 cancers for percentage surviving 5 years post-diagnosis, 17 cancers for cancer incidence and 13 cancers for median age-at-diagnosis. SD, standard deviation; OR, Odds ratio.

Figure 3. Comparison of genetic and prospective observational studies[†] of the association between telomere length and disease

Legend to Figure 3

*from fixed-effects meta-analysis of independent observational studies described in Table S3; [†]search strategy and characteristics for observational studies are described in Tables S3 and S4; ‡CCHS and CGPS; +PLCO, ATBC & SWHS (acronyms explained in Table S3); CI, confidence interval

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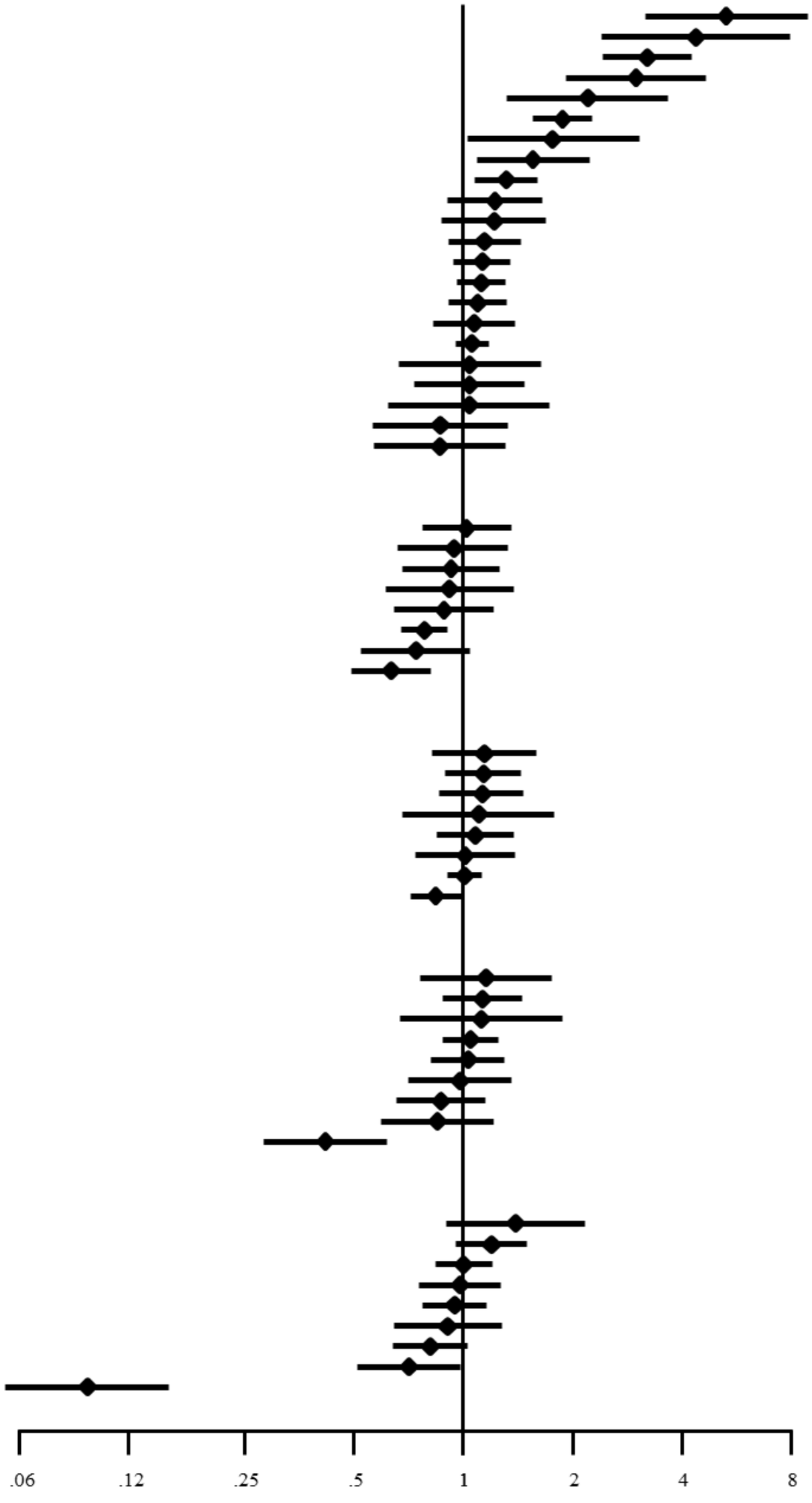
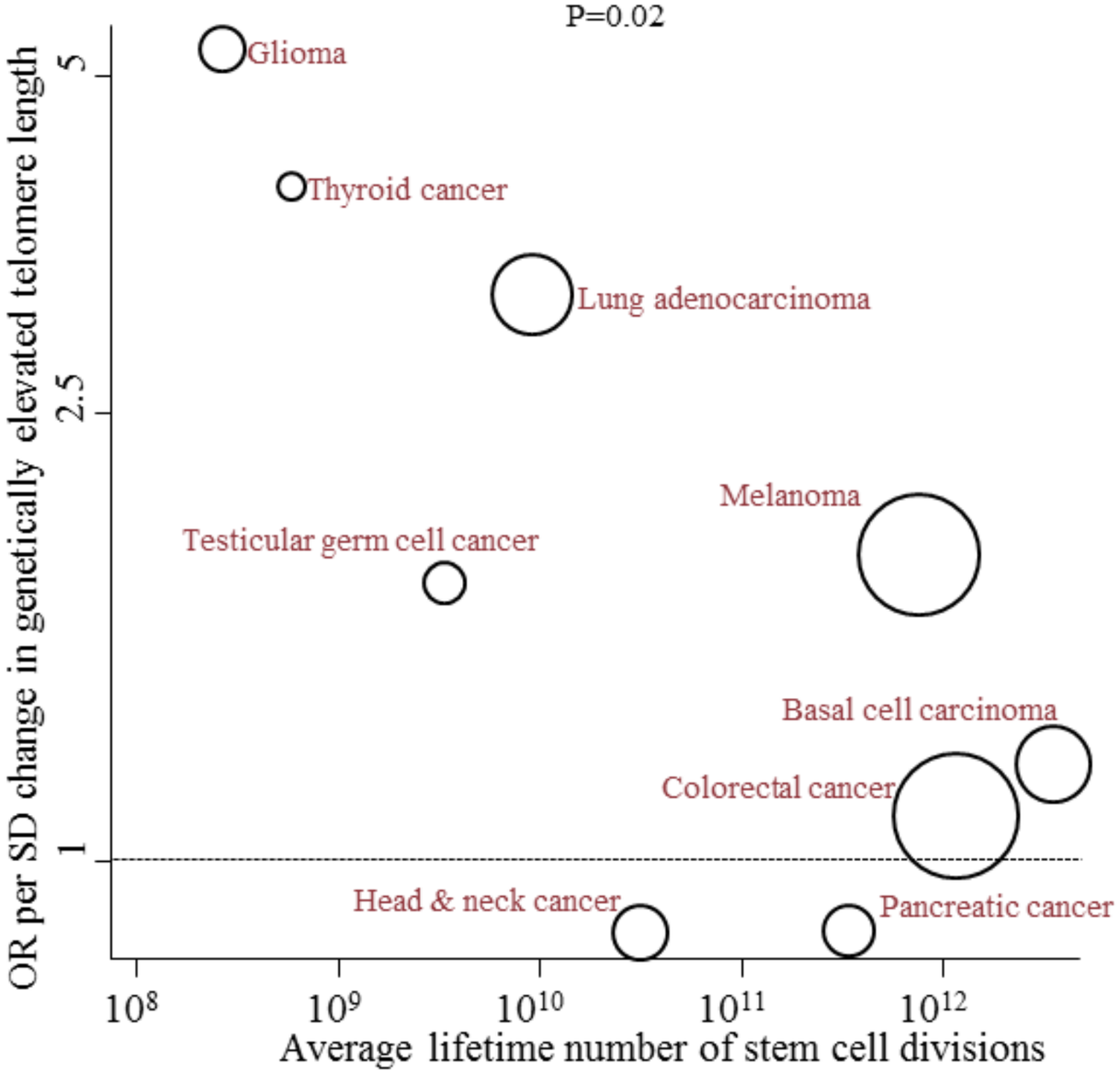
	Tumor/disease subtype	No. of cases	No. of SNPs	P*	P_{het}
Cancer					
Glioma	-	1130	12	$2.45x10^{-10}$	.0135
Ovarian cancer	Serous LMP	972	13	$1.62x10^{-6}$	.082
Lung cancer	Adenocarcinoma	3442	13	$6.66x10^{-16}$	.0001
Neuroblastoma	-	2101	12	$1.11x10^{-6}$	.3799
Bladder cancer	-	1601	10	.0026	.2541
Skin cancer	Melanoma	12814	13	$5.79x10^{-11}$	.086
Testicular germ cell cancer	-	985	11	.0423	.3002
Kidney cancer	-	2461	12	.0164	.251
Endometrial cancer	-	6607	12	.0091	.1436
Skin cancer	Basal cell carcinoma	3361	13	.203	.0398
Ovarian cancer	Endometriod	2154	13	.2499	.3319
Breast cancer	ER-ve	7465	13	.2542	<0.0001
Ovarian cancer	Serous invasive	9608	13	.2088	.0407
Prostate cancer	-	22297	11	.1533	<0.0001
Colorectal cancer	-	14537	9	.3436	.0156
Lung cancer	Squamous cell carcinoma	3275	13	.6212	.9042
Breast cancer	ER+	27074	13	.2912	.0228
Ovarian cancer	Clear cell	1016	13	.8676	.3226
Ovarian cancer	Mucinous	1643	13	.8396	.3147
Esophageal cancer	Squamous cell carcinoma	1942	8	.9055	.4513
Pancreatic cancer	Adenocarcinoma	5105	12	.5009	.0016
Head & neck cancer	-	2082	12	.4767	.0763
Cardiovascular diseases					
Heart failure	-	2526	13	.8931	.5348
Ischemic stroke	Small vessel disease	1894	13	.7141	.2358
Sudden cardiac arrest	-	3954	13	.62	.5400
Intracerebral stroke	-	5503	12	.6719	.0002
Ischemic stroke	Cardioembolic	2365	13	.4464	.0374
Coronary heart disease	-	22233	13	.0009	.2441
Ischemic stroke	Large vessel disease	2167	13	.0801	.1578
Abdominal aortic aneurysm	-	4972	13	.0003	.0617
Neurological / psychiatric diseases					
Anorexia Nervosa	-	2907	9	.4406	.1797
Bipolar disorder	-	7481	9	.315	.1427
Amyotrophic lateral sclerosis	-	6100	12	.4049	.6331
Tourette syndrome	-	1177	13	.6936	.4978
Major depressive disorder	-	9240	8	.5646	.254
Autism	-	4949	7	.9514	.8232
Schizophrenia	-	9379	12	.9245	.0053
Alzheimer's disease	-	17008	12	.0296	.1451
Autoimmune/inflammatory diseases					
Alopecia areata	-	2332	7	.4994	.9505
Inflammatory bowel disease	Crohn's disease	5956	11	.3586	.0585
Periodontitis	-	888	13	.6702	.0066
Atopic dermatitis	-	10788	13	.6094	.1194
Inflammatory bowel disease	Ulcerative colitis	6968	12	.8303	.0984
Multiple sclerosis	-	14498	3	.8885	.1455
Rheumatoid arthritis	-	5538	11	.3184	.1828
Juvenile idiopathic arthritis	-	1866	11	.3669	.922
Celiac disease	-	4533	3	$1.00x10^{-5}$	.0028
Other diseases					
Retinopathy	-	1126	12	.1453	.3831
Age-related macular degeneration		7473	13	.1206	.209
Type 2 diabetes	-	10415	11	.9837	.6811
Endometriosis	-	4604	11	.8606	.0576
Chronic kidney disease	-	5807	13	.5859	.6972
COPD	-	2812	12	.5598	.3807
Asthma	-	13034	4	.0779	.3213
Type 1 diabetes	-	7514	6	.0378	.0586
Interstitial lung disease	-	1616	9	$2.02x10^{-19}$	.0014



Average lifetime number of stem cell divisions

Adjusted R^2=52.63%

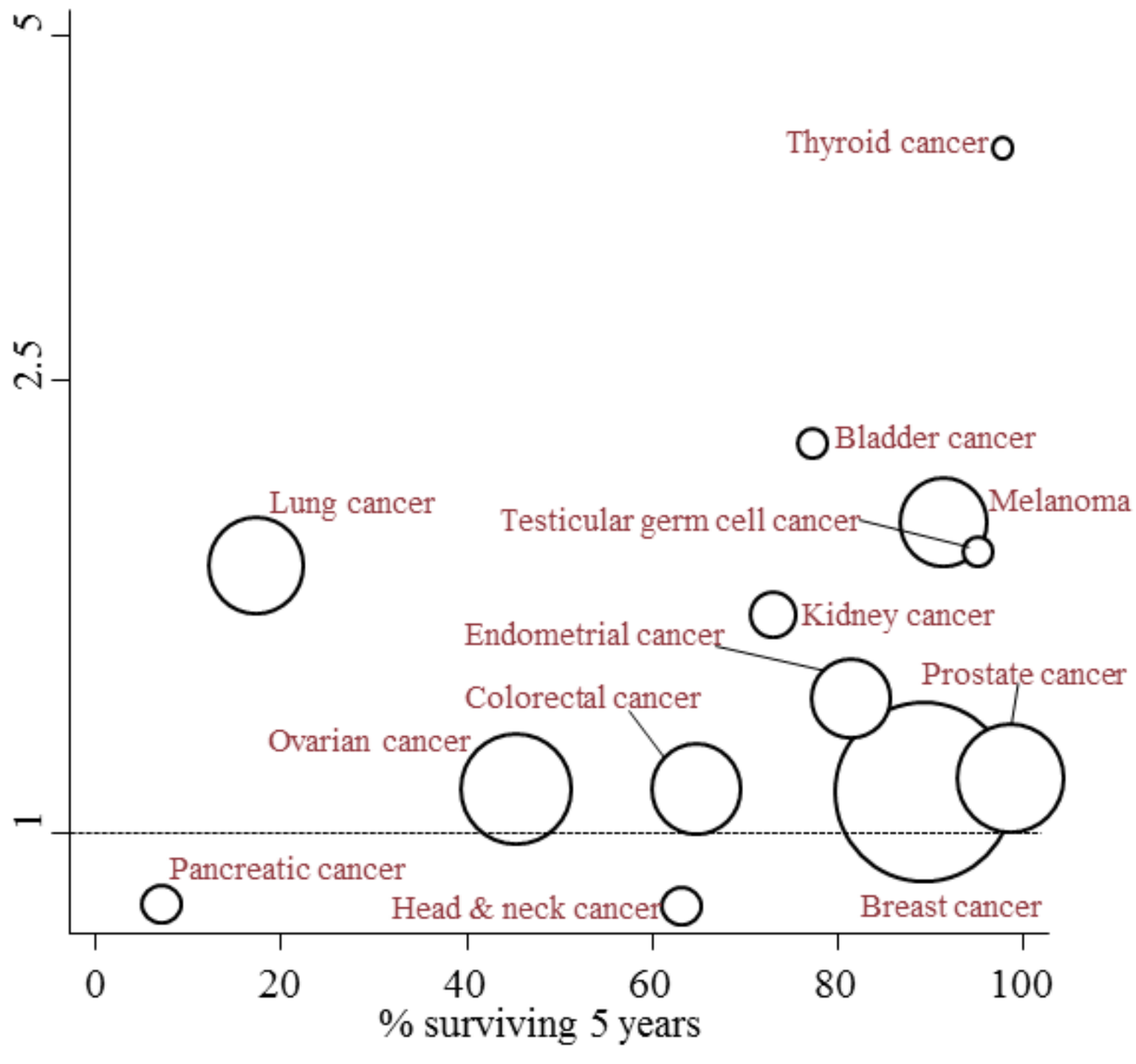
P=0.02



% surviving 5 years

Adjusted R^2=-19.49%

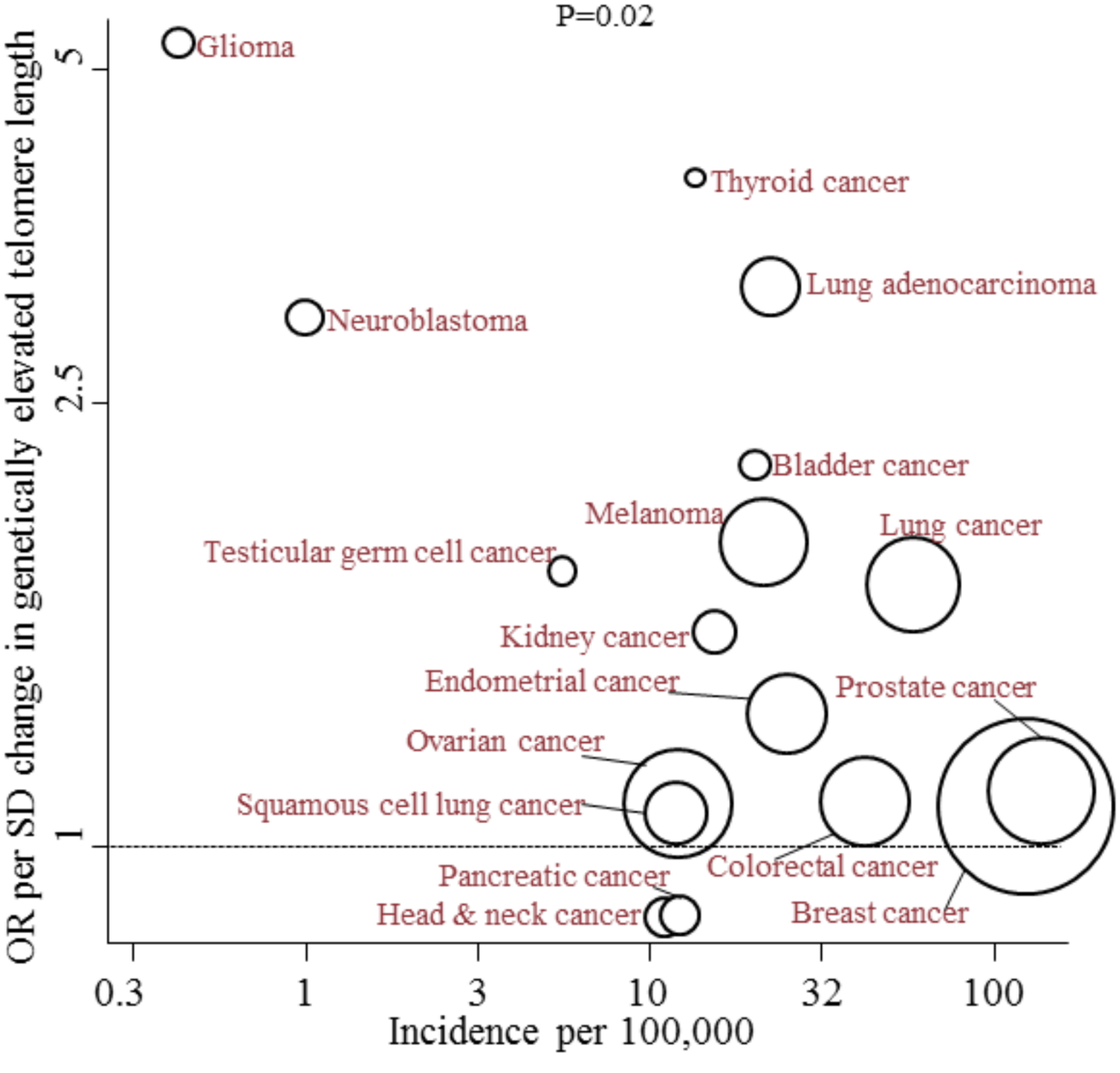
P=0.37



Cancer incidence

Adjusted R^2=32.12%

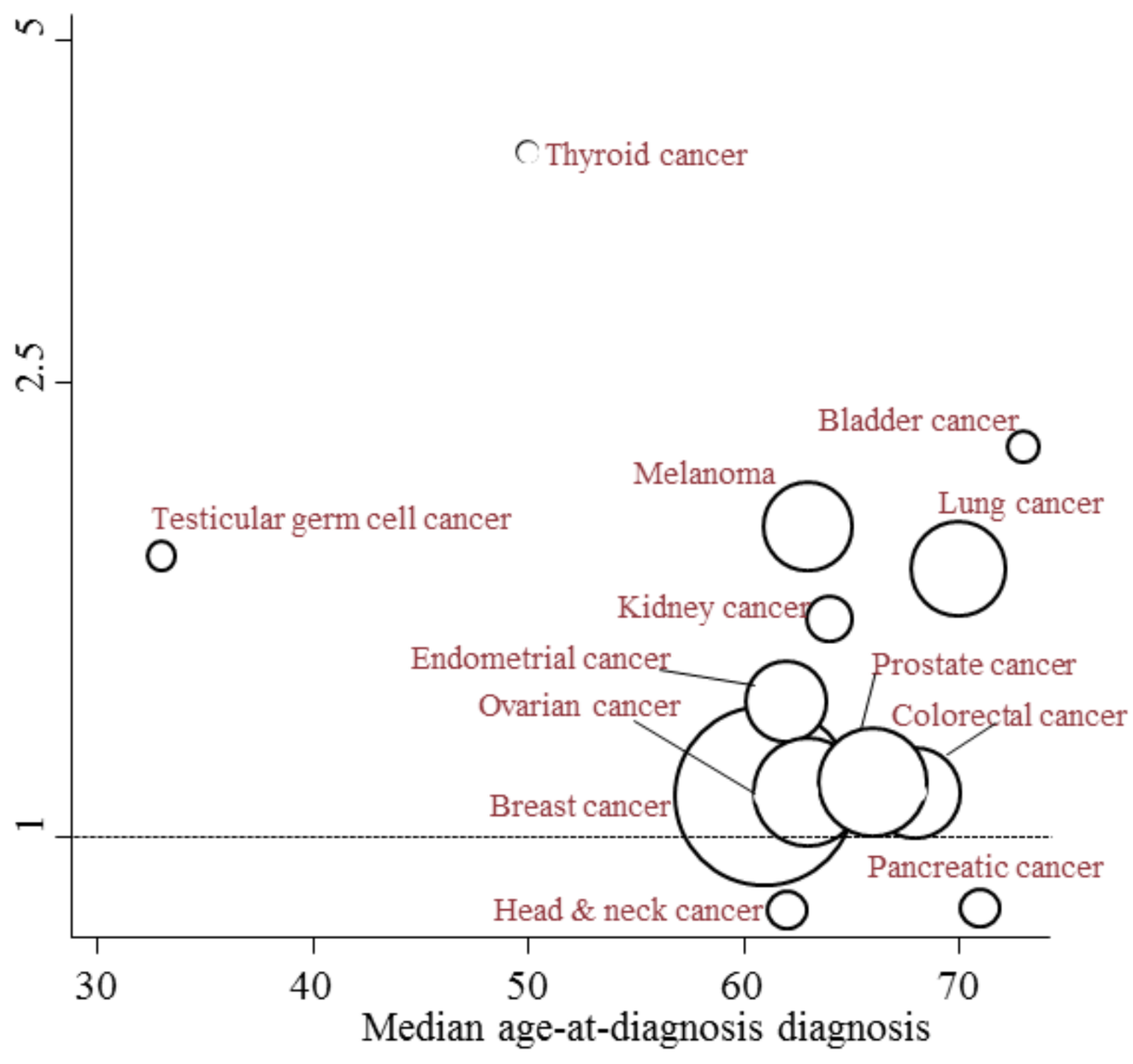
P=0.02



Median age-at-diagnosis diagnosis

Adjusted R^2=-8.86%

P=0.41



	No. of cases	Odds ratio (95% CI) per standard deviation increase in telomere length
Cancer		
Breast cancer		
Genetic study	48155	1.08 (0.99, 1.19)
Observational study*	1716	1.02 (0.99, 1.05)
Prostate cancer		
Genetic study	22297	1.12 (0.96, 1.30)
Observational study*	1340	1.07 (1.01, 1.14)
Ovarian cancer		
Genetic study	15397	1.09 (0.94, 1.27)
Observational study	96	1.13 (0.98, 1.32)
Colorectal cancer		
Genetic study	14537	1.09 (0.91, 1.31)
Observational study*	1447	1.04 (0.97, 1.11)
Lung cancer		
Genetic study	11348	1.71 (1.44, 2.04)
Observational study‡	522	0.94 (0.87, 1.02)
Observational study+	847	1.28 (1.12, 1.46)
Endometrial cancer		
Genetic study	6608	1.31 (1.07, 1.61)
Observational study*	382	1.06 (0.95, 1.19)
Pancreatic cancer		
Genetic study	5105	0.86 (0.56, 1.32)
Observational study*	648	1.05 (0.95, 1.17)
Lung adenocarcinoma		
Genetic study	3442	3.19 (2.40, 4.22)
Observational study	288	1.44 (1.14, 1.82)
Skin basal cell carcinoma		
Genetic study	3361	1.22 (0.90, 1.65)
Observational study	363	0.96 (0.85, 1.09)
Lung squamous cell carcinoma		
Genetic study	3275	1.07 (0.82, 1.39)
Observational study	163	1.05 (0.78, 1.42)
Kidney cancer		
Genetic study	2461	1.55 (1.08, 2.23)
Observational study*	268	0.94 (0.81, 1.10)
Head & neck cancer		
Genetic study	2082	0.86 (0.57, 1.30)
Observational study	76	0.89 (0.72, 1.09)
Melanoma		
Genetic study	12814	1.88 (1.54, 2.28)
Observational study*	734	1.17 (1.06, 1.29)
Bladder cancer		
Genetic study	1601	2.19 (1.32, 3.66)
Observational study	184	1.28 (1.02, 1.61)
Testicular cancer		
Genetic study	986	1.76 (1.02, 3.04)
Observational study	10	0.94 (0.56, 1.55)
Glioma		
Genetic study	1130	5.27 (3.15, 8.81)
Observational study	101	0.90 (0.68, 1.18)
Non-neoplastic diseases		
Coronary heart disease		
Genetic study	22233	0.78 (0.67, 0.90)
Observational study	2272	0.86 (0.78, 0.94)
Ischemic stroke		
Genetic study	12389	0.85 (0.73, 1.00)
Observational study	824	0.94 (0.82, 1.08)
Type 2 diabetes		
Genetic study	10415	1.00 (0.84, 1.20)
Observational study	2011	0.90 (0.83, 0.97)

Supplementary material

Mendelian randomization study of the association between telomere length and risk of cancer and non-neoplastic diseases

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7 supplementary figures / 6 supplementary tables

Contents

SUPPLEMENTARY METHODS

Additional details on the design strategy

Identification of genetic instruments for telomere length

To identify genetic variants to serve as instruments for telomere length, we searched the genome-wide association study (GWAS) catalog[1,2] on the 15 January 2015, to identify reported single nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with additional potential instruments, we also searched the original study reports curated by the GWAS catalog.[3–11] 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 six GWASs of leukocyte telomere length, conducted in 9,190 participants of European ancestry.[4] Telomere length in the six studies was measured by Southern blotting. GWAS analyses in the 6 studies 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.[4] The following summary data were acquired for each SNP 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 effect allele frequency. We combined the effect estimates from the six separate studies by fixed effects meta-analysis. We then excluded SNPs 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[3–10] or ii) a meta-analysis of summary data

from Mangino et al[4] and other GWASs of telomere length,[3,5–10] with any overlapping studies excluded from Mangino et al.[4] 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≤0.001).

Acquisition of summary data from disease and risk factor studies

We extracted the following summary data for each genetic instrument 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 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-values 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 disease and risk factor 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≤0.001), Hardy–Weinberg disequilibrium (P≤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[12] 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 for non-communicable diseases 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,[3–10] and the sample size available for each outcome.

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.[13] Sensitivity analyses were based on two approaches: the weighted median[14] and MR-Egger regression.[15] 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[16] and 1000 Genomes phase 3 data for European samples.[17] 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 instruments 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.[16] The base pair position and chromosome id for each SNP, in GCRCh38 format, was extracted from Ensembl through the R biomart package.[18–20] 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 instruments 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 instrument, 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 the 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.[13] The standard deviation of telomere length corresponds to approximately 650 base pairs.[4] The variance-covariance matrix was estimated using 1000 Genomes phase 3 data for Europeans.[13] 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 SNP-telomere-length associations, $\boldsymbol{\beta_{GD}}$ is a vector of the SNP-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 SNP-telomere-length 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[13] 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 change 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: the SNPs are associated with telomere length (IV1); the SNPs are independent of confounders (IV2); and the SNPs are independent of disease adjusted for telomere length and confounders (IV3). See Supplementary Figure S7 for further details of the Mendelian randomization assumptions and Supplementary Table S6 for a glossary of terms.

198

199 *The weighted median approach*[14]

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

201 Now define

202 $$w^*_{(j)} = \frac{w_j}{S_J}, \quad \text{where} \quad S_J = \sum_j w_j ,$$

203 where w_j is the inverse variance of $\hat{\beta}_{(j)}$,

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

205 $$p^w_{(j)} = \frac{100}{S_J}\left(S_{(j)} - \frac{w_{(j)}}{2} \right).$$

206 $p^w_{(j)}$ represents the quantile from the weighted empirical distribution function of the ordered

207 estimates $\hat{\beta}_{(1)},\ldots,\hat{\beta}_{(J)}$. The weighted median estimate, $\hat{\beta}_{WM}$ is defined as the 50th percentile of this

208 weighted distribution. Typically the 50th percentile will lie between two estimates ($\hat{\beta}_{(l)}$ and $\hat{\beta}_{(m)}$,

209 say), in which case $\hat{\beta}_{WM}$ is found by linear interpolation. $\hat{\beta}_{WM}$ is a consistent estimate for β provided

210 that at least 50% of the 'weight' making up S_J comes from genetic variants that are valid

211 instruments. In other words, the weighted median function provides a valid estimate of the causal

212 effect of telomere length on disease if at least half of the genetic information comes from valid

213 instruments (assumptions illustrated in Supplementary Figure S7; glossary of terms in

214 Supplementary Table S6).[14]

215

216 *The MR-Egger approach*

217 The MR-Egger method[15] performs a weighted linear regression of the SNP-disease coefficients on

218 the SNP-exposure coefficients (where exposure in this study is telomere length):

219 $$\frac{\hat{\Gamma}_j}{\sigma_{Yj}} = \frac{\beta_{0E}}{\sigma_{Yj}} + \beta_{1E}\frac{\hat{\gamma}_j}{\sigma_{Yj}}$$

where Γ corresponds to the SNP-disease coefficients, γ corresponds to the SNP-exposure coefficients and σ_{yj} is the standard error of $\hat{\Gamma}_j$. If all SNPs 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 SNPs. 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* SNPs are invalid, provided that

- Across all SNPs, the magnitude of the SNP-exposure associations are independent of their pleiotropic effects (also known as the InSIDE [Instrument Strength Independent of Direct Effect] assumption)
- The number of SNPs, J, grows large (i.e. tends to infinity).

See Supplementary Figure S7 for further details on the assumptions and Supplementary Table S6 for a glossary of terms.

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) (Supplementary Figure S2). In analyses of secondary non-neoplastic diseases, genetically increased telomere length was associated with reduced odds of panic disorder (P<0.05) (Supplementary Figure S2). In secondary analyses of 44 risk factors for non-communicable diseases (Supplementary 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) (Supplementary Figure S5). There was some evidence for an association between genetically increased telomere length and ever smoking status (P=0.03, Supplementary Figure S6) but this association is unlikely to be reliable given that the SNP-telomere-length associations were adjusted for smoking history; the association may therefore reflect collider bias.[21]

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 are 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.[22] *CTC1* encodes a component of the CST complex, which plays a role in protecting telomeres from degradation.

Bias from sample overlap and strength of the association between SNPs and telomere length

The selected genetic instruments 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 telomere length and disease and risk factor GWASs.[23] 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.

Misconceptions about Mendelian randomization

A common misconception about Mendelian randomization studies is that genetic instruments should explain a substantial proportion of the variation in target exposures (e.g. telomere length in this study) in order to provide robust inferences about exposure-disease associations. However, if the genetic instruments are valid (i.e. conform to Mendelian randomization assumptions,

Supplementary Figure S7), the variation explained by the instrument only affects statistical power and does not generally affect validity of the causal inference. In this sense, genotype assignment in a Mendelian randomization study is analogous to treatment assignment in a randomized controlled trial, e.g. of blood pressure lowering drugs.[24] Although experimental interventions to reduce blood pressure may only explain a small fraction of the total variation in blood pressure in a typical RCT, we can still make causal inferences about blood pressure as a whole (and not just the proportion of variation in blood pressure due to the experimental intervention). 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).[24] If Mendelian randomization assumptions were violated, however, then the limited variation explained by our genetic instruments might not behave in similar manner to other sources of variation in telomere length, which would undermine our ability to draw causal inferences. See the above section 'Estimating the association between genetically increased telomere length and outcome traits' and Supplementary Figure S7 for details on the assumptions. See Supplementary Table S6 for an explanation of Mendelian randomization terminology. See Haycock et al[25] and Davey Smith and Hemani[26] for reviews on Mendelian randomization.

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).[3,27–44] In addition, these studies all made some allowance for population stratification in their analyses: 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 we used to defined genetic instruments for telomere length[4] also adjusted for principal component scores; and lambdas for genomic inflation 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.[44,45]

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).[46–50]

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Supplementary Table S1. Study characteristics for secondary non-communicable diseases and diseases from independent studies for replication analyses

	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.[51]
Chronic myeloid leukemia	201	497	8	0.07	EA	Kim[52]
Ewing's sarcoma	401	684	4	0.06	EUR	Postel-Vinay[53]
Follicular lymphoma	212	748	3	0.04	EUR	Conde[54]
Gallbladder cancer	41	866	2	0.01	EA	Cha[55]
Gastric cancer						
Cardia adenocarcinoma	1126	2111	11	0.47	EA	Abnet[56]
Noncardia adenocarcinoma	632	2111	11	0.29	EA	Abnet[56]
Multiple myeloma	4692	10990	1	0.37	EUR	Chubb/GWAS cat.[57]
Nasopharyngeal carcinoma	1583	1894	2	0.17	EA	Bei[58]
B-cell Non-Hodgkin lymphoma	253	1438	10	0.13	EA	Tan[59]
Skin squamous cell carcinoma	449	11518	13	0.34	EUR	Zhang[60]
Thyroid cancer	649	431	12	0.16	EUR	Kohler[61]
Upper gastrointestinal cancers	3523	2100	2	0.28	EA	Li/dbGAP[62]
Autoimmune/inflammatory diseases						
Inflammatory psoriatic arthritis	609	990	13	0.29	EUR	Huffmeier[63]
Kawasaki disease	405	6252	11	0.26	EUR	Khor[64]
Narcolepsy	1188	1985	9	0.46	EA	Han[65]
Psoriasis	1139	1132	9	0.34	EA	Zhang[66]
Sarcoidosis	564	1575	9	0.16	EUR	Fischer[67]
Systemic lupus erythematosus	1311	1783	4	0.20	EUR	Hom/dbGAP[68]
Vitiligo	1117	1429	2	0.12	EA	Quan[69]
Wegener's granulomatosis	459	1503	10	0.20	EUR	Xie[70]
Neurological / psychiatric diseases						
Bulimia nervosa	151	2291	8	0.07	EUR	Wade[71]
Panic disorder	718	1717	8	0.28	EA	**JCTGPD**[72]
Parkinson's disease	1713	3978	4	0.35	EUR	Simón-Sánchez/dbGAP[73]

Other						
Hirschsprung's disease	173	615	6	0.04	EA	Tang[74]
Paget's disease	741	2699	12	0.43	EUR	Albagha[75]
Vascular dementia	84	200	8	0.03	EA	Kim[76]
Independent disease studies for replication analyses						
Bladder cancer	7712	13125	1	0.56	EUR	Figueroa/GWAS cat.[77]
Colorectal cancer	728	3282	9	0.39	EA	Zhang[78]
Coronary heart disease	15399	15050	4	1.00	Mix	C4D[79]
Glioma	1854	4955	1	0.12	EUR	GliomaScan/GWAS cat.[80]
Interstitial lung disease†	542	542	11	0.15	EUR	Noth[81]
Interstitial lung disease‡	242	1469	1	0.02	EA	Mushiroda/GWAS cat.[82]
Pancreatic cancer	4164	3792	10	0.90	EUR	PanC4[83]
Multiple sclerosis	978	883	4	0.11	EUR	Baranzini/dbGAP[84]
Nasopharyngeal carcinoma	277	285	2	0.03	EA	Tse[85]
Type 2 diabetes	8569	8923	10	1.00	EA	Li[86]

†≤17% cases overlapped with cases from Fingerlin et al[31] 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 Catalog of published genome wide association studies; **JCTGPD**, Japanese Collaboration Team for GWAS of Panic Disorder. **Abbreviations**: EUR, European; EA, East Asian; **No.**, number; **Pop.**, population; **SNP**, single nucleotide polymorphism.

Supplementary Table S2. Study characteristics of 44 risk factors for non-communicable diseases

	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[87]
Birth weight	26836	547.5	g	12	1.00	EUR	EGG[88]
Body mass index	241253	4.8	kg/m^2	13	1.00	EUR	GIANT[89]
Childhood obesity	13848	NA	log_e odds	12	0.78	EUR	EGG[90]
Head circumference	10705	1.5	cm	13	1.00	EUR	EGG[91]
Height	253288	0.1	m	13	1.00	EUR	GIANT[92]
Hip circumference	224459	8.5	cm	13	1.00	EUR	GIANT[93]
Waist circumference	224459	12.5	cm	13	1.00	EUR	GIANT[93]
Waist-to-hip ratio	224459	0.1	ratio	13	1.00	EUR	GIANT[93]
Smoking behaviors							
Age of smoking initiation	47961	0.3	log_e years	13	1.00	EUR	TAG[94]
Cigarettes smoked per day	68028	11.7	CPD	13	1.00	EUR	TAG[94]
Ever smoker	74035	NA	log_e odds	13	1.00	EUR	TAG[94]
Ex smoker	41969	NA	log_e odds	13	1.00	EUR	TAG[94]
Blood pressure							
Diastolic blood pressure	66466	10.7	mm Hg	12	1.00	EUR	ICBP[95]
Mean arterial pressure	27803	12.8	mm Hg	13	1.00	EUR	ICBP[96]
Pulse pressure	70903	13.5	mm Hg	13	1.00	EUR	ICBP[96]
Systolic blood pressure	66473	18.2	mm Hg	12	1.00	EUR	ICBP[95]
Education							
College completion	95427	NA	log_e odds	13	1.00	EUR	SSGAC[97]
Years of educational attainment	126559	1.2	years	13	1.00	EUR	SSGAC[97]
Glycemic							
2 hr glucose	15234	1.27	mmol/L	11	1.00	EUR	MAGIC[98]
Beta-cell function (HOMA-B)	46186	0.96	log_e HOMA	12	1.00	EUR	MAGIC[99]
Fasting glucose	46186	0.73	mmol/L	12	1.00	EUR	MAGIC[99]
Fasting insulin	38238	0.79	log_e pmol/L	12	1.00	EUR	MAGIC[99]

Fasting proinsulin	10701	0.81	$\log_e$ pmol/L	12	1.00	EUR	MAGIC[99]
Gycated hemoglobin (HbA1c)	46368	0.53	%	12	1.00	EUR	MAGIC[100]
Insulin resistance (HOMA-IR)	46186	0.67	$\log_e$ HOMA	12	1.00	EUR	MAGIC[99]
Hemotological							
Hemoglobin	54287	1.3	g/dL	12	1.00	EUR	van der Harst[101]
Mean cell hemoglobin	45969	1.99	pg	12	1.00	EUR	van der Harst[101]
Mean cell hemoglobin concentration	49632	1.01	g/dL	12	1.00	EUR	van der Harst[101]
Mean cell volume	51277	5.2	fl	12	1.00	EUR	van der Harst[101]
Packed cell volume	46848	5.9	%	12	1.00	EUR	van der Harst[101]
Red blood cell count	47873	0.5	10^{12}/L	12	1.00	EUR	van der Harst[101]
Lipids							
HDL cholesterol	103019	15.51	mg/dL	11	1.00	EUR	GLGC[102]
LDL cholesterol	97562	38.67	mg/dL	11	1.00	EUR	GLGC[102]
Total cholesterol	103266	41.75	mg/dL	11	1.00	EUR	GLGC[102]
Triglycerides	99050	90.72	mg/dL	11	1.00	EUR	GLGC[102]
Renal function							
Microalbuminuria	30482	NA	$\log_e$ odds	13	0.82	EUR	CKDGen[103]
Serum creatinine	67093	0.24	$\log_e$ ml/min/1.73m²	13	1.00	EUR	CKDGen[103]
Serum cystatin	20957	0.23	$\log_e$ ml/min/1.73m²	13	1.00	EUR	CKDGen[103]
Urinary albumin-to-creatinine ratio	31580	1.0	$\log_e$ mg/g	13	1.00	EUR	CKDGen[103]
Other							
Grade of nuclear cataract	7140	0.8	grade	11	1.00	ASN	SEEDS[104]
Hepatic steatosis	7176	5.6	Hounsfield units	12	1.00	EUR	Speliotes[105]
Percent emphysema	7914	0.71	$\log_e$ %+1	12	1.00	ME	MESA[106]
Uric acid	42742	1.3	mg/dL	12	1.00	EUR	GUGC[107]

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**, Multi-Ethnic Study of Atherosclerosis; **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[108]	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[109]	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[110]	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	0.17	2
Sister Study[111]	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%)		1
EPIC[112]	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[113]	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[114]	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[109]	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[115]	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[112]	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[116]	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	0.11	2
CCHS, CGPS[109]	Endometrial cancer	2013	PC	25262	103	0.85 (0.71 to 1.02)	per 1000 bp (1.29 SD)	-1.29	1.13 (0.99 to 1.31)	+++++	EUR		1

							decrease						
PLCO[117]	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[109]	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[109]	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[118]	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[119]	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[109]	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	<0.001	1
PLCO, ATBC, SWHS[119]	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%)		1
PLCO, ATBC, SWHS[119]	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[109]	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[120]	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[109]	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[109]	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[121]	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[122]	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[109]	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[123]	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[124]	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[109]	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[‖125]	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[#125]	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[126]	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[127] (2011) and Wentzensen et al[128] (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

333 **Supplementary Table S6.** Glossary of terms

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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 (see Supplementary Figure S7 for an illustration of these assumptions).
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 separate effects of a third variable (the confounder) on the exposure and the outcome. Mendelian randomization studies are less susceptible to confounding in comparison to observational studies (but confounding by pleiotropy or population stratification is possible).
Pleiotropy	Occurs when a genetic variant is associated with multiple traits or phenotypes. Vertical pleiotropy occurs when the phenotypes are 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. 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 strength of the F statistic.

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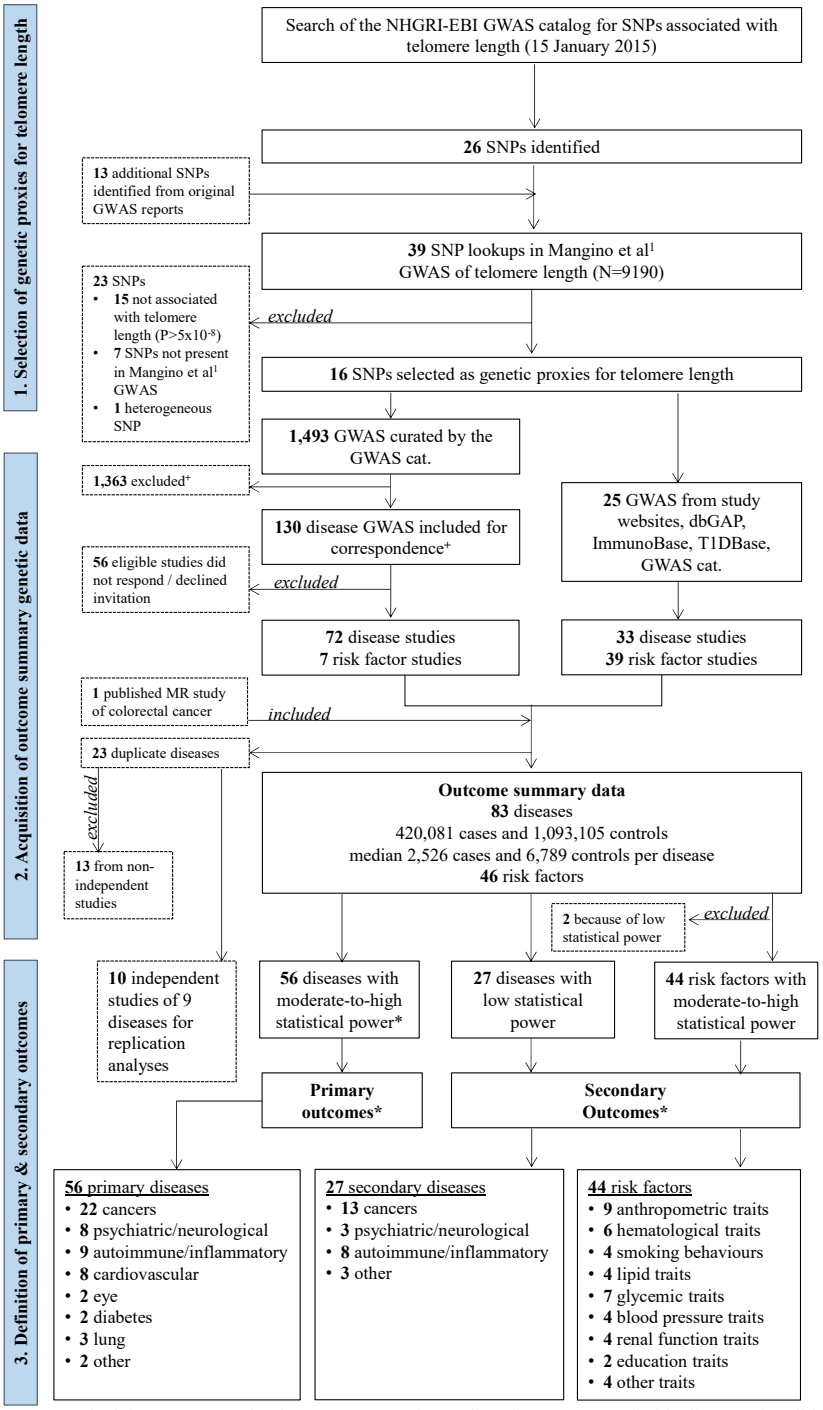
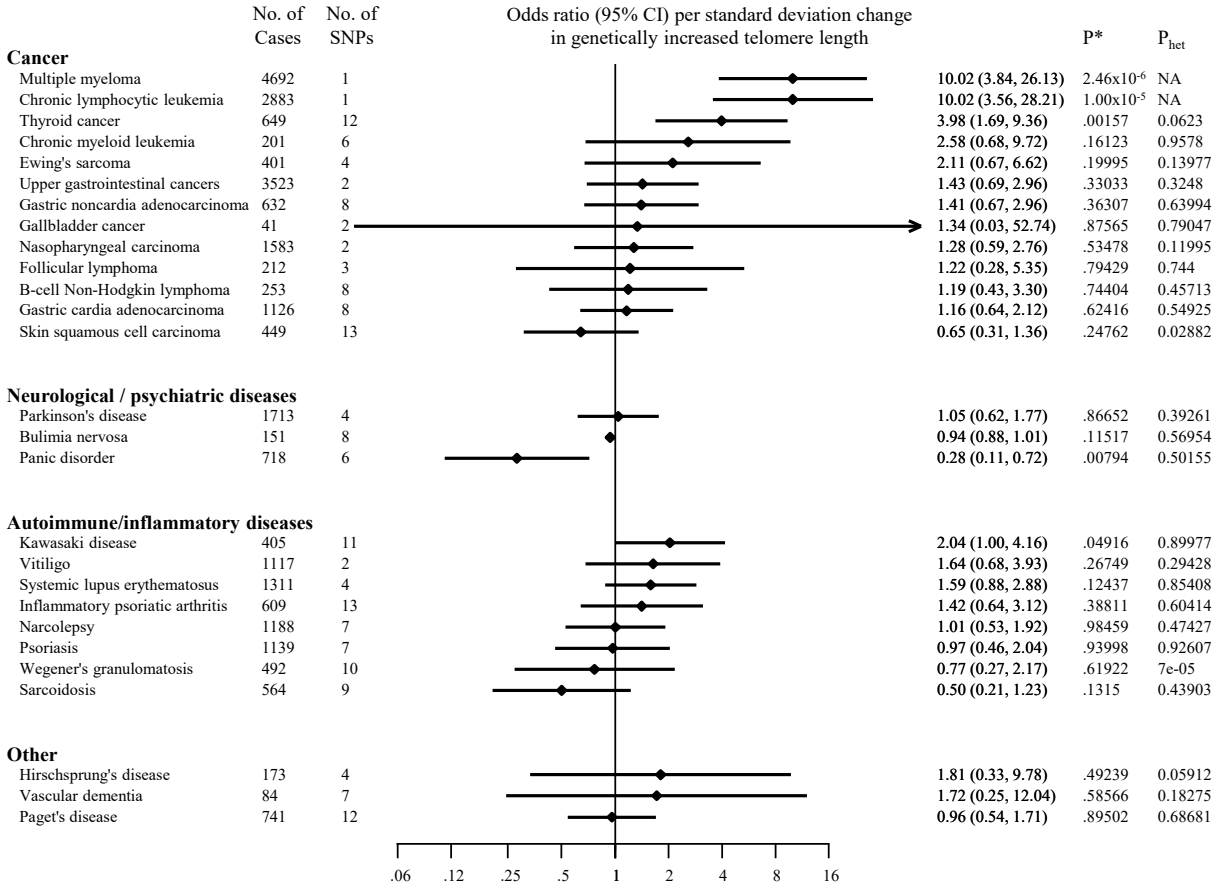
Supplementary Figure S1. Study design



+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, we classified 773 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 were diseases with <50% power to detect odds ratios ≥2.0 per standard deviation change in genetically increased telomere length (alpha assumed to be 0.01). All risk factors were classified as secondary outcomes. **GWAS**, genome-wide association study; **GWAS Cat.**, NHGRI-EBI GWAS catalogue; **SNP**, single nucleotide polymorphism; **NHGRI**, National Human Genome Research Institute; **EBI,** European Bioinformatics Institute

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



*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

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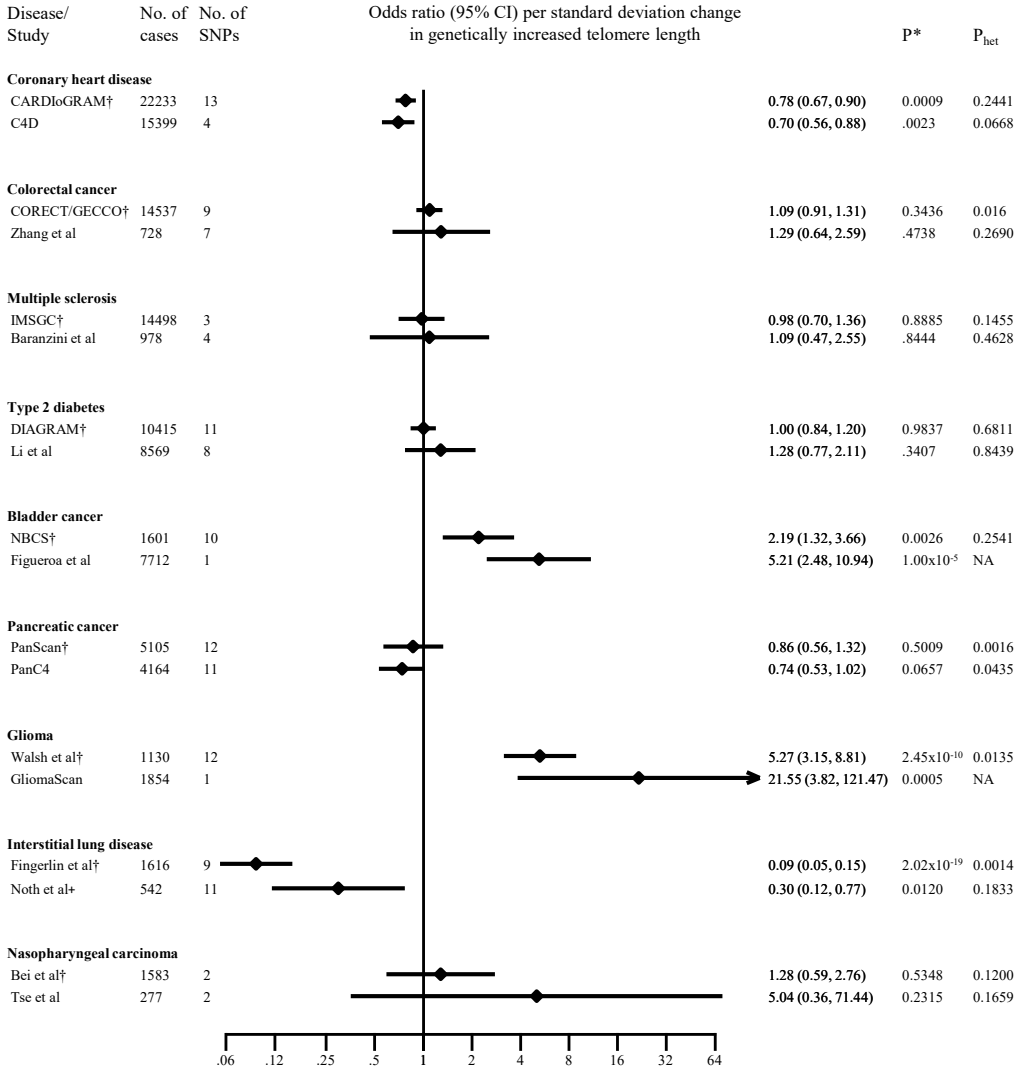
Supplementary Figure S3. Replication of association between genetically increased telomere length and odds of non-communicable diseases in independent datasets



*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[81]: ≤17% of the cases overlapped with cases from Fingerlin et al[31] and 77% of cases had idiopathic pulmonary fibrosis; ‡An inverse association was also observed in Mushiroda et al[82]. 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.

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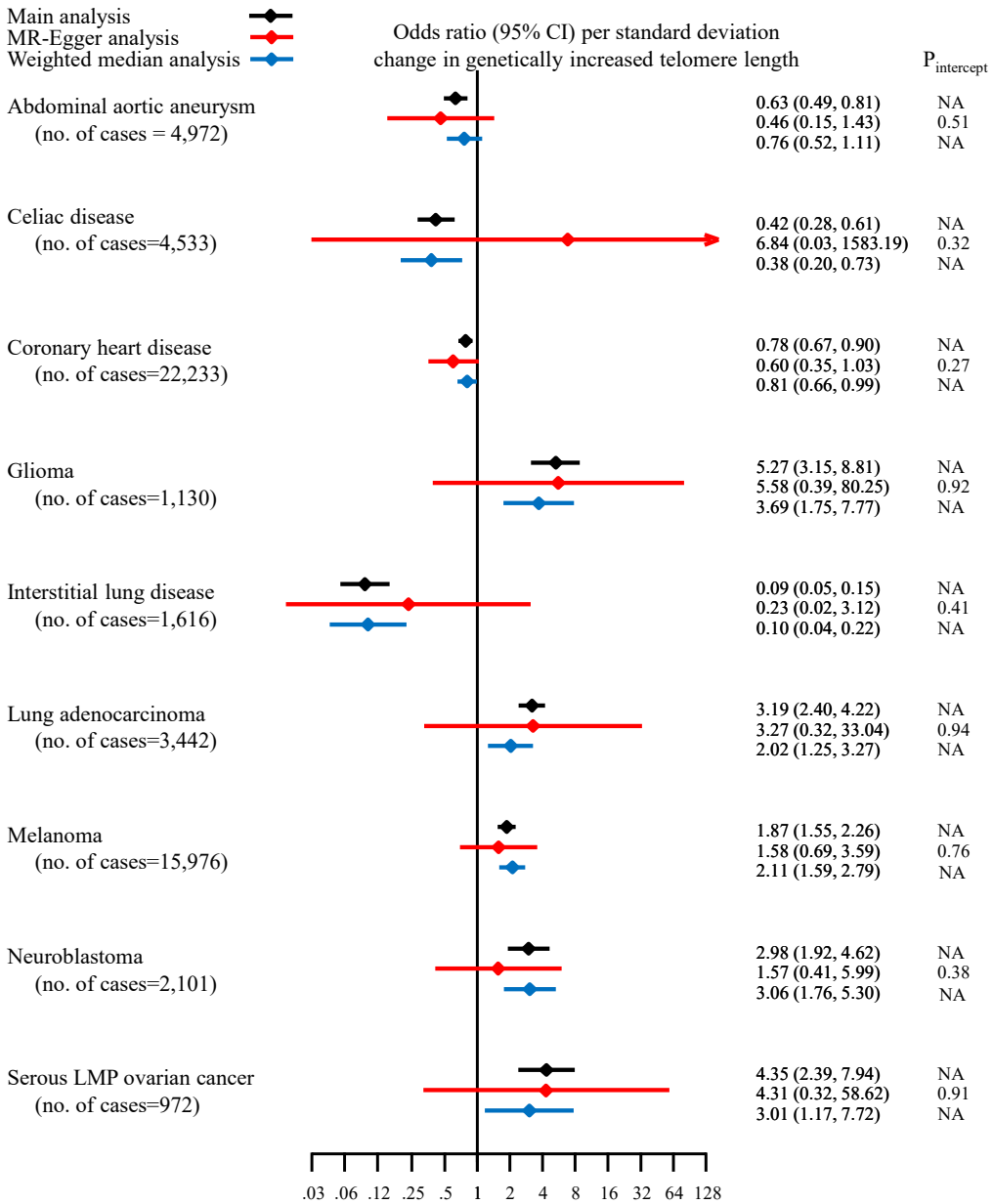
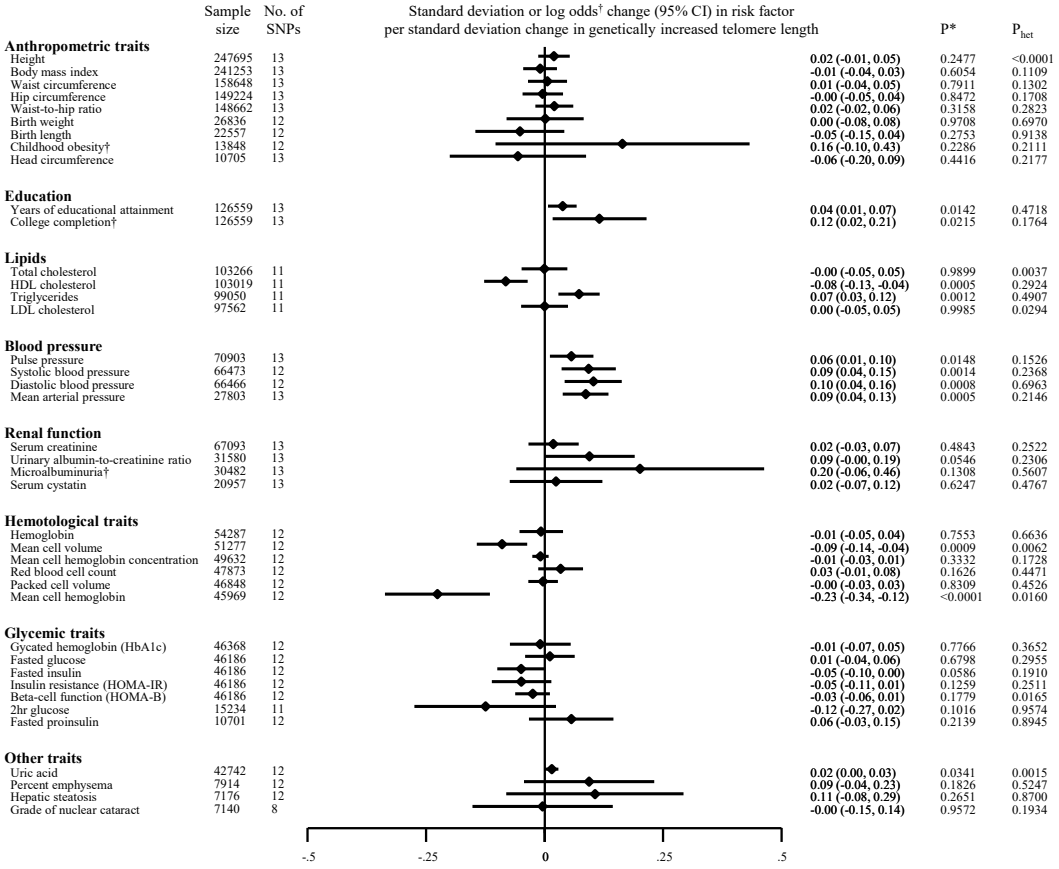
Supplementary Figure S4. Sensitivity analyses of association between genetically increased telomere length and odds of non-communicable diseases



LMP, low malignancy potential; CI, confidence interval. The $P_{intercept}$ from MR-Egger regression tests the null hypothesis that the intercept is zero and can be interpreted as a statistical test for the presence of directional (bias inducing) pleiotropy; the smaller the $P_{intercept}$ value the stronger the evidence for directional pleiotropy.

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

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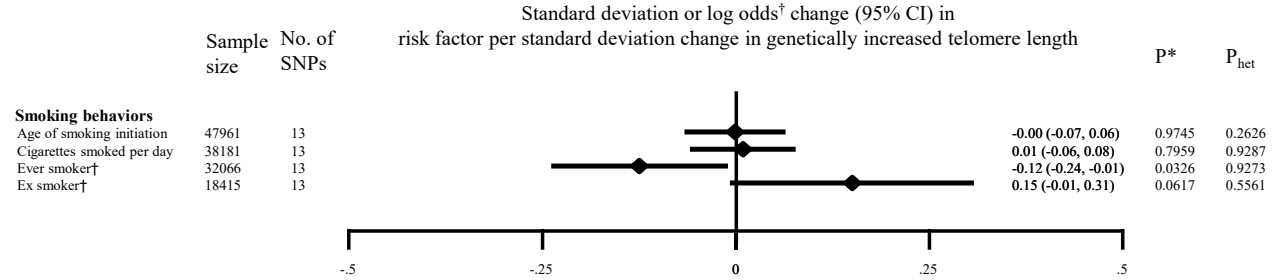
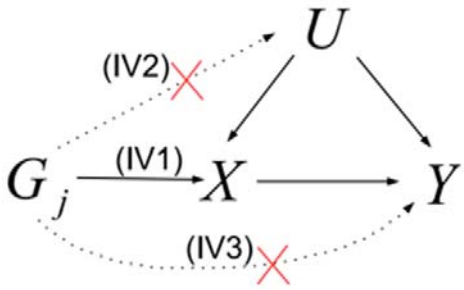
Supplementary Figure S6. Association between genetically increased telomere length and smoking



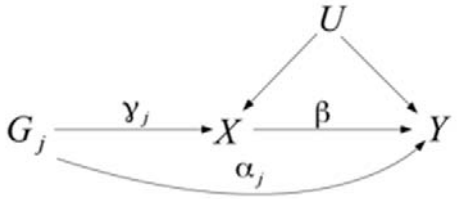
*P value for association between genetically increased telomere length and risk factor from maximum likelihood; P_{het}, P value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval; †for binary risk factors results reflect the log 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_j, single nucleotide polymorphism j; X, telomere length; Y, outcome (disease or risk factor); U, confounder; α, G-Y association not mediated by telomere length (often described as a horizontal pleiotropic or direct effect); γ, SNP-telomere-length association.

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). Under the InSIDE assumption, MR-Egger can consistently estimate the causal effect of X on Y, represented by the parameter β in (b).

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ACKNOWLEDGEMENTS OF THE CONTRIBUTING STUDIES AND CONSORTIA

Amyotrophic lateral sclerosis GWAS consortium

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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Funding/Support

I. Fogh was supported by funds from Motor Neurone Disease Association of Great Britain and Northern Ireland (grant n.905-793, 6058).

J.Powell, A.Al-Chalabi and I.Fogh received salary support from the National Institute for Health Research (NIHR) Dementia Biomedical Research Unit at South London and Maudsley NHS Foundation Trust and King's College London. The UK National DNA Bank for MND Research was funded by the Motor Neurone Disease Association (grant 3/3), the Wellcome Trust (grant

070122/A/02/Z) and the NIHR Dementias and Neurodegenerative Diseases Research Network (DeNDRoN).

V. Silani was supported by Agenzia Italiana per la Ricerca sulla SLA-AriSLA (grant NOVALS 2012 cofinanced with the contribution of 5 x 1000, Healthcare Research support of the Ministry of Health), the Italian Ministry of Health (Grant ALS-FTD, Ric. Finalizzata 2009 no.276) and Associazione Amici "Centro Dino Ferrari".

J.H. Veldink was supported by the Netherlands Organisation for Health Research and Development.

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.[28,129,130] 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[28,131] and were therefore unscreened for AAA.

NZ AAA Genetics Study (with two separate cohorts: set 1 with 608 cases and 612 controls; set 2 with 397 cases and 384 controls): The Vascular Research Consortium of New Zealand recruited

New Zealand men and women with a proven history of AAA (infra-renal aortic diameter ≥ 30 mm proven on ultrasound or CT scan). Approximately 80% had undergone surgical AAA repair (typically AAA's > 50-55 mm in diameter). The vast majority of cases (>97%) were of Anglo-European ancestry. The control group underwent an abdominal ultrasound scan to exclude (>25 mm) concurrent abdominal aortic aneurysm and Anglo-European ancestry was required for inclusion. Controls were also screened for peripheral artery disease (PAD; using ankle brachial index), carotid artery disease (ultrasound) and other cardiovascular risk factors.

Geisinger Vascular Clinic AAA Study, Pennsylvania, USA: AAA patients (n=724) were enrolled through the Department of Vascular Surgery at Geisinger Medical Center, Danville, PA. Details of this case-control set have been reported previously, and the samples have been used in previous association studies.[129,132] To identify cases and controls from the electronic medical records, an ePhenotyping algorithm was developed[29]. AAA cases were defined as infrarenal aortic diameter ≥ 30 mm as revealed by abdominal imaging. Approximately 20% of individuals with AAA had a family history of AAA. A control group (n=1231) was obtained through the Geisinger MyCode® Project, a cohort of Geisinger Clinic patients recruited for genomic studies. The MyCode® controls were matched for age distribution and sex to the Geisinger Vascular Clinic AAA cases. Based on electronic medical records, controls had no ICD-9 codes for AAA in their records, but they were not screened by ultrasonography for AAA. Both cases and controls from the Geisinger Clinic were of European descent. The eMERGE Network Imputed GWAS for 41 Phenotypes (the dbGaP eMERGE Phase 1 and 2 Merged data Submission) accession number is: phs000888.v1.p1 which includes the Geisinger AAA data.

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[129] 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[129], 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.[28,129,130,132] 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[133] 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:

Data provided by the original Aneurysm Consortium was funded by the Wellcome Trust (award number 084695) and made use of data generated by the WTCCC. A full list of the investigators who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the WTCCC project was provided by the Wellcome Trust under award 076113 and 085475. Funding for the New Zealand project was provided by the Health Research Council of New Zealand (08-75, 14-155). The Geisinger sample collection was funded in part by the Pennsylvania Commonwealth Universal Research Enhancement program, the Geisinger Clinical Research Fund, the American Heart Association, and the Ben Franklin Technology Development Fund of Pennsylvania. The generation and management of GWAS genotype data for the Rotterdam Study (control samples for the Dutch GWAS) is supported by the Netherlands Organization of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/NWO project nr. 050-060-810.

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542 **Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM)**
543 **consortium and The Coronary Artery Disease (C4D) Genetics consortium**
544 We thank the CARDIoGRAM and C4D consortia for making summary data available to the
545 research community. Data on coronary artery disease / myocardial infarction have been contributed
546 by CARDIoGRAMplusC4D investigators and have been downloaded from

www.CARDIOGRAMPLUSC4D.ORG. The investigators within CARDIoGRAM and C4D did not participate in the analysis, writing or interpretation of this report.

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For a full list of CHARGE – Heart Failure working group members contributing to this work and for CHARGE – Heart Failure acknowledgements please see PMID 20445134.

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The COPDGene project was supported by Award Number R01HL089897 and Award Number R01HL089856 from the National Heart, Lung, And Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health. The COPDGene project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovion, and GlaxoSmithKline.

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Early Growth Genetics (EGG) Consortium

Summary data on birth anthropometrics has been contributed by the EGG Consortium and has been downloaded from www.egg-consortium.org.The investigators within the EGG did not participate in the analysis, writing or interpretation of this paper.

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L.Paternoster is supported by an MRC Population Health Scientist Fellowship (MR/J012165/1).

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Glioma GWAS

Work at University of California, San Francisco was supported by the National Institutes of Health (grant numbers R01CA52689, P50CA097257, R01CA126831, R01CA139020 and R25CA112355), as well as the National Brain Tumor Foundation, the Stanley D. Lewis and Virginia S. Lewis Endowed Chair in Brain Tumor Research, the Robert Magnin Newman Endowed Chair in Neuro-oncology, and by donations from families and friends of John Berardi, Helen Glaser, Elvera Olsen, Raymond E. Cooper, and William Martinusen.

The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement # U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

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958 The results published here are in whole or part based upon data generated by The Cancer Genome
959 Atlas managed by the NCI and NHGRI. Information about TCGA can be found
960 athttp://cancergenome.nih.gov

961

962 **Endometriosis GWA meta-analysis**

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Funding

QIMR: The QIMR study was supported by grants from the National Health and Medical Research Council (NHMRC) of Australia (241944, 339462, 389927, 389875, 389891, 389892, 389938, 443036, 442915, 442981, 496610, 496739, 552485 and 552498), the Cooperative Research Centre for Discovery of Genes for Common Human Diseases (CRC), Cerylid Biosciences (Melbourne) and donations from N. Hawkins and S. Hawkins. D.R.N. was supported by the NHMRC Fellowship (339462 and 613674) and Australian Research Council (ARC) Future Fellowship (FT0991022) schemes. S.M. was supported by NHMRC Career Development Awards (496674 and 613705). E.G.H. (631096) and G.W.M. (339446 and 619667) were supported by the NHMRC Fellowship scheme. The HCS was funded by the University of Newcastle, the Gladys M Brawn Fellowship scheme and the Vincent Fairfax Family Foundation in Australia. ***OX:*** The work presented here was

supported by a grant from the Wellcome Trust (WT084766/Z/08/Z) and makes use of Wellcome Trust Case Control Consortium 2 (WTCCC2) control data generated by the WTCCC. A full list of the investigators who contributed to the generation of these data is available at the Wellcome Trust website (http://www.wtccc.org.uk/). Funding for the WTCCC project was provided by the Wellcome Trust under awards 076113 and 085475. C.A.A. was supported by a grant from the Wellcome Trust (098051). A.P.M. was supported by a Wellcome Trust Senior Research Fellowship. S.H.K. is supported by the Oxford Partnership Comprehensive Biomedical Research Centre, with funding from the Department of Health National Institute for Health Research (NIHR) Biomedical Research Centres funding scheme. K.T.Z. is supported by a Wellcome Trust Research Career Development Fellowship (WT085235/Z/08/Z). ***BBJ:*** We thank the members of the Rotary Club of Osaka-Midosuji District 2660 Rotary International in Japan for supporting our study. This work was conducted as part of the BioBank Japan Project that was supported by the Ministry of Education, Culture, Sports, Science and Technology of the Japanese government.

European Periodontitis Genetics Group (EPG)

The GWAS of aggressive periodontitis (AgP) was supported by a research grant of the Deutsche Forschungsgemeinschaft DFG (GZ: SCHA 1582/3-1). The cohort case description has been previously reported in Schaefer A.S. *et al*. Genetic evidence for PLASMINOGEN as a shared genetic risk factor of coronary artery disease and periodontitis. *Circ Cardiovasc Genet* **8**, 159-67 (2015). The investigators who contributed to the generation of this case sample are: Henrik Dommisch[1], Christian Graetz[2], Inga Harks[3], Yvonne Jockel-Schneider[4], Jörg Eberhardt[5], Joerg Meyle[6], Peter Eickholz[7], Mathias Folwaczny[8], Barbara Noack[9], Wolfgang Lieb[10], Christof Doerfer[2], Corinna Bruckmann[11], Søren Jepsen[12]

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Genotyping of the AgP cases was performed on an IScan system with HumanOmni BeadChips (Illumina) at the Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, Germany. We specially thank Andre Franke and Stefan Schreiber.

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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The International Genomics of Alzheimer's Project (IGAP)

We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i–Select chips was funded by the French National Foundation on Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF): Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES contract N01–AG–12100, the NHLBI grant R01 HL105756, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant ADGC–10–196728.

Material and methods

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

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The melanoma meta-analysis consortium was supported by CRUK Programme grants (C588/A19167 C8197/A10123, C8197/A10865), NIH grant (R01CA083115, RO1CA001833) NIH NCI (CA88363, CA83115, CA122838, CA87969, CA055075, CA100264, CA133996 and CA49449), the NHMRC (200071, 241944, 339462, 380385, 389927, 389875, 389891, 389892, 389938, 443036, 442915, 442981, 496610, 496675, 496739, 552485, 552498, 66946, 107359, 211172, 402761, 535074, 1023911).

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The MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-001079, UL1-TR-000040, and DK063491. Funding for SHARe genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at

Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston, Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0. Funding support for the Lung CT dataset was provided by grants R01-HL077612 and RC1-HL100543.NIH Intramural award ZIAEY00403 supported the collection of eye-related data in MESA.

The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS)

We would like to thank the participants and staff of the Nurses' Health Study, the Health Professionals Follow-Up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. This work was supported by NIH R01 CA49449, P01 CA87969, UM1 CA186107, and UM1 CA167552.

GWAS of non-alcoholic fatty liver disease (hepatic steatosis)

Bratati Kahali and Elizabeth K Speliotes were supported by the Doris Duke Medical Foundation, NIH grant R01DK106621-01, the University of Michigan Internal Medicine Department, Division of Gastroenterology, the University of Michigan Biological Sciences Scholars Program and The Central Society for Clinical Research.

Pancreatic cancer case-control consortium (PanC4)

The Mayo Clinic Molecular Epidemiology of Pancreatic Cancer study was supported by the Mayo Clinic SPORE in Pancreatic Cancer (P50CA102701). The Yale University study was supported by grant number 5R01CA098870 from the NCI. The work at Johns Hopkins University was supported by NCI Grants P50CA62924 and R01CA97075 and the Lustgarten Foundation for Pancreatic Cancer Research. The Pancreas Tumor Registry at Memorial Sloan Kettering Cancer Center was supported by NIH P30CA008748 and the Goldstein Fund for Prevention, Control and Population

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Pancreatic Cancer Cohort Consortium (PanScan)

PanScan is the NCI cohort consortium genome-wide association study for pancreatic cancer. This research was supported by the Intramural Research Program of the National Institutes of Health, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study

The coordination of EPIC is financially supported by the European Commission (DG-SANCO) andthe International Agency for Research on Cancer. The national cohorts are supported by the Health Research Fund (FIS) of the Spanish Ministry of Health,Regional Governments of Andalucía, Asturias, Basque Country, Murcia (no.6236), Navarra and the Catalan Institute of Oncology, La Caixa (BM 06-130),Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0018; RD06/0020/0091; Spain); Danish Cancer Society (Denmark); Ligue contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale,Institut National de la Santé et de la Recherche Médicale (INSERM; France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum (DKFZ) and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare, and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON

(Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), and Statistics Netherlands (The Netherlands); Nordic Center of Excellence in Food, Nutrition, and Health Helga (Norway); Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skane and Vasterbotten (Sweden); Cancer Research UK (C570/A16491, R.C. Travis; 14136, K.T. Khaw) and Medical Research Council (G1000143, K.T. Khaw; United Kingdom).

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Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen

Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund.

Sarcoidosis GWAS

This work was supported by the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (SysInflame grant 01ZX1306A). This project received infrastructure support from the DFG Excellence Cluster No. 306 "Inflammation at Interfaces". Andre Franke receives an endowment professorship by the Foundation for Experimental Medicine (Zuerich, Switzerland).

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Acknowledgements of studies that contributed to the GWAS meta-analysis of telomere length[4]

The Framingham Heart Study

The Framingham Heart Study is funded by National Institutes of Health contract N01-HC-25195. The Framingham GWAS component of this project was funded by the Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

TwinsUK

The study was funded by the Wellcome Trust; European Community's Seventh Framework Programme (FP7/2007-2013). The study also receives support from the National Institute for Health Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London.

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