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

Philip Haycock[1]; Stephen Burgess[2]; Aayah Nounu[1]; Jie Zheng[1]; George N Okoli[3]; Jack Bowden[1,4]; Kaitlin Wade[1]; Nicholas Timpson[1]; David M. Evans[1,5]; Peter Willeit[2,6]; Abraham Aviv[7]; Tom R. Gaunt[1]; Gibran Hemani[1]; Massimo Mangino[8,9]; Hayley Patricia Ellis[10]; Kathreena Mary Kurian[10]; Karen Pooley[11] on behalf of the BCAC and OCAC consortia; Rosalind Eeles[12] on behalf of the PRACTICAL consortium; Jeffrey E Lee[13]; Shenying Fang[13]; Wei Chen[13]; Matthew H Law[14], Lisa M Bowdler[15] and Mark M Iles[16] on behalf of the Melanoma meta-analysis consortium; Qiong Yang[17], Bradford B. Worrall[18] and Hugh Stephen Markus[19] on behalf of the METASTROKE project of the ISGC; Rayjean J. Hung[20,21] and Chris I Amos[22] on behalf of the ILCCO consortium; Amanda Spurdle[23], Deborah J Thompson[24] and Tracy O'Mara[23] on behalf of the ECAC consortium; Brian Wolpin[25], Laufey Amundadottir[26] and Rachael Stolzenberg-Solomon[27] on behalf of the PanScan consortium; Joanne Elena[28]; Antonia Trichopoulou[29,30], Charlotte Onland-Moret[31], Eiliv Lund[32], Eric Jeffrey Duell[33], Federico Canzian[34], Gianluca Severi[35,36,37,38], Kim Overvad[39], Marc J Gunter[40], Rosario Tumino[41] and Ulrika Svenson[42] on behalf of EPIC; Andre van Rij[43], Annette F Baas[44], Matthew J Bown[45], Nilesh J Samani[45], Paul IW de Bakker[44], Femke NG van t'Hof[44], Gerard Tromp[46,47], Gregory T Jones[43], Helena Kuivaniemi[46,47] and James R Elmore[48] on behalf of the Aneurysm Consortium; Mattias Johansson[49]; James Mckay[49]; Ghislaine Scelo[49]; Robert Carreras-Torres[49]; Valerie Gaborieau[49]; Paul Brennan[49]; Paige M. Bracci[50], Rachel E Neale[15], Sara H Olson[51], Steven Gallinger[20], Donghui Li[52], Gloria M. Petersen[54], Harvey Risch[55], and Alison P. Klein[56] on behalf of PanC[4]; Jiali Han[57,58]; Christian C. Abnet[59]; Neal D. Freedman[59]; Philip R. Taylor[59]; John M Maris[60]; Katja K Aben[61,62]; Lambertus A Kiemeney[61]; Sita H Vermeulen[61]; John K Wiencke[63,64]; Kyle M Walsh[63,64]; Margaret Wrensch[63,64]; Terri Rice[63]; Clare Turnbull[65]; Kevin Litchfield[66]; Lavinia Paternoster[1] and Marie Standl[67] on behalf of the EAGLE consortium; Gonçalo R Abecasis[68]; John Paul SanGiovanni[69]; Lars G Fritsche[68]; Yong Li[70] and Vladan Mijatovic[71] on behalf of the CKDGen consortium; Yadav Sapkota[15]; Siew-Kee Low[72]; Krina T Zondervan[73,74]; Grant W Montgomery[15]; Dale R. Nyholt[75,15]; David A van Heel[76]; Karen Hunt[76]; Dan E. Arking[77], Foram N. Ashar[77] and Nona Sotoodehnia[78] on behalf of the CHARGE-Sudden Cardiac Arrest Working Group; Daniel Woo[79]; Jonathan Rosand[80]; Mary Comeau[81]; W. Mark Brown[82]; Edwin K. Silverman[83], John E Hokanson[84] and Michael Cho[83] on behalf of COPDGene; Jennie Hui[85,86,87,88], Manuel Ferreira[15] and Philip J. Thompson[89] on behalf of the AAGC

consortium; Alanna C. 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]; Paul KH Tam[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; Caroline Relton[1]; Richard M Martin[1,3,160]; George Davey Smith[1]

[1] MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK

[2] Department of Public Health and Primary Care, University of Cambridge

[3] School of Social and Community Medicine, University of Bristol, Bristol, UK

[4] MRC Biostatistics Unit, Cambridge, UK.

[5] University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, Queensland, Australia

[6] Department of Neurology, Innsbruck Medical University, Austria

[7] Center of Human Development and Aging, Department of Pediatrics, New Jersey Medical School, Rutgers, The State University of New Jersey

[8] Department of Twin Research and Genetic Epidemiology, King's College London, London UK
[9] NIHR Biomedical Research Centre at Guy's and St. Thomas' Foundation Trust, London, UK
[10] Brain Tumour Research Group, Institute of Clinical Neuroscience, Learning and Research Building, Southmead Hospital, University of Bristol
[11] Strangeways Research Laboratory, University of Cambridge, Cambridge, UK
[12] The Institute of Cancer Research, London, UK
[13] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX.
[14] Statistical Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia
[15] QIMR Berghofer Medical Research Institute, Brisbane, Australia
[16] Section of Epidemiology and Biostatistics, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK
[17] Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United States of America and the Framingham Heart Study, Framingham, Massachusetts, United States of America
[18] Departments of Neurology and Public Health Sciences University of Virginia Charlottesville, Virginia 22908
[19] Department of Clinical Neurosciences, University of Cambridge, UK
[20] Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
[21] Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, 60 Murray St. Rm L5-215, Box 18, Toronto, ON M5T 3L9, Canada
[22] Geisel School of Medicine, Dartmouth College
[23] Genetics and Computational Biology Division, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia
[24] Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, CB1 8RN, UK.
[25] Dana-Farber Cancer Institute
[26] Laboratory of Translational Genomics, Division of Cancer Epidemiology & Genetics, National Cancer Institute
[27] Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS.
[28] Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville MD USA
[29] Hellenic Health Foundation, Athens, Greece
[30] WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Dept. of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Greece
[31] Dept of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht
[32] Institute of community medicine, UiT The Artcic University of Norway
[33] Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Bellvitge Biomedical Research Institute (IDIBELL), Catalan Institute of Oncology (ICO), Avda Gran Via 199-203, 08908 L'Hospitalet de Llobregat, Barcelona, Spain
[34] Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany
[35] Université Paris-Saclay, Université Paris-Sud, UVSQ, CESP, INSERM, Villejuif, France
[36] Gustave Roussy, F-94805, Villejuif, France
[37] Human Genetics Foundation (HuGeF), Torino, Italy
[38] Cancer Council Victoria and University of Melbourne, Australia
[39] Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark
[40] School of Public Health, Imperial College London, London W2 1PG
[41] Cancer Registry, Azienda Ospedaliera "Civile M.P.Arezzo", via Dante 109, Ragusa, IT

[42] Department of Medical Biosciences, Umea University, Umea, Sweden

[43] Surgery Department, University of Otago, Dunedin, New Zealand

[44] Department of Medical Genetics, Center for Molecular Medicine and Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[45] The Department of Cardiovascular Sciences and the NIHR Leicester Cardiovascular Biomedical Research Unit, University of Leicester, Leicester, LE2 7LX, UK.

[46] Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, 7505, South Africa

[47] The Sigfried and Janet Weis Center for Research, Geisinger Health System, Danville, PA, USA

[48] Department of Vascular and Endovascular Surgery, Geisinger Health System, Danville, PA 17822, USA

[49] Genetic Epidemiology Group, International Agency for Research on Cancer, Lyon, France

[50] Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California

[51] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA.

[52] Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[54] Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

[55] Yale School of Public Health & Yale School of Medicine & Yale Cancer Center, 60 College St., PO Box 208034, New Haven, CT 06520-8034

[56] Departments of Oncology, Pathology and Epidemiology, Johns Hopkins School of Medicine, Baltimore Maryland 21231

[57] Department of Epidemiology, Fairbanks School of Public Health, Indiana University

[58] Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA

[59] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville MD USA

[60] Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania

[61] Radboud university medical center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

[62] Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands

[63] Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA

[64] Institute of Human Genetics, University of California, San Francisco, San Francisco, CA

[65] William Harvey Research Institute, Queen Mary University, London, UK

[66] Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK

[67] Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

[68] Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA

[69] National Eye Institute, Division of Epidemiology and Clinical Research Clinical Trials Branch National Institutes of Health, Bethesda, USA

[70] Department of Internal Medicine IV, University Hospital Freiburg

[71] Department of Life and Reproduction Sciences, University of Verona

[72] Laboratory of Statistical Analysis, Centre for Integrative Medical Sciences, The Institute of Physical and Chemical Research (RIKEN], Yokohama, Japan

[73] Genetic and Genomic Epidemiology Unit, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

[74] Nuffield Department of Obstetrics and Gynecology, University of Oxford, John Radcliffe Hospital, Oxford, UK

[75] Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

[76] Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK
[77] McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD USA
[78] Division of Cardiology and Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, Washington 98101
[79] University of Cincinnati College of Medicin, Department of Neurology, Cincinnati, OH, USA 45267
[80] Massachusetts General Hospital, Neurology, Center for Human Genetic Research, MA, USA
[81] Center for Public Health Genomics, Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157
[82] Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157
[83] Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA 02115
[83] Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, 02115
[84] Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA
[85] Busselton Population Medical Research Institute Inc, Sir Charles Gairdner Hospital, Perth, Australia
[86] PathWest Laboratory Medicine of Western Australia (WA), Perth, Australia
[87] School of Pathology and Laboratory Medicine, University of WA, Perth, Australia
[88] School of Population Health, University of WA, Perth, Australia
[89] The Lung Health Clinic and Institute for Respiratory Health, University of Western Australia, Perth, Australia
[90] Department of Epidemiology, Human Genetics, and Environmental Sciences, University of Texas Health Science Center at Houston, Houston, TX 77030 USA
[91] Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[92] Department of Epidemiology, University of Washington, Seattle WA 98101 USA
[93] Departments of Dermatology and Genetics & Development, Columbia University, New York, NY, US
[94] Departments of Dermatology and Epidemiology, Columbia University, New York, NY, US
[95] Institute of Human Genetics, University of Bonn, Bonn D-53127, Germany
[96] Institute of Dermatology & Department of Dermatology, First Affiliated Hospital of Anhui Medical University
[97] Director, Center for Public Health Genomics, Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157
[98] Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics,University of Cincinnati College of Medicine, Cincinnati, OH, USA
[99] Institute for Nutritional Sciences, SIBS, Chinese Academy of Sciences, Shanghai, 200031, PR China
[100] Key Laboratory of Nutrition and Metabolism, Chinese Academy of Sciences, Shanghai, 200031, PR China
[101] University of Colorado, 12631 East 17th Avenue, B178, Aurora, CO 80045
[102] Department of Biomedical Research, National Jewish Health Hospital
[103] Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center
[104] Departments of Pediatrics and Medicine, 1124 W. Carson Street, Harbor-UCLA Medical Center, Torrance, CA 90502
[105] Epidemiology Branch, Division of Epidemiology and Clinical Applications, NIH Intramural Research Program, National Eye Institute, National Institutes of Health, Clinical Research Center 3A2521,
[106] Cardiovascular Health Research Unit, University of Washington, Seattle, Washington, USA
[107] Department of Medicine, University of Washington, Seattle, Washington, USA
[108] Charité – University Medicine Berlin, CC 03, Institute of Dental, Oral and Maxillary Medicine, Dept. of Periodontology and Synoptic Dentistry, Aßmannshauser Str. 4-6, 14197 Berlin, Germany

[109] Department of Pulmonary Medicine, Peking University People's Hospital, 100044 Beijing, China

[110] Stanford University, Center for Sleep Sciences, Palo Alto, CA, USA

[111] Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK

[112] Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

[113] Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Tennessee

[114] Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

[115] Department of Psychiatry, Shonan Kamakura General Hospital, Kanagawa, Japan

[116] Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[117] Graduate School of Clinical Psychology, Teikyo Heisei University Major of Professional Clinical Psychology, Tokyo, Japan

[118] Department of Physical and Health Education, Graduate School of Education, The University of Tokyo, Tokyo, Japan

[119] Infectious Diseases, Genome Institute of Singapore, Singapore

[120] Division of Infectious diseases, Department of medicine, Imperial College London, UK

[121] Human genetics, Genome Institute of Singapore, Singapore

[122] Departments of Medicine, Immunology, Molecular Genetics, University of Toronto

[123] Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine Guangzhou 510060, P. R. China

[124] Peking Union Medical College, Beijing 100730, P.R. China

[125] Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

[126] Center for Primary Health Care Research, Clinical Research Center, Lund University, Malmö, Sweden

[127] Department of Biology, University of Pisa, Pisa, Italy

[128] Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany.

[129] University Hospital Schleswig-Holstein, Kiel, Germany

[130] Research Unit, Hospital Universitario N.S. de Candelaria, Tenerife, Spain

[131] CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain

[132] Section of Pulmonary and Critical Care Medicine, University of Chicago, 5841 S. Maryland Ave., Chicago IL 60637-6076

[133] Human Genetics, Genome Institute of Singapore, A*STAR, Singapore 138672, Singapore

[134] Dept. of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan, University School of Medicine, Ilwon-dong 50, Gangnam-gu, Seoul, Korea, 135-710

[135] Cancer Research Center of Lyon, INSERM U1052, Lyon, France

[136] Inserm U830, Institut Curie, PSL University, 26 rue d'Ulm, 75248 Paris Cedex 05 France, France.

[137] Department of Epidemiology, University of Alabama at Birmingham. 1665 University Boulevard, Birmingham, AL 35294-0022, USA

[138] Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, SAR China

[139] Department of Otolaryngology - Head and Neck Surgery, Chang Gung Memorial Hospital at Lin-Kou, Taoyuan, Taiwan,

[140] Department of Biomedical Sciences, Graduate Institute of Biomedical Sciences, College of Medicine, Molecular Medicine Research Center, Chang Gung University, Taoyuan, Taiwan

[141] Molecular Medicine Research Center, Chang Gung University, Taoyuan, Taiwan

[142] School of Psychology, Flinders University

[143] School of Systems Biomedical Science, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 156-743, Korea

[144] RIKEN Center for Integrative Medical Science, 1-7-22, Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa 230-0045, JAPAN

[145] Division of Molecular Brain Science, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-chou, Chuo-ku, Kobe 650-0017, Japan
[146] Center for Personalized Therapeutics, The University of Chicago, 900E 57th Street, Chicago IL 60637 USA
[147] The NHLBI's Framingham Heart Study, Framingham, MA, Population Sciences Branch of the National Heart, Lung, and Blood Institute, Bethesda, MD.
[148] Department of Genetic Medicine, Weill Cornell Medicine in Qatar, Doha, Qatar
[149] Human Genetics, Wellcome Trust Sanger Institute, Genome Campus, Hinxton Cambridge
[150] Center for Public Health Genomics, Department of Public Health Sciences, University of Virginia, Charlottesville, VA USA
[151] Department of Medicine and Department of Epidemiology, Columbia University Medical Center, New York, NY 10032, USA
[152] Department of Internal Medicine, Division of Gastroenterology and Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI 48109, USA
[153] Department of Medicine, University of Maryland, Baltimore, MD 21201, USA
[154] Singapore Eye Research Institute, Singapore National Eye Center, Singapore 168751, Singapore
[155] Department of Ophthalmology, National University of Singapore and National University Health System, Singapore
[156] Duke-National University of Singapore Graduate Medical School, Singapore
[157] Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Science Key Lab, Beijing, China
[158] Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karls-University Heidelberg, Mannheim, Germany
[159] Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[160] University of Bristol / University Hospitals Bristol NHS Foundation Trust National Institute for Health Research Bristol Nutrition Biomedical Research Unit, Bristol, UK

Correspondence: Philip Haycock

MRC Integrative Epidemiology Unit

University of Bristol

Bristol

UK

philip.haycock@bristol.ac.uk

Tel: +44 1173 310 088

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ABSTRACT 339 WORDS

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

Objective To appraise the causal relevance of telomere length for risk of cancer and non-neoplastic diseases using germline genetic variants as instrumental variables.

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, 103 shared data for our study.

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 1-SD higher telomere length due to germline genetic variation.

Results Summary data were available for 35 cancers and 47 non-neoplastic diseases, corresponding to 409,819 cases (median 2,092 per disease) and 1,404,633 controls (median 7,738 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 higher genetically estimated 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 1.97 (1.14-3.41); 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 with cancer were stronger for rarer cancers and tissue sites with lower rates of stem cell division ($P<0.05$). There was

generally little evidence of association between 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 Genetically longer telomeres are associated with increased risk for several cancers, but the relative increase in risk is highly heterogeneous across cancer types, and with reduced risk for some non-neoplastic diseases, including cardiovascular diseases.

INTRODUCTION

Telomeres are DNA-protein structures at the end of linear chromosomes that protect the genome from damage; and shorten progressively over time in most somatic tissues.[1] Shorter leukocyte telomeres are correlated with older age, male sex and other known risk factors for non-communicable diseases[2–4] and are generally associated with higher risk of cardiovascular diseases[5,6], type 2 diabetes[7] and non-vascular non-neoplastic causes of mortality.[6] 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.[8–12] 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. For example, changes in telomere length in people who go on to develop cancer can typically be detected 3-4 years prior to diagnosis[12], meaning that even well designed prospective studies remain susceptible to reverse causation.

The aim of the present report was to circumvent these limitations through a Mendelian randomization study, using germline genetic variants as instrumental variables for telomere length. 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 proxies for telomere length; 2) the acquisition of summary data for the genetic proxies from genome wide association studies (GWASs) of diseases and risk factors; 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[13,14] on the 15 January 2015, to identify single nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with additional potential proxies, we also searched the original study reports curated by the GWAS catalog (using a P value threshold of $5x10^{-8}$).[15–23] 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.[16] SNPs initially identified as potential proxies for telomere length were subsequently excluded if they lacked strong evidence of association with telomere length. We defined strong evidence of association as a p-value $<5x10^{-8}$ in: i) the discovery stage of at least one published GWAS of telomere length[15–22] or ii) a meta-analysis of summary data from Mangino et al[16] and other GWASs of telomere length,[15,17–22] with any overlapping studies excluded from Mangino et al.[16] We also excluded SNPs with a minor allele frequency <0.05 or showing strong evidence of between-study heterogeneity in associations with telomere length ($P \leq 0.001$).

The second key component of our design strategy involved the acquisition of summary data, corresponding to the selected genetic proxies 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[13,14] 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 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% power (i.e. moderate-to-high statistical power) and secondary outcomes defined as diseases with <50% power (i.e. low statistical power) to detect odds ratios ≥2.0 per standard deviation increase in telomere length (alpha assumed to be 0.01). All risk factors were defined as secondary outcomes. Risk factors with low statistical power were excluded from all analyses. Further details on the power calculations and the study design are provided in the supplementary methods.

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 standard deviation scale using previously described methods.[24] 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 genetic risk score, using maximum likelihood to estimate the slope of the relationship between β_{GD} and β_{GP} and a variance-covariance matrix to make allowance for linkage disequilibrium between SNPs,[25] where β_{GD} is the change in disease or risk factor per copy of the effect allele and β_{GP} is the standard deviation change in telomere length per copy of the effect allele (see supplementary methods for technical details). The slope from this approach can be interpreted as the log odds ratio for binary outcomes, or the unit change for continuous risk factors, per standard deviation change in genetically increased telomere length. P values for heterogeneity in the estimated associations between telomere length and disease amongst SNPs were estimated by likelihood ratio tests.[25] Associations between genetically increased telomere length and continuous risk factors were transformed into standard deviation units. For six diseases where only a single SNP was available for analysis, we estimated associations using the Wald ratio: $\beta_{GD}/\beta_{GP,}$ with standard errors approximated by the delta method.[26]

Inference of causality in the estimated etiological associations between telomere length and disease depends on satisfaction of Mendelian randomization assumptions.[27,28] The assumptions are: 1) the genetic proxies must be associated with telomere length; 2) the genetic proxies should not be associated with confounders; and 3) the genetic proxies must be associated with disease exclusively through their effect on telomere length. When these assumptions are satisfied, genetic proxies are said to be valid instrumental variables. We modeled the impact of violations of these assumptions through two sets of sensitivity analyses: a weighted median function[29] and MR-Egger regression[27] (see supplementary methods for technical details). We restricted our sensitivity analyses to diseases showing the strongest evidence of association with genetically increased telomere length (defined as $P_{Bonferroni}<0.05$).

We used meta-regression to appraise potential sources of clinical heterogeneity in our findings for cancer outcomes. The association of genetically increased telomere length with the log odds of cancer was regressed on cancer incidence, survival time and median age at diagnosis, downloaded from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program,[30] and tissue-specific rates of stem cell division from Tomasetti and Vogelstein.[31] As the downloaded cancer characteristics from SEER correspond to the United States population, 77% of which was of white ancestry in 2015[32], the meta-regression analyses excluded genetic studies conducted in East Asian populations.

All analyses were performed in R version 3.1.2[33] 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 genetic proxies for telomere length (Fig. S1 & Table 1). The selected SNPs correspond to 10 independent genomic loci 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 risk score, constructed from these 10 independent genomic loci, is strongly associated with telomere length (see supplementary discussion for a more detailed consideration).[34] Summary data for the genetic proxies for telomere length were available for 83 non-communicable diseases and 44 risk factors, corresponding to 409,819 cases (median 2,092 per disease) and 1,404,633 controls (median 7,738 per disease) (Fig. S1, Table 2 and Table S1). The median number of SNPs available across disease datasets was 11 (min=1, max=13) and across risk factor datasets was 13 (min=10, max=13). Of the 83 diseases, 55 were classified as primary outcomes and 28 as secondary outcomes (Table 2, Fig. S1 and Table S1).

The results from primary analyses of non-communicable diseases are presented in Figure 1; results from secondary analyses of risk factors and diseases with low *a priori* power are presented in the supplementary materials (Fig. S2, S5 and S6). Genetically increased telomere length was associated with higher odds of disease for 9 of 22 primary cancer outcomes, including glioma, endometrial cancer, kidney cancer, testicular germ cell cancer, melanoma, bladder cancer, neuroblastoma, lung adenocarcinoma and serous low malignancy potential ovarian cancer ($P<0.05$) (Fig. 1). The associations were, however, highly variable across cancer types, varying from an odds ratio of 0.86 (95% confidence interval: 0.50 to 1.48) for head and neck cancer to 5.27 (3.15, 8.81) for glioma. Substantial variability was also observed within tissue sites. For example, the odds ratio for lung adenocarcinoma was 3.19 (2.40 to 4.22) compared to 1.07 (0.82 to 1.39) for squamous cell lung cancer. For serous

low malignancy potential ovarian cancer the odds ratio was 4.35 (2.39 to 7.94) compared to odds ratios of 1.21 (0.87 to 1.68) for endometrioid ovarian cancer, 1.12 (0.938 to 1.34) for serous invasive ovarian cancer, 1.04 (0.66 to 1.63) for clear cell ovarian cancer and 1.04 (0.732 to 1.47) for mucinous ovarian cancer. The strongest evidence of association was observed for glioma, lung adenocarcinoma, neuroblastoma and serous low malignancy potential ovarian cancer ($P_{Bonferroni}<0.05$). Results for glioma and bladder cancer showed evidence for replication in independent datasets (independent datasets were not available for other cancers) (Fig. S3).

Genetically increased telomere length was associated with reduced odds of disease for 6 of 32 primary non-neoplastic diseases, including coronary heart disease, abdominal aortic aneurysm, Alzheimer's disease, celiac disease, interstitial lung disease and type 1 diabetes ($P<0.05$) (Figure 1). The strongest evidence of association was observed for coronary heart disease, 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 approach were broadly similar to the main results for glioma, lung adenocarcinoma, serous low malignancy potential ovarian cancer, neuroblastoma, abdominal aortic aneurysm, coronary heart disease,

interstitial lung disease and celiac disease (Fig. S4). In the second set of sensitivity analyses, implemented by MR-Egger regression, we found little evidence for the presence of pleiotropy ($P \geq 0.27$) (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 ($P=0.4$).

DISCUSSION

Summary of main findings

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, including coronary heart disease, abdominal aortic aneurysm, celiac disease and interstitial lung disease. The findings for cancer were, however, subject to substantial variation between and within tissue sites, which our results suggest could be partly attributable to differences in cancer incidence and rates of stem cell division. 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 bias in comparison to observational studies. Nevertheless, although compatible with causality, our results could reflect violations of Mendelian randomization assumptions, such as confounding by pleiotropic pathways, population stratification or ancestry.[35] 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 that the disease GWAS results were generally adjusted for both (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.[9,10,36–39] The contradictory findings may reflect reverse causation bias 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.[8–11,38,40–59] 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.[60–63] 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,[64,65] suggesting that the association could be "J" or "U" shaped.[41,54] 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 distribution.

Mechanisms of association

Our cancer findings are compatible with known biology.[66] 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.[66] Rates of cell division are, however, highly variable amongst tissues[31] 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 almost 9-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.[31] 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.[31] 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.[30] On the other hand, individuals with chronically short telomeres, such as those with dyskeratosis congenita, could be more susceptible to genome instability and chromosomal end-to-end fusions, which could underlie their increased susceptibility to cancer.[64–66]

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.[67,68]

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.[41,54,64] Third, our results assume that the samples used to define the genetic proxies for telomere length[16] 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.[69] 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 would potentially bias the magnitude of the estimated 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).[70] 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.[71]

Conclusion

Genetically longer telomeres are associated with increased risk for several cancers, but the relative increase in risk is highly heterogeneous across cancer types, and with reduced risk for some non-neoplastic diseases, including cardiovascular diseases.

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Tables and Figures

Table 1. Single nucleotide polymorphisms used as genetic proxies for 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[19]
rs6772228	3	58390292	*PXK*	T	A	0.87	0.041	0.014	0.049721	0.77	6	8630	3.91E-10	0.200	Pooley[15]
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[20]
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[19]
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[16]
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[15]
rs7675998	4	163086668	*NAF1*	G	A	0.80	0.048	0.012	0.008912	0.077	6	9161	4.35E-16	0.190	Codd[19]
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[19]
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[16]
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[19]
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[23]
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[16]
rs8105767	19	22032639	*ZNF208*	G	A	0.25	0.064	0.011	0.000169	0.412	6	9096	1.11E-09	0.090	Codd[19]
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[16]
rs6028466	20	39500359	*DHX35*	A	G	0.17	0.058	0.013	0.003972	0.533	6	9190	2.57E-08†	0.041	Mangino[16] & Gu[18]
rs755017	20	63790269	*ZBTB46*	G	A	0.17	0.019	0.0129	0.339611	0.757	5	8026	6.71E-09	0.090	Codd[19]

*Summary data from Mangino et al[16]; 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[16] and Gu[18] 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[72]
Breast cancer	48155	43612	13	1.00	EUR	BCAC[15,73]
Estrogen receptor –ve	7465	42175	13	1.00	EUR	BCAC[15,73]
Estrogen receptor +ve	27074	41749	13	1.00	EUR	BCAC[15,73]
Colorectal cancer	14537	16922	9	1.00	EUR	CORECT/GECC[60,74]
Endometrial cancer	6608	37925	12	1.00	EUR	ECAC[75,76]
Esophageal SCC	1942	2111	11	0.64	EA	Abnet[77]
Glioma	1130	6300	12	0.72	EUR	Wrensch[78] & Walsh[62]
Head & neck cancer	2082	3477	12	1.00	EUR	McKay et al[79]
Kidney cancer	2461	5081	12	0.99	EUR	KIDRISK[80]
Lung cancer	11348	15861	13	1.00	EUR	ILCCO[81]
Adenocarcinoma	3442	14894	13	1.00	EUR	ILCCO[81]
Squamous cell carcinoma	3275	15038	13	1.00	EUR	ILCCO[81]
Skin cancer						
Melanoma	1804	1026	12	1.00	EUR	NCCC[82]
Basal cell carcinoma	3361	11518	13	1.00	EUR	NHS/HPFS[83]
Neuroblastoma	2101	4202	12	0.87	EUR	Diskin[84]
Ovarian cancer	15397	30816	13	1.00	EUR	OCAC[15,85]
Clear cell	1016	30816	13	0.76	EUR	OCAC[15,85]
Endometriod	2154	30816	13	0.98	EUR	OCAC[15,85]
Mucinous	1643	30816	13	0.94	EUR	OCAC[15,85]
Serous invasive	9608	30816	13	1.00	EUR	OCAC[15,85]
Serous LMP	972	30816	13	0.73	EUR	OCAC[15,85]
Pancreatic cancer	5105	8739	12	1.00	EUR	PANSCAN[86]
Prostate cancer	22297	22323	11	1.00	EUR	PRACTICAL[87,88]
Testicular germ cell cancer	986	4946	11	0.52	EUR	Turnbull[89] & Rapley[90]
Autoimmune/inflammatory diseases						
Atopic dermatitis	10788	30047	13	1.00	EUR	EAGLE[91]
Celiac disease	4533	10750	3	0.82	EUR	Dubois[92]
Inflammatory bowel disease						
Crohn's disease	5956	14927	11	1.00	EUR	IIBDGC[93]
Ulcerative colitis	6968	20464	12	1.00	EUR	IIBDGC[93]
Juvenile idiopathic arthritis†	1866	14786	11	0.87	EUR	Thompson[94]
Multiple sclerosis	14498	24091	1	0.87	EUR	IMSGC[95]
Aggressive periodontitis	888	6789	13	0.63	EUR	Schaefer[96]
Rheumatoid arthritis	5538	20163	11	1.00	EUR	Stahl[97]
Cardiovascular diseases						
Abdominal aortic aneurysm	4972	99858	13	1.00	EUR	AC[98–103]
Coronary heart disease	22233	64762	13	1.00	EUR	CARDIoGRAM[104]
Heart failure	2526	20926	13	0.99	EUR	CHARGE-HF[105]
Hemorrhagic stroke	2963	5503	12	0.96	EUR	METASTROKE/ISGC[106]
Ischemic stroke	12389	62004	13	1.00	EUR	METASTROKE/ISGC[107,108]
large vessel disease	2167	62004	13	0.99	EUR	METASTROKE/ISGC[107,108]
small vessel disease	1894	62004	13	0.97	EUR	METASTROKE/ISGC[107]
cardioembolic	2365	62004	13	0.99	EUR	METASTROKE/ISGC[107]
Sudden cardiac arrest	3954	21200	13	1.00	EUR	Unpublished
Diabetes						
Type 1 diabetes	7514	9045	6	0.95	EUR	T1Dbase[109]
Type 2 diabetes	10415	53655	11	1.00	EUR	DIAGRAM[110]
Eye disease						
AMD	7473	51177	13	1.00	EUR	AMD Gene[111]
Retinopathy	1122	18289	12	0.75	EUR	Jensen[112]

Lung diseases						
Asthma	13034	20638	4	1.00	EUR	Ferreira/GABRIEL[113,114]
COPD	2812	2534	12	0.85	EUR	COPDGene[115]
Interstitial lung disease	1616	4683	9	0.60	EUR	Fingerlin[116]
Neurological / psychiatric diseases						
ALS	6100	7125	12	1.00	EUR	SLAGEN/ALSGEN[117]
Alzheimer's disease	17008	37154	12	1.00	EUR	IGAP[118]
Anorexia nervosa	2907	14860	9	0.93	EUR	GCAN[119]
Autism	4949	5314	7	0.82	EUR	PGC[120]
Bipolar disorder	7481	9250	9	1.00	EUR	PGC[121]
Major depressive disorder	9240	9519	8	0.99	EUR	PGC[122]
Schizophrenia	35476	46839	12	1.00	EUR	PGC[123]
Tourette syndrome	1177	4955	13	0.74	EUR	Scharf[124]
Other						
Chronic kidney disease	5807	56430	13	1.00	EUR	CKDGen[125]
Endometriosis	4604	9393	11	1.00	Mix	Nyholt[126]

†includes unpublished data; **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 COPD; **CKDGen**, Chronic Kidney Disease; **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; **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; **METASTROKE/ISGC**, METASTROKE project of the International Stroke Genetics Consortium; **NBCS**, Nijmegen Bladder Cancer Study; **NHS**, Nurses' Health Study; **OCAC**, Ovarian Cancer Association Consortium; **NCCC**, Dartmouth-Hitchcock Norris Cotton Cancer Center; **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. **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.

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 in the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval; LMP, low malignancy potential; ER, estrogen receptor; -VE, negative; +VE, positive.

Legend to Figure 2

The plotted data show how the strength of the relationship between genetically longer telomeres 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.[30] Data for average lifetime number of stem cell divisions was downloaded from Tomasetti and Vogelstein.[31] SD, standard deviation; OR, Odds ratio. Not all cancers had information available for the selected characteristics (hence the number of cancers varies across the subplots). Information was available for 12 cancers for tissue-specific rates of stem cell division, 18 cancers for percentage surviving 5 years post-diagnosis, 23 cancers for cancer incidence and 18 cancers for median age-at-diagnosis.

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

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

	Tumor/disease subtype	No. of cases	No. of SNPs	Odds ratio† (95% CI) per standard deviation change in genetically increased telomere length	P*
Cancer					
Glioma	-	692	10	7.31 (3.65, 14.63)	1.92x10
Ovarian cancer	Serous LMP	972	13	4.35 (2.39, 7.94)	1.62x10
Lung cancer	Adenocarcinoma	3442	13	3.19 (2.40, 4.22)	6.66x10
Neuroblastoma	-	2101	12	2.98 (1.92, 4.62)	1.11x10
Bladder cancer	-	1601	10	2.19 (1.32, 3.66)	0.0026
Skin cancer	Melanoma	15976	12	1.97 (1.14, 3.41)	0.0157
Testicular germ cell cancer	-	985	11	1.76 (1.02, 3.04)	0.0423
Kidney cancer	-	2461	12	1.55 (1.08, 2.23)	0.0164
Endometrial cancer	-	6608	12	1.31 (1.07, 1.61)	0.0091
Skin cancer	Basal cell carcinoma	3361	13	1.22 (0.90, 1.65)	0.2030
Ovarian cancer	Endometriod	2154	13	1.21 (0.87, 1.68)	0.2499
Breast cancer	ER-ve	7465	13	1.14 (0.91, 1.43)	0.2543
Ovarian cancer	Serous invasive	9608	13	1.12 (0.94, 1.34)	0.2089
Prostate cancer	-	22297	11	1.12 (0.96, 1.30)	0.1533
Colorectal cancer	-	14537	9	1.09 (0.91, 1.31)	0.3436
Lung cancer	Squamous cell carcinoma	3275	13	1.07 (0.82, 1.39)	0.6212
Breast cancer	ER+ve	27074	13	1.06 (0.95, 1.17)	0.2912
Ovarian cancer	Clear cell	1016	13	1.04 (0.66, 1.63)	0.8676
Ovarian cancer	Mucinous	1643	13	1.04 (0.73, 1.47)	0.8396
Esophageal cancer	Squamous cell carcinoma	1942	8	1.03 (0.62, 1.72)	0.9055
Pancreatic cancer	Adenocarcinoma	5105	12	0.86 (0.56, 1.32)	0.5009
Head & neck cancer	-	2082	12	0.86 (0.57, 1.30)	0.4768
Neurological / psychiatric diseases					
Anorexia Nervosa	-	2907	9	1.14 (0.82, 1.58)	0.4406
Bipolar disorder	-	7481	9	1.13 (0.89, 1.44)	0.3150
Amyotrophic lateral sclerosis	-	6100	12	1.12 (0.86, 1.47)	0.4050
Tourette syndrome	-	1177	13	1.10 (0.68, 1.78)	0.6936
Major depressive disorder	-	9240	8	1.07 (0.84, 1.37)	0.5646
Autism	-	4949	7	1.01 (0.73, 1.39)	0.9515
Schizophrenia	-	35476	12	1.01 (0.90, 1.12)	0.9245
Alzheimer's disease	-	17008	12	0.84 (0.71, 0.98)	0.0296
Cardiovascular diseases					
Heart failure	-	2526	13	1.02 (0.77, 1.35)	0.8931
Ischaemic stroke	Small vessel disease	1894	13	0.94 (0.66, 1.33)	0.7141
Sudden cardiac arrest	-	3954	13	0.92 (0.68, 1.26)	0.6200
Hemorrhagic stroke	-	2963	12	0.92 (0.61, 1.37)	0.6719
Ischemic stroke	Cardioembolic	2365	13	0.88 (0.64, 1.22)	0.4464
Coronary heart disease	-	22233	13	0.78 (0.67, 0.90)	0.0009
Ischaemic stroke	Large vessel disease	2167	13	0.74 (0.52, 1.04)	0.0801
Abdominal aortic aneurysm	-	4972	13	0.63 (0.49, 0.81)	0.0003
Autoimmune/inflammatory diseases					
Inflammatory bowel disease	Crohn's disease	5956	11	1.12 (0.87, 1.45)	0.3586
Periodontitis	-	888	13	1.12 (0.67, 1.87)	0.6702
Atopic dermatitis	-	10788	13	1.05 (0.88, 1.24)	0.6095
Inflammatory bowel disease	Ulcerative colitis	6968	12	1.03 (0.81, 1.29)	0.8303
Multiple sclerosis	-	14498	3	0.98 (0.70, 1.36)	0.8885
Rheumatoid arthritis	-	5538	11	0.87 (0.65, 1.15)	0.3184
Juvenile idiopathic arthritis	-	1866	11	0.85 (0.59, 1.21)	0.3669
Celiac disease	-	4533	3	0.42 (0.28, 0.61)	1.00x10
Other diseases					
Retinopathy	-	1126	12	1.39 (0.89, 2.16)	0.1453
Age-related macular degeneration	-	7473	13	1.19 (0.96, 1.48)	0.1206
Type 2 diabetes	-	10415	11	1.00 (0.84, 1.20)	0.9837
Endometriosis	-	4604	11	0.98 (0.75, 1.27)	0.8606
Chronic kidney disease	-	5807	13	0.94 (0.77, 1.16)	0.5859
Chronic obstructive pulmonary disease	-	2812	12	0.90 (0.64, 1.27)	0.5598
Asthma	-	13034	4	0.81 (0.64, 1.02)	0.0779
Type 1 diabetes	-	7514	6	0.71 (0.51, 0.98)	0.0378
Interstitial lung disease	-	1616	9	0.09 (0.05, 0.15)	2.02x10

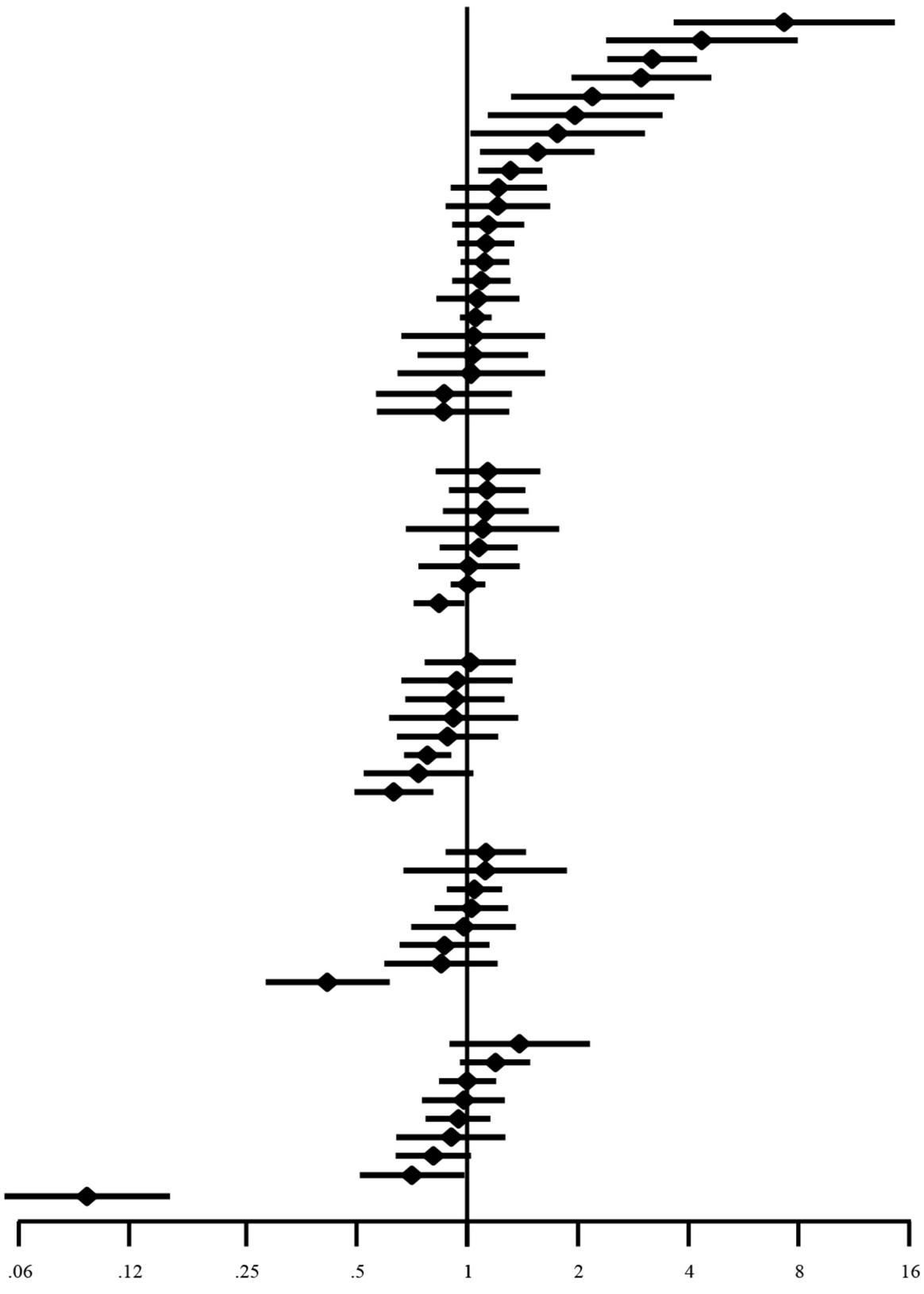

Figure 2. Association between genetically increased telomere length and odds of cancer as a function of selected characteristics

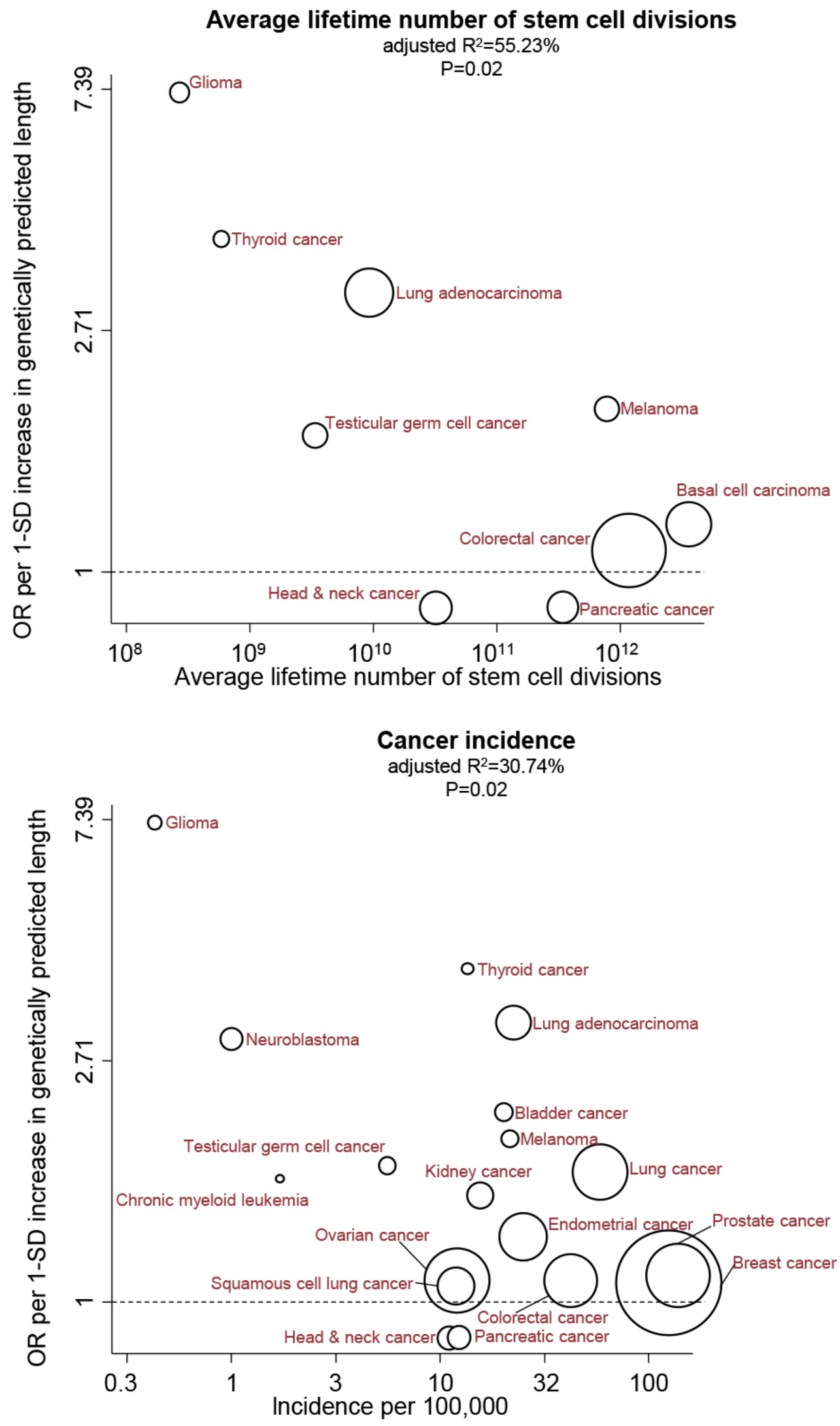

Figure 3. Comparison of genetic and prospective observational studies† of the association between telomere length and disease