

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

3

4 The Telomeres Mendelian Randomization Collaboration

5

6

7

8 Correspondence: Philip Haycock

9 MRC Integrative Epidemiology Unit

10 University of Bristol

11 Bristol

12 UK

13

14 philip.haycock@bristol.ac.uk

15 Tel: +44 1173 310 088

16 2995 words [word limit 3000]

17 3 figures, 2 tables, 132 references; 7 supplementary figures / 6 supplementary tables

18

19

20

21

22

23

24

25

26 **ABSTRACT 349 WORDS**

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

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

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

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

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

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

42 **Results** Summary data were available for 35 cancers and 48 non-neoplastic diseases,
43 corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median
44 6,789 per disease). Increased telomere length due to germline genetic variation was generally
45 associated with increased risk for site-specific cancers. The strongest associations were
46 observed for (ORs per 1-SD change in genetically increased telomere length): glioma 5.27
47 (3.15-8.81), serous low-malignant-potential ovarian cancer 4.35 (2.39-7.94), lung
48 adenocarcinoma 3.19 (2.40-4.22), neuroblastoma 2.98 (1.92-4.62), bladder cancer 2.19 (1.32-
49 3.66), melanoma 1.87 (1.55-2.26), testicular cancer 1.76 (1.02-3.04), kidney cancer 1.55

50 (1.08-2.23) and endometrial cancer 1.31 (1.07-1.61). Associations were stronger for rarer
51 cancers and at tissue sites with lower rates of stem cell division ($P < 0.05$). There was
52 generally little evidence of association between genetically increased telomere length and risk
53 of psychiatric, autoimmune, inflammatory, diabetic and other non-neoplastic diseases, except
54 for coronary heart disease (0.78 [0.67-0.90]), abdominal aortic aneurysm (0.63 [0.49-0.81]),
55 celiac disease (0.42 [0.28-0.61]) and interstitial lung disease (0.09 [0.05- 0.15]).

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

58

59

60

61

62

63

64

65

66

67

68

69

70

71 **INTRODUCTION**

72

73 At the ends of chromosomes, telomeres are DNA-protein structures that protect the genome
74 from damage, shorten progressively over time in most somatic tissues¹ and are proposed
75 physiological markers of ageing.^{2,3} Shorter leukocyte telomeres are correlated with older age,
76 male sex and other known risk factors for non-communicable diseases⁴⁻⁶ and are generally
77 associated with higher risk for cardiovascular diseases^{7,8}, type 2 diabetes⁹ and non-vascular
78 non-neoplastic causes of mortality.⁸ Whether these associations are causal, however, is
79 unknown. Telomere length has also been implicated in risk of cancer but the direction and
80 magnitude of the association is uncertain and contradictory across observational studies.¹⁰⁻¹⁴
81 The uncertainty reflects the considerable difficulty of designing observational studies of
82 telomere length and cancer incidence that are robust to reverse causation, confounding and
83 measurement error.

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

94

95 **METHODS**

96

97 *Study design*

98 The design of our study, illustrated in Figure S1, had three key components: 1) the
99 identification of genetic variants to serve as instruments for telomere length; 2) the
100 acquisition of summary data for the genetic instruments from genome wide association
101 studies (GWASs) of diseases and risk factors for non-communicable diseases; and 3) the
102 classification of diseases and risk factors into primary or secondary outcomes based on *a*
103 *priori* statistical power. As a first step, we searched the GWAS catalog^{15,16} on the 15 January
104 2015, to identify single nucleotide polymorphisms (SNPs) associated with telomere length.
105 To supplement the list with additional potential instruments, we also searched the original
106 study reports curated by the GWAS catalog (using a P-value threshold of 5×10^{-8}).¹⁷⁻²⁵ We
107 acquired summary data for all SNPs identified by our search from a meta-analysis of GWASs
108 of telomere length, involving 9,190 participants of European ancestry.¹⁸

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

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

119 as diseases with sufficient cases and controls for >50% statistical power and secondary
120 outcomes defined as diseases with <50% statistical power to detect odds ratios ≥ 2.0 per
121 standard deviation (SD) change in genetically increased telomere length (alpha assumed to be
122 0.01). All risk factors were defined as secondary outcomes. Risk factors with <50% statistical
123 power were excluded.

124

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

126

127 *Comparison with prospective observational studies*

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

137

138 *Statistical analysis*

139 We combined summary data across SNPs into a single instrument, using maximum
140 likelihood to estimate the slope of the relationship between β_{GD} and β_{GP} and a variance-
141 covariance matrix to make allowance for linkage disequilibrium between SNPs,²⁸ where β_{GD}
142 is the change in disease log odds or risk factor levels per copy of the effect allele and β_{GP} is
143 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: β_{GD}/β_{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 function³² and MR-Egger regression³⁰ (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 $P_{\text{Bonferroni}} \leq 0.05$).

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)

169 Program,³³ and tissue-specific rates of stem cell division from Tomasetti and Vogelstein.³⁴ As
170 the downloaded cancer characteristics from SEER correspond to the United States
171 population, 77% of which was of white ancestry in 2015³⁵, the meta-regression analyses
172 excluded genetic studies conducted in East Asian populations.

173

174 All analyses were performed in R version 3.1.2³⁶ and Stata release 13.1 (StataCorp, College
175 Station, TX). P-values were two-sided and evidence of association was declared at $P < 0.05$.
176 Where indicated, Bonferroni corrections were used to make allowance for multiple testing,
177 although this is likely to be overly conservative given the non-independence of many of the
178 outcomes tested.

179

180 **RESULTS**

181

182 We selected 16 SNPs as instruments for telomere length (Fig. S1 & Table 1). The selected
183 SNPs correspond to 10 independent genomic regions that collectively account for 2-3% of
184 the variance in leukocyte telomere length, which is equivalent to an F statistic of ~ 18 . This
185 indicates that the genetic instrument, constructed from these 10 independent genomic regions,
186 is strongly associated with telomere length (details in supplementary discussion).³⁷ Summary
187 data for the genetic instruments were available for 83 non-communicable diseases,
188 corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median
189 6,789 per disease), and 44 risk factors (Fig. S1, Table 2 and Table S1). The median number
190 of SNPs available across diseases was 11 (min=1, max=13) and across risk factors was 12
191 (min=11, max=13). Of the 83 diseases, 56 were classified as primary outcomes and 27 as
192 secondary outcomes (Table 2, Fig. S1 and Table S1). For 9 of the 83 non-communicable
193 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 ($P_{\text{Bonferroni}} < 0.05$). 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

219 disease (0.42 [0.28-0.61]), interstitial lung disease (0.09 [0.05-0.15]) and type 1 diabetes
220 (0.71 [0.51-0.98]) ($P < 0.05$) (Figure 1). The strongest evidence of association was observed
221 for coronary heart disease ($P_{\text{Bonferroni}} = 0.05$) and abdominal aortic aneurysm, celiac disease and
222 interstitial lung disease ($P_{\text{Bonferroni}} < 0.05$). The associations with coronary heart disease and
223 interstitial lung disease showed evidence for replication in independent datasets (Fig. S3).

224

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

229

230 In sensitivity analyses, we appraised the potential impact of confounding by pleiotropic
231 pathways on our results. Associations estimated by the weighted median and MR-Egger were
232 broadly similar to the main results for glioma, lung adenocarcinoma, serous LMP ovarian
233 cancer, neuroblastoma, abdominal aortic aneurysm, coronary heart disease and interstitial
234 lung disease (Fig. S4). In the second set of sensitivity analyses, implemented by MR-Egger
235 regression, we found little evidence for the presence of pleiotropy ($P_{\text{intercept}} \geq 0.27$) (Fig. S4).
236 The MR-Egger analyses were, however, generally underpowered, as reflected by the wide
237 confidence intervals in the estimated odds ratios.

238

239 In meta-regression analyses, we observed that genetically increased telomere length tended to
240 be more strongly associated with rarer cancers ($P = 0.02$) and cancers at tissue-sites with lower
241 rates of stem cell division ($P = 0.02$) (Figure 2). The associations showed little evidence of
242 varying by percentage survival five years after diagnosis or median age-at-diagnosis ($P \geq 37$).

243

244 **DISCUSSION**

245 In this report we show that genetically increased telomere length is associated with
246 increased risk of several cancers and with reduced risk of some non-neoplastic diseases.
247 Given the random distribution of genotypes in the general population with respect to
248 lifestyle and other environmental factors, as well as the fixed nature of germline
249 genotypes, these results should be less susceptible to confounding and reverse causation
250 in comparison to observational studies. Our results are therefore compatible with
251 causality. On the other hand, our results could reflect violations of Mendelian
252 randomization assumptions, such as confounding by pleiotropy, population stratification
253 or ancestry.³⁸ Although we cannot entirely rule out this possibility, the majority of our
254 results persisted in sensitivity analyses that made allowance for violations of Mendelian
255 randomization assumptions. Confounding by population stratification or ancestry is also
256 unlikely, given the adjustments made for ancestry in the disease GWASs (see
257 supplementary discussion).

258

259 *Comparison with previous studies*

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

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

279

280 *Mechanisms of association*

281 Our cancer findings are compatible with known biology.⁷⁰ By limiting the proliferative
282 potential of cells, telomere shortening may serve as a tumour suppressor; and individuals with
283 longer telomeres may be more likely to acquire somatic mutations owing to increased
284 proliferative potential.⁷⁰ Rates of cell division are, however, highly variable amongst tissues³⁴
285 and thus the relative gain in cell proliferative potential, conferred by having longer telomeres,
286 may also be highly variable across tissues. This could explain the ~6-fold variation in odds
287 ratios observed across cancer types in the present study, as well as the tendency of our results
288 to be stronger at tissue sites with lower rates of stem cell division. For example, the
289 association was strongest for glioma (OR=5.27) and comparatively weak for colorectal
290 cancer (OR=1.09) and the rates of stem cell division in the tissues giving rise to these cancers
291 differ by several orders of magnitude. In neural stem cells, which give rise to gliomas, the
292 number of divisions is ~270 million and for colorectal stem cells is ~1.2 trillion over the
293 average lifetime of an individual.³⁴ The observation that genetically increased telomere

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

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

302

303 *Study limitations*

304 Our study is subject to some limitations, in addition to the Mendelian randomization
305 assumptions already considered above. First, our method assumes that the magnitude of the
306 association between SNPs and telomere length is consistent across tissues. Second, our study
307 assumed a linear shape of association between telomere length and disease risk, whereas the
308 shape could be “J” or “U” shaped.^{44,57,68} Third, our results assume that the samples used to
309 define the genetic instrument for telomere length¹⁸ and the various samples used to estimate
310 the SNP-disease associations are representative of the same general population, practically
311 defined as being of similar ethnicity, age and sex distribution.⁷³ This assumption would, for
312 example, not apply in the case of the SNP-disease associations derived from East Asian or
313 pediatric populations. Generally speaking, violation of the aforementioned assumptions could
314 bias the magnitude of the association between genetically increased telomere length and
315 disease; but would be unlikely to increase the likelihood of false positives (i.e. incorrectly
316 inferring an association when none exists).⁷⁴ Our results should therefore remain informative
317 for the direction and broad magnitude of the average association at the population level, even

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

323

324 *Clinical relevance of findings*

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

334

335 *Conclusion*

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

341

342 The Telomeres Mendelian Randomization Collaboration

343

344 Philip Haycock¹; Stephen Burgess²; Aayah Nounu¹; Jie Zheng¹; George N Okoli³; Jack
345 Bowden^{1,4}; Kaitlin Wade¹; Nicholas Timpson¹; David M. Evans^{1,5}; Peter Willeit^{2,6}; Abraham
346 Aviv⁷; Tom R. Gaunt¹; Gibran Hemani¹; Massimo Mangino^{8,9}; Hayley Patricia Ellis¹⁰;
347 Kathreena Mary Kurian¹⁰; Karen Pooley¹¹ on behalf of the BCAC and OCAC consortia;
348 Rosalind Eeles¹² on behalf of the PRACTICAL consortium; Jeffrey E Lee¹³; Shenying
349 Fang¹³; Wei Chen¹³; Matthew H Law¹⁴, Lisa M Bowdler¹⁵ and Mark M Iles¹⁶ on behalf of the
350 Melanoma meta-analysis consortium; Qiong Yang¹⁷, Bradford B. Worrall¹⁸ and Hugh
351 Stephen Markus¹⁹ on behalf of the METASTROKE project of the ISGC; Rayjean J. Hung^{20,21}
352 and Chris I Amos²² on behalf of the ILCCO consortium; Amanda Spurdle²³, Deborah J
353 Thompson²⁴ and Tracy O'Mara²³ on behalf of the ECAC consortium; Brian Wolpin²⁵, Laufey
354 Amundadottir²⁶ and Rachael Stolzenberg-Solomon²⁷ on behalf of the PanScan consortium;
355 Antonia Trichopoulou^{29,30}, Charlotte Onland-Moret³¹, Eiliv Lund³², Eric J Duell³³, Federico
356 Canzian³⁴, Gianluca Severi^{35,36,37,38}, Kim Overvad³⁹, Marc J Gunter⁴⁰, Rosario Tumino⁴¹ and
357 Ulrika Svenson⁴² on behalf of EPIC; Andre van Rij⁴³, Annette F Baas⁴⁴, Matthew J Bown⁴⁵,
358 Nilesh J Samani⁴⁵, Paul IW de Bakker⁴⁴, Femke NG van t'Hof⁴⁴, Gerard Tromp^{46,47}, Gregory
359 T Jones⁴³, Helena Kuivaniemi^{46,47} and James R Elmore⁴⁸ on behalf of the Aneurysm
360 Consortium; Mattias Johansson⁴⁹; James Mckay⁴⁹; Ghislaine Scelo⁴⁹; Robert Carreras-
361 Torres⁴⁹; Valerie Gaborieau⁴⁹; Paul Brennan⁴⁹; Paige M. Bracci⁵⁰, Rachel E Neale¹⁵, Sara H
362 Olson⁵¹, Steven Gallinger²⁰, Donghui Li⁵², Gloria M. Petersen⁵⁴, Harvey Risch⁵⁵, and Alison
363 P. Klein⁵⁶ on behalf of PanC⁴; Jiali Han^{57,58}; Christian C. Abnet⁵⁹; Neal D. Freedman⁵⁹; Philip
364 R. Taylor⁵⁹; John M Maris⁶⁰; Katja K Aben^{61,62}; Lambertus A Kiemeny⁶¹; Sita H
365 Vermeulen⁶¹; John K Wiencke^{63,64}; Kyle M Walsh^{63,64}; Margaret Wrensch^{63,64}; Terri Rice⁶³;
366 Clare Turnbull⁶⁵; Kevin Litchfield⁶⁶; Lavinia Paternoster¹ and Marie Standl⁶⁷ on behalf of the
367 EAGLE consortium; Gonçalo R Abecasis⁶⁸; John Paul SanGiovanni⁶⁹; Lars G Fritsche⁶⁸;
368 Yong Li⁷⁰ and Vladan Mijatovic⁷¹ on behalf of the CKDGen consortium; Yadav Sapkota¹⁵;
369 Siew-Kee Low⁷²; Krina T Zondervan^{73,74}; Grant W Montgomery¹⁵; Dale R. Nyholt^{75,15};
370 David A van Heel⁷⁶; Karen Hunt⁷⁶; Dan E. Arking⁷⁷, Foram N. Ashar⁷⁷ and Nona
371 Sotoodehnia⁷⁸ on behalf of the CHARGE-Sudden Cardiac Arrest Working Group; Daniel
372 Woo⁷⁹; Jonathan Rosand⁸⁰; Mary Comeau⁸¹; W. Mark Brown⁸²; Edwin K. Silverman⁸³, John
373 E Hokanson⁸⁴ and Michael Cho⁸³ on behalf of COPDGene; Jennie Hui^{85,86,87,88}, Manuel
374 Ferreira¹⁵ and Philip J. Thompson⁸⁹ on behalf of the AAGC consortium; Alanna C.

375 Morrison⁹⁰, Janine F Felix⁹¹ and Nicholas L Smith⁹² on behalf of the CHARGE-Heart Failure
376 Working Group; Angela M Christiano⁹³; Lynn Petukhova⁹⁴; Regina C. Betz⁹⁵; Xing Fan⁹⁶;
377 Xuejun Zhang⁹⁶; Caihong Zhu⁹⁶; Carl Langefeld⁹⁷; Susan D. Thompson⁹⁸; Feijie Wang⁹⁹; Xu
378 Lin^{99,100}; David A. Schwartz¹⁰¹; Tasha Fingerlin¹⁰²; Jerome I. Rotter^{103,104}, Mary Frances
379 Cotch¹⁰⁵ and Richard A Jensen on behalf of the CHARGE-Eye Working Group^{106,107};
380 Matthias Munz¹⁰⁸, Henrik Dommisch¹⁰⁸ and Arne S Schaefer¹⁰⁸ on behalf of the European
381 Periodontitis Genetics Group; Fang Han¹⁰⁹; Hanna M Ollila¹¹⁰; Ryan P. Hillary¹¹⁰; Omar
382 Albagha¹¹¹; Stuart H. Ralston¹¹²; Chenjie Zeng¹¹³; Wei Zheng¹¹³; Xiao-Ou Shu¹¹³; Andre
383 Reis¹¹⁴; Steffen Uebe¹¹⁴; Ulrike Hüffmeier¹¹⁴; Yoshiya Kawamura¹¹⁵, Takeshi Otowa^{116,117}
384 and Tsukasa Sasaki¹¹⁸ on behalf of the Japanese Collaboration Team for GWAS of Panic
385 Disorder; Martin Lloyd Hibberd¹¹⁹; Michael Levin¹²⁰; Sonia Davila¹²¹; Gang Xie^{122,20};
386 Katherine Siminovitch^{122,20}; Jin-Xin Bei¹²³; Yi-Xin Zeng^{123,124}; Asta Försti^{125,126}; Bowang
387 Chen¹²⁵; Stefano Landi¹²⁷; Andre Franke¹²⁸; Annegret Fischer^{128,129}; David Ellinghaus¹²⁸;
388 Carlos Flores^{130,131}; Imre Noth¹³²; Shwu-Fan Ma¹³²; Jia Nee Foo¹³³; Jianjun Liu¹³³; Jong-Won
389 Kim¹³⁴; David G. Cox¹³⁵; Olivier Delattre¹³⁶; Olivier Mirabeau¹³⁶; Christine F. Skibola¹³⁷;
390 Clara S. Tang¹³⁸; Merce Garcia-Barcelo¹³⁸; Kai-Ping Chang¹³⁹; Wen-Hui Su¹⁴⁰; Yu-Sun
391 Chang¹⁴¹; Nicholas G Martin¹⁵; Scott Gordon¹⁵; Tracey Wade¹⁴²; Chaeyoung Lee¹⁴³;
392 Michiaki Kubo¹⁴⁴; Pei-Chieng Cha¹⁴⁵; Yusuke Nakamura¹⁴⁶; Daniel Levy¹⁴⁷; Masayuki
393 Kimura⁷; Shih-Jen Hwang¹⁴⁷; Steven Hunt¹⁴⁸; Tim Spector⁸; Nicole Soranzo¹⁴⁹; Ani W
394 Manichaikul¹⁵⁰; R Graham Barr¹⁵¹; Bratati Kahali¹⁵², Elizabeth Speliotes¹⁵² and Laura M
395 Yerges-Armstrong¹⁵³ on behalf of the GOLD Consortium; Ching-Yu Cheng^{154,155,156}, Jost B.
396 Jonas^{157,158} and Tien Yin Wong^{154,155,156} on behalf of the SEED consortium; Isabella Fogh¹⁵⁹;
397 Kuang Lin¹⁵⁹ and John F. Powell¹⁵⁹ on behalf of the SLAGEN and ALSGEN consortia;
398 Kenneth Rice¹⁶⁰ on behalf of the ICBP; Caroline Relton¹; Richard M Martin^{1,3,161}; George
399 Davey Smith¹

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,
6 Australia
7 Department of Neurology, Innsbruck Medical University, Austria
8 Center of Human Development and Aging, Department of Pediatrics, New Jersey Medical School,
9 Rutgers, The State University of New Jersey
10 Department of Twin Research and Genetic Epidemiology, King's College London, London UK
11 NIHR Biomedical Research Centre at Guy's and St. Thomas' Foundation Trust, London, UK
12 Brain Tumour Research Group, Institute of Clinical Neuroscience, Learning and Research Building,
13 Southmead Hospital, University of Bristol
14 Strangeways Research Laboratory, University of Cambridge, Cambridge, UK
15 The Institute of Cancer Research, London, UK
16 Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston,
17 TX.
18 Statistical Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia
19 QIMR Berghofer Medical Research Institute, Brisbane, Australia
20 Section of Epidemiology and Biostatistics, Leeds Institute of Cancer and Pathology, University of
21 Leeds, Leeds, UK
22 Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United
23 States of America and the Framingham Heart Study, Framingham, Massachusetts, United States of
24 America
25 Departments of Neurology and Public Health Sciences University of Virginia Charlottesville, Virginia
26 22908
27 Department of Clinical Neurosciences, University of Cambridge, UK
28 Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
29 Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, 60 Murray St.
30 Rm L5-215, Box 18, Toronto, ON M5T 3L9, Canada
31 Geisel School of Medicine, Dartmouth College
32 Genetics and Computational Biology Division, QIMR Berghofer Medical Research Institute, Brisbane,
33 QLD 4006, Australia
34 Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of
35 Cambridge, Cambridge, CB1 8RN, UK.
36 Dana-Farber Cancer Institute
37 Laboratory of Translational Genomics, Division of Cancer Epidemiology & Genetics, National Cancer
38 Institute
39 Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS.
40
41 Hellenic Health Foundation, Athens, Greece
42 WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in
43 Public Health, Dept. of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical
44 School, Greece
45 Dept of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center
46 Utrecht
47 Institute of community medicine, UiT The Arctic University of Norway
48 Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Bellvitge Biomedical Research
49 Institute (IDIBELL), Catalan Institute of Oncology (ICO), Avda Gran Via 199-203, 08908 L'Hospitalet
50 de Llobregat, Barcelona, Spain
51 Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany
52 Université Paris-Saclay, Université Paris-Sud, UVSQ, CESP, INSERM, Villejuif, France
53 Gustave Roussy, F-94805, Villejuif, France
54 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 Medicine, 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 Kusunokichou, 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 Dept of Biostatistics, University of Washington, Seattle, USA
161 University of Bristol / University Hospitals Bristol NHS Foundation Trust National Institute for Health Research Bristol Nutrition Biomedical Research Unit, Bristol, UK

400

401 Affiliations of the Telomeres Mendelian Randomization Collaboration

402

403 **Acknowledgements**

404 This work was supported by CRUK grant number C18281/A19169 (the Integrative Cancer

405 Epidemiology Programme). Dr Haycock is supported by CRUK Population Research

406 Postdoctoral Fellowship C52724/A20138. The MRC Integrative Epidemiology Unit is

407 supported by grants MC_UU_12013/1 and MC_UU_12013/2. Dr Martin is supported by the

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

410

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

433 database of immunologically related human diseases), **IMSGC** (International Multiple
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 Amyotrophic 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 Gummy, 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	<i>ACYP2</i>	A	C	0.16	0.065	0.012	0.000606	0.313	6	9177	8.00E-10	0.080	Codd ²¹
rs6772228	3	58390292	<i>PXK</i>	T	A	0.87	0.041	0.014	0.049721	0.77	6	8630	3.91E-10	0.200	Pooley ¹⁷
rs12696304	3	169763483	<i>TERC</i>	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	<i>TERC</i>	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	<i>TERC</i>	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	<i>TERC</i>	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	<i>NAF1</i>	G	A	0.80	0.048	0.012	0.008912	0.077	6	9161	4.35E-16	0.190	Codd ²¹
rs2736100	5	1286401	<i>TERT</i>	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	<i>OBFC1</i>	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	<i>OBFC1</i>	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	<i>OBFC1</i>	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	<i>CTC1</i>	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	<i>ZNF208</i>	G	A	0.25	0.064	0.011	0.000169	0.412	6	9096	1.11E-09	0.090	Codd ²¹
rs412658	19	22176638	<i>ZNF676</i>	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	<i>DHX35</i>	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	<i>ZBTB46</i>	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 al¹⁸; 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 Mangino¹⁸ and Gu²⁰ 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}
<i>Estrogen receptor -ve</i>	7465	42175	13	1.00	EUR	BCAC ^{17,77}
<i>Estrogen receptor +ve</i>	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	Wrenschr 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
<i>Adenocarcinoma</i>	3442	14894	13	1.00	EUR	ILCCO ⁸⁵
<i>Squamous cell carcinoma</i>	3275	15038	13	1.00	EUR	ILCCO ⁸⁵
Skin cancer						
<i>Melanoma</i>	12814	23203	13	1.00	EUR	MC ⁸⁶
<i>Basal cell carcinoma</i>	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}
<i>Clear cell</i>	1016	30816	13	0.76	EUR	OCAC ^{17,89}
<i>Endometrioid</i>	2154	30816	13	0.98	EUR	OCAC ^{17,89}
<i>Mucinous</i>	1643	30816	13	0.94	EUR	OCAC ^{17,89}
<i>Serous invasive</i>	9608	30816	13	1.00	EUR	OCAC ^{17,89}
<i>Serous LMP</i>	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						
<i>Crohn's disease</i>	5956	14927	11	1.00	EUR	IIBDGC ⁹⁸
<i>Ulcerative colitis</i>	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}
<i>large vessel disease</i>	2167	62004	13	0.99	EUR	METASTROKE/ISGC ^{112,113}
<i>small vessel disease</i>	1894	62004	13	0.97	EUR	METASTROKE/ISGC ¹¹²
<i>cardioembolic</i>	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 ^{114,115}
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

454 **REFERENCES**

- 455 1. Blackburn EH, Epel ES, Lin J. Human telomere biology: A contributory and
456 interactive factor in aging, disease risks, and protection. *Science* (80-)
457 2015;350(6265):1193–8.
- 458 2. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of
459 aging. *Cell* 2013;153(6):1194–217.
- 460 3. Samani NJ, van der Harst P. Biological ageing and cardiovascular disease. *Heart*
461 2008;94(5):537–9.
- 462 4. Weischer M, Bojesen SE, Nordestgaard BG. Telomere shortening unrelated to
463 smoking, body weight, physical activity, and alcohol intake: 4,576 general population
464 individuals with repeat measurements 10 years apart. *PLoS Genet*
465 2014;10(3):e1004191.
- 466 5. Houben MJM, Moonen HJJ, van Schooten FJ, Hageman GJ. Telomere length
467 assessment: biomarker of chronic oxidative stress? *Free Radic Biol Med*
468 2008;44(3):235–46.
- 469 6. Marchesi V. Risk factors: Short telomeres: association with cancer survival and risk.
470 *Nat Rev Clin Oncol* 2013;10(5):247.
- 471 7. Haycock PC, Heydon EE, Kaptoge S, Butterworth a. S, Thompson A, Willeit P.
472 Leucocyte telomere length and risk of cardiovascular disease: systematic review and
473 meta-analysis. *BMJ* 2014;349(jul08 3):g4227–g4227.
- 474 8. Rode L, Nordestgaard BG, Bojesen SE. Peripheral blood leukocyte telomere length
475 and mortality among 64,637 individuals from the general population. *J Natl Cancer*
476 *Inst* 2015;107(6):dju074.
- 477 9. Zhao J, Miao K, Wang H, Ding H, Wang DW. Association between telomere length
478 and type 2 diabetes mellitus: a meta-analysis. *PLoS One* 2013;8(11):e79993.
- 479 10. Weischer M, Nordestgaard BG, Cawthon RM, Freiberg JJ, Tybjaerg-Hansen A,
480 Bojesen SE. Short telomere length, cancer survival, and cancer risk in 47102
481 individuals. *J Natl Cancer Inst* 2013;105(7):459–68.
- 482 11. Ma H, Zhou Z, Wei S, et al. Shortened telomere length is associated with increased
483 risk of cancer: a meta-analysis. *PLoS One* 2011;6(6):e20466.
- 484 12. Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA. The association of telomere
485 length and cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*
486 2011;20(6):1238–50.
- 487 13. Pooley KA, Sandhu MS, Tyrer J, et al. Telomere length in prospective and
488 retrospective cancer case-control studies. *Cancer Res* 2010;70(8):3170–6.
- 489 14. Hou L, Joyce BT, Gao T, et al. Blood Telomere Length Attrition and Cancer
490 Development in the Normative Aging Study Cohort. *EBioMedicine* 2015;2(6):591–6.
- 491 15. Welter D, MacArthur J, Morales J, et al. The NHGRI GWAS Catalog, a curated
492 resource of SNP-trait associations. *Nucleic Acids Res* 2014;42(Database
493 issue):D1001–6.

- 494 16. Burdett T, Hall P, Hastings E, et al. The NHGRI-EBI Catalog of published genome-
495 wide association studies [Internet]. [cited 2015 Jan 15];Available from:
496 www.ebi.ac.uk/gwas
- 497 17. Pooley KA, Bojesen SE, Weischer M, et al. A genome-wide association scan (GWAS)
498 for mean telomere length within the COGS project: identified loci show little
499 association with hormone-related cancer risk. *Hum Mol Genet* 2013;22(24):5056–64.
- 500 18. Mangino M, Hwang S-J, Spector TD, et al. Genome-wide meta-analysis points to
501 CTC1 and ZNF676 as genes regulating telomere homeostasis in humans. *Hum Mol*
502 *Genet* 2012;21(24):5385–94.
- 503 19. Prescott J, Kraft P, Chasman DI, et al. Genome-wide association study of relative
504 telomere length. *PLoS One* 2011;6(5):e19635.
- 505 20. Gu J, Chen M, Shete S, et al. A genome-wide association study identifies a locus on
506 chromosome 14q21 as a predictor of leukocyte telomere length and as a marker of
507 susceptibility for bladder cancer. *Cancer Prev Res (Phila)* 2011;4(4):514–21.
- 508 21. Codd V, Nelson CP, Albrecht E, et al. Identification of seven loci affecting mean
509 telomere length and their association with disease. *Nat Genet* 2013;45(4):422–7.
- 510 22. Codd V, Mangino M, van der Harst P, et al. Common variants near TERC are
511 associated with mean telomere length. *Nat Genet* 2010;42(3):197–9.
- 512 23. Liu Y, Cao L, Li Z, et al. A genome-wide association study identifies a locus on TERT
513 for mean telomere length in Han Chinese. *PLoS One* 2014;9(1):e85043.
- 514 24. Saxena R, Bjonnes A, Prescott J, et al. Genome-wide association study identifies
515 variants in casein kinase II (CSNK2A2) to be associated with leukocyte telomere
516 length in a Punjabi Sikh diabetic cohort. *Circ Cardiovasc Genet* 2014;7(3):287–95.
- 517 25. Levy D, Neuhausen SL, Hunt SC, et al. Genome-wide association identifies OBFC1 as
518 a locus involved in human leukocyte telomere biology. *Proc Natl Acad Sci U S A*
519 2010;107(20):9293–8.
- 520 26. Hindorff LA LA, MacArthur J, Morales J, et al. A catalog of published genome-wide
521 association studies [Internet]. [cited 2015 Jan 15];Available from:
522 www.genome.gov/gwastudies
- 523 27. Chene G, Thompson SG. Methods for Summarizing the Risk Associations of
524 Quantitative Variables in Epidemiologic Studies in a Consistent Form. *Am J*
525 *Epidemiol* 1996;144(6):610–21.
- 526 28. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG, EPIC-InterAct
527 Consortium. Using published data in Mendelian randomization: a blueprint for
528 efficient identification of causal risk factors. *Eur J Epidemiol* 2015;30(7):543–52.
- 529 29. Thomas DC, Lawlor DA, Thompson JR. Re: Estimation of bias in nongenetic
530 observational studies using “Mendelian triangulation” by Bautista et al. *Ann*
531 *Epidemiol* 2007;17(7):511–3.
- 532 30. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid
533 instruments: effect estimation and bias detection through Egger regression. *Int J*
534 *Epidemiol* 2015;44(2):512–25.

- 535 31. VanderWeele TJ, Tchetgen Tchetgen EJ, Cornelis M, Kraft P. Methodological
536 challenges in mendelian randomization. *Epidemiology* 2014;25(3):427–35.
- 537 32. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in
538 Mendelian randomization with some invalid instruments using a weighted median
539 estimator. *Genet Epidemiol*
- 540 33. National Cancer Institute. Surveillance, Epidemiology, and End Results Program
541 [Internet]. [cited 2015 Aug 1]; Available from: www.seer.cancer.gov
- 542 34. Tomasetti C, Vogelstein B. Variation in cancer risk among tissues can be explained by
543 the number of stem cell divisions. *Science* 2015;347(6217):78–81.
- 544 35. U.S. Census Bureau [Internet]. [cited 2016 Jul 11]; Available from: U.S. Census
545 Bureau
- 546 36. R Core Team. A language and environment for statistical computing. 2013;
- 547 37. Burgess S, Thompson SG. Bias in causal estimates from Mendelian randomization
548 studies with weak instruments. *Stat Med* 2011;30(11):1312–23.
- 549 38. Davey Smith G, Ebrahim S. What can mendelian randomisation tell us about
550 modifiable behavioural and environmental exposures? *BMJ Br Med J*
551 2005;330(7499):1076–9.
- 552 39. Anic GM, Sondak VK, Messina JL, et al. Telomere length and risk of melanoma,
553 squamous cell carcinoma, and basal cell carcinoma. *Cancer Epidemiol*
554 2013;37(4):434–9.
- 555 40. Pellatt AJ, Wolff RK, Torres-Mejia G, et al. Telomere length, telomere-related genes,
556 and breast cancer risk: the breast cancer health disparities study. *Genes Chromosomes*
557 *Cancer* 2013;52(7):595–609.
- 558 41. Caini S, Raimondi S, Johansson H, et al. Telomere length and the risk of cutaneous
559 melanoma and non-melanoma skin cancer: a review of the literature and meta-analysis.
560 *J Dermatol Sci* 2015;80(3):168–74.
- 561 42. Sanchez-Espiridon B, Chen M, Chang JY, et al. Telomere length in peripheral blood
562 leukocytes and lung cancer risk: a large case-control study in Caucasians. *Cancer Res*
563 2014;74(9):2476–86.
- 564 43. Campa D, Mergarten B, De Vivo I, et al. Leukocyte telomere length in relation to
565 pancreatic cancer risk: a prospective study. *Cancer Epidemiol Biomarkers Prev*
566 2014;23(11):2447–54.
- 567 44. Cui Y, Cai Q, Qu S, et al. Association of leukocyte telomere length with colorectal
568 cancer risk: nested case-control findings from the Shanghai Women’s Health Study.
569 *Cancer Epidemiol Biomarkers Prev* 2012;21(10):1807–13.
- 570 45. De Vivo I, Prescott J, Wong JYY, Kraft P, Hankinson SE, Hunter DJ. A prospective
571 study of relative telomere length and postmenopausal breast cancer risk. *Cancer*
572 *Epidemiol Biomarkers Prev* 2009;18(4):1152–6.
- 573 46. Han J, Qureshi AA, Prescott J, et al. A prospective study of telomere length and the
574 risk of skin cancer. *J Invest Dermatol* 2009;129(2):415–21.
- 575 47. Hofmann JN, Lan Q, Cawthon R, et al. A prospective study of leukocyte telomere

- 576 length and risk of renal cell carcinoma. *Cancer Epidemiol Biomarkers Prev*
577 2013;22(5):997–1000.
- 578 48. Julin B, Shui I, Heaphy CM, et al. Circulating leukocyte telomere length and risk of
579 overall and aggressive prostate cancer. *Br J Cancer* 2015;112(4):769–76.
- 580 49. Kim S, Sandler DP, Carswell G, et al. Telomere length in peripheral blood and breast
581 cancer risk in a prospective case-cohort analysis: results from the Sister Study. *Cancer*
582 *Causes Control* 2011;22(7):1061–6.
- 583 50. Lan Q, Cawthon R, Shen M, et al. A prospective study of telomere length measured by
584 monochrome multiplex quantitative PCR and risk of non-Hodgkin lymphoma. *Clin*
585 *Cancer Res* 2009;15(23):7429–33.
- 586 51. Lee I-M, Lin J, Castonguay AJ, Barton NS, Buring JE, Zee RYL. Mean leukocyte
587 telomere length and risk of incident colorectal carcinoma in women: a prospective,
588 nested case-control study. *Clin Chem Lab Med* 2010;48(2):259–62.
- 589 52. Liang G, Qureshi AA, Guo Q, De Vivo I, Han J. No association between telomere
590 length in peripheral blood leukocytes and the risk of nonmelanoma skin cancer. *Cancer*
591 *Epidemiol Biomarkers Prev* 2011;20(5):1043–5.
- 592 53. Lynch SM, Major JM, Cawthon R, et al. A prospective analysis of telomere length and
593 pancreatic cancer in the alpha-tocopherol beta-carotene cancer (ATBC) prevention
594 study. *Int J Cancer* 2013;133(11):2672–80.
- 595 54. McGrath M, Wong JYY, Michaud D, Hunter DJ, De Vivo I. Telomere length,
596 cigarette smoking, and bladder cancer risk in men and women. *Cancer Epidemiol*
597 *Biomarkers Prev* 2007;16(4):815–9.
- 598 55. Nan H, Du M, De Vivo I, et al. Shorter telomeres associate with a reduced risk of
599 melanoma development. *Cancer Res* 2011;71(21):6758–63.
- 600 56. Prescott J, McGrath M, Lee I-M, Buring JE, De Vivo I. Telomere length and genetic
601 analyses in population-based studies of endometrial cancer risk. *Cancer*
602 2010;116(18):4275–82.
- 603 57. Qu S, Wen W, Shu X-O, et al. Association of leukocyte telomere length with breast
604 cancer risk: nested case-control findings from the Shanghai Women’s Health Study.
605 *Am J Epidemiol* 2013;177(7):617–24.
- 606 58. Risques RA, Vaughan TL, Li X, et al. Leukocyte telomere length predicts cancer risk
607 in Barrett’s esophagus. *Cancer Epidemiol Biomarkers Prev* 2007;16(12):2649–55.
- 608 59. Seow WJ, Cawthon RM, Purdue MP, et al. Telomere length in white blood cell DNA
609 and lung cancer: a pooled analysis of three prospective cohorts. *Cancer Res*
610 2014;74(15):4090–8.
- 611 60. Shen M, Cawthon R, Rothman N, et al. A prospective study of telomere length
612 measured by monochrome multiplex quantitative PCR and risk of lung cancer. *Lung*
613 *Cancer* 2011;73(2):133–7.
- 614 61. Walcott F, Rajaraman P, Gadalla SM, et al. Telomere length and risk of glioma.
615 *Cancer Epidemiol* 2013;37(6):935–8.
- 616 62. Zee RYL, Castonguay AJ, Barton NS, Buring JE. Mean telomere length and risk of

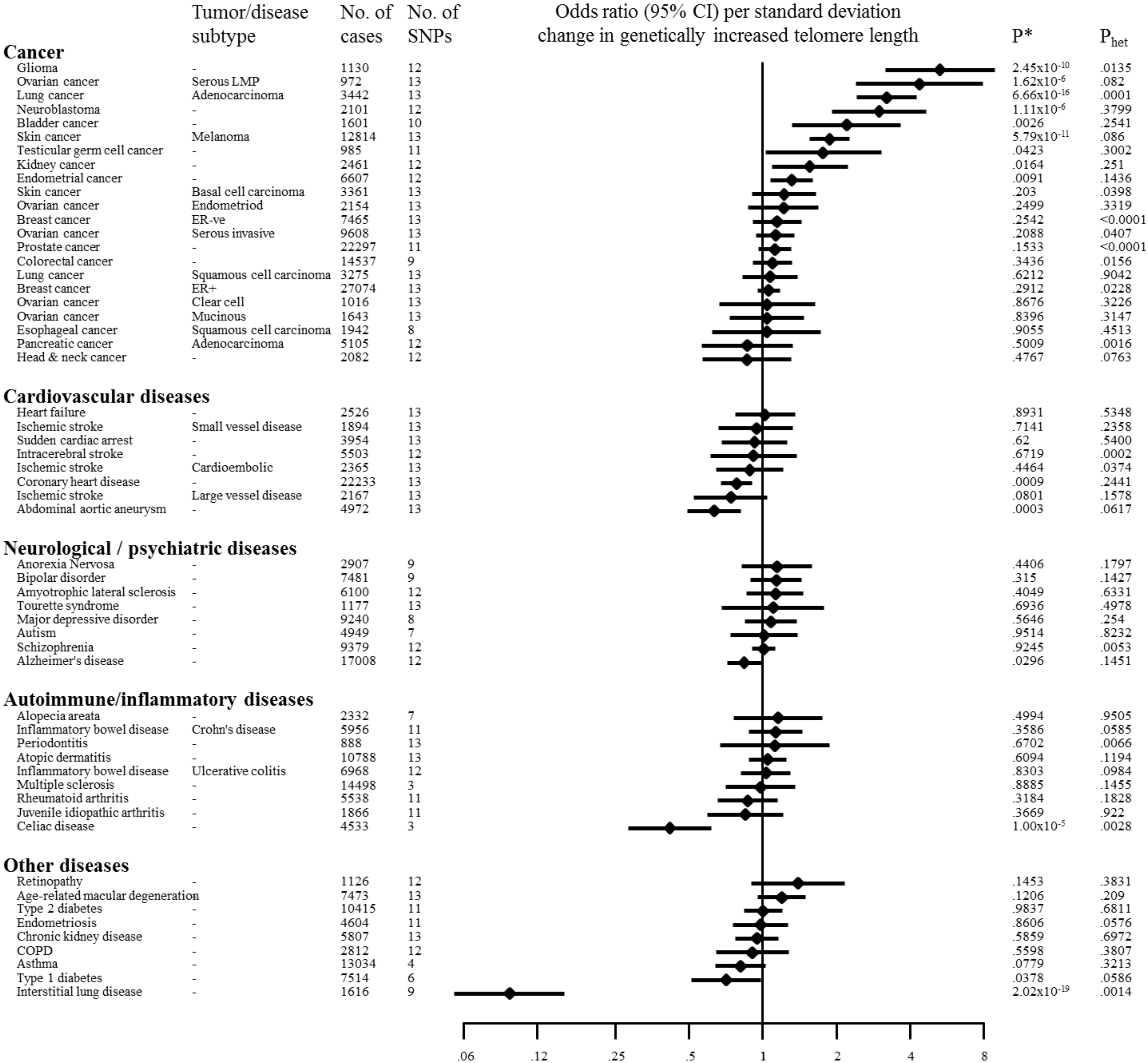
- 617 incident colorectal carcinoma: a prospective, nested case-control approach. *Cancer*
618 *Epidemiol Biomarkers Prev* 2009;18(8):2280–2.
- 619 63. Willeit P, Willeit J, Mayr A, et al. Telomere length and risk of incident cancer and
620 cancer mortality. *Jama* 2010;304(1538–3598 (Electronic)):69–75.
- 621 64. Zhang C, Doherty J a., Burgess S, et al. Genetic determinants of telomere length and
622 risk of common cancers: a Mendelian randomization study. *Hum Mol Genet*
623 2015;24(18):5356–66.
- 624 65. Iles MM, Bishop DT, Taylor JC, et al. The effect on melanoma risk of genes
625 previously associated with telomere length. *J Natl Cancer Inst* 2014;106(10).
- 626 66. Walsh KM, Codd V, Rice T, et al. Longer genotypically-estimated leukocyte telomere
627 length is associated with increased adult glioma risk. *Oncotarget* 2015;6(40):42468–
628 77.
- 629 67. Ojha J, Codd V, Nelson CP, et al. Genetic Variation Associated with Longer Telomere
630 Length Increases Risk of Chronic Lymphocytic Leukemia. *Cancer Epidemiol*
631 *Biomarkers Prev* 2016;25(7):1043–9.
- 632 68. Armanios M, Blackburn EH. The telomere syndromes. *Nat Rev Genet*
633 2012;13(10):693–704.
- 634 69. Armanios M. Syndromes of telomere shortening. *Annu Rev Genomics Hum Genet*
635 2009;10(46):45–61.
- 636 70. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*
637 2011;144(5):646–74.
- 638 71. Blasco MA. Telomere length, stem cells and aging. *Nat Chem Biol* 2007;3(10):640–9.
- 639 72. Stone RC, Horvath K, Kark JD, Susser E, Tishkoff SA, Aviv A. Telomere Length and
640 the Cancer-Atherosclerosis Trade-Off. *PLoS Genet* 2016;12(7):e1006144.
- 641 73. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies:
642 subsample and 2-sample instrumental variable estimators. *Am J Epidemiol*
643 2013;178(7):1177–84.
- 644 74. Burgess S, Butterworth AS, Thompson JR. Beyond Mendelian randomization: how to
645 interpret evidence of shared genetic predictors. *J Clin Epidemiol* 2015;1–9.
- 646 75. Centers for Disease Control and Prevention [Internet]. [cited 2016 Jul 14];Available
647 from: <http://www.cdc.gov/nchs/fastats/deaths.htm>
- 648 76. Rafnar T, Sulem P, Thorleifsson G, et al. Genome-wide association study yields
649 variants at 20p12.2 that associate with urinary bladder cancer. *Hum Mol Genet*
650 2014;23(20):5545–57.
- 651 77. Michailidou K, Hall P, Gonzalez-Neira A, et al. Large-scale genotyping identifies 41
652 new loci associated with breast cancer risk. *Nat Genet* 2013;45(4):353–61, 361–2.
- 653 78. Schumacher FR, Schmit SL, Jiao S, et al. Genome-wide association study of colorectal
654 cancer identifies six new susceptibility loci. *Nat Commun* 2015;6:7138.
- 655 79. Spurdle AB, Thompson DJ, Ahmed S, et al. Genome-wide association study identifies
656 a common variant associated with risk of endometrial cancer. *Nat Genet*

- 657 2011;43(5):451–4.
- 658 80. Painter JN, O’Mara TA, Batra J, et al. Fine-mapping of the HNF1B multicancer locus
659 identifies candidate variants that mediate endometrial cancer risk. *Hum Mol Genet*
660 2015;24(5):1478–92.
- 661 81. Abnet CC, Freedman ND, Hu N, et al. A shared susceptibility locus in PLCE1 at
662 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. *Nat*
663 *Genet* 2010;42(9):764–7.
- 664 82. Wrensch M, Jenkins RB, Chang JS, et al. Variants in the CDKN2B and RTEL1
665 regions are associated with high-grade glioma susceptibility. *Nat Genet*
666 2009;41(8):905–8.
- 667 83. McKay JD, Truong T, Gaborieau V, et al. A genome-wide association study of upper
668 aerodigestive tract cancers conducted within the INHANCE consortium. *PLoS Genet*
669 2011;7(3):e1001333.
- 670 84. Purdue MP, Johansson M, Zelenika D, et al. Genome-wide association study of renal
671 cell carcinoma identifies two susceptibility loci on 2p21 and 11q13.3. *Nat Genet*
672 2010;43(1):60–5.
- 673 85. Wang Y, McKay JD, Rafnar T, et al. Rare variants of large effect in BRCA2 and
674 CHEK2 affect risk of lung cancer. *Nat Genet* 2014;46(7).
- 675 86. Law MH, Bishop DT, Lee JE, et al. Genome-wide meta-analysis identifies five new
676 susceptibility loci for cutaneous malignant melanoma. *Nat Genet* 2015;47(9):987–95.
- 677 87. Zhang M, Song F, Liang L, et al. Genome-wide association studies identify several
678 new loci associated with pigmentation traits and skin cancer risk in European
679 Americans. *Hum Mol Genet* 2013;22(14):2948–59.
- 680 88. Diskin SJ, Capasso M, Schnepf RW, et al. Common variation at 6q16 within HACE1
681 and LIN28B influences susceptibility to neuroblastoma. *Nat Genet* 2012;44(10):1126–
682 30.
- 683 89. Pharoah PDP, Tsai Y-Y, Ramus SJ, et al. GWAS meta-analysis and replication
684 identifies three new susceptibility loci for ovarian cancer. *Nat Genet* 2013;45(4):362–
685 70, 370-2.
- 686 90. Wolpin BM, Rizzato C, Kraft P, et al. Genome-wide association study identifies
687 multiple susceptibility loci for pancreatic cancer. *Nat Genet* 2014;46(9):994–1000.
- 688 91. Eeles RA, Olama AA Al, Benlloch S, et al. Identification of 23 new prostate cancer
689 susceptibility loci using the iCOGS custom genotyping array. *Nat Genet*
690 2013;45(4):385–91, 391-2.
- 691 92. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals
692 identifies 23 new susceptibility loci for prostate cancer. *Nat Genet* 2014;46(10):1103–
693 9.
- 694 93. Turnbull C, Rapley E a, Seal S, et al. Variants near DMRT1, TERT and ATF7IP are
695 associated with testicular germ cell cancer. *Nat Genet* 2010;42(7):604–7.
- 696 94. Rapley EA, Turnbull C, Al Olama AA, et al. A genome-wide association study of
697 testicular germ cell tumor. *Nat Genet* 2009;41(7):807–10.

- 698 95. Betz RC, Petukhova L, Ripke S, et al. Genome-wide meta-analysis in alopecia areata
699 resolves HLA associations and reveals two new susceptibility loci. *Nat Commun*
700 2015;6:5966.
- 701 96. EARly Genetics and Lifecourse Epidemiology (EAGLE) Eczema Consortium,
702 Australian Asthma Genetics Consortium(AAGC), Australian Asthma Genetics
703 Consortium AAGC. Multi-ancestry genome-wide association study of 21,000 cases
704 and 95,000 controls identifies new risk loci for atopic dermatitis. *Nat Genet*
705 2015;47(12):1449–56.
- 706 97. Dubois PC a, Trynka G, Franke L, et al. Multiple common variants for celiac disease
707 influencing immune gene expression. *Nat Genet* 2010;42(4):295–302.
- 708 98. Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38
709 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk
710 across populations. *Nat Genet* 2015;47(9):979–86.
- 711 99. Thompson SD, Marion MC, Sudman M, et al. Genome-wide association analysis of
712 juvenile idiopathic arthritis identifies a new susceptibility locus at chromosomal region
713 3q13. *Arthritis Rheum* 2012;64(8):2781–91.
- 714 100. Beecham AH, Patsopoulos NA, Xifara DK, et al. Analysis of immune-related loci
715 identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet*
716 2013;45(11):1353–60.
- 717 101. Schaefer AS, Richter GM, Nothnagel M, et al. A genome-wide association study
718 identifies *GLT6D1* as a susceptibility locus for periodontitis. *Hum Mol Genet*
719 2010;19(3):553–62.
- 720 102. Stahl EA, Raychaudhuri S, Remmers EF, et al. Genome-wide association study meta-
721 analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet* 2010;42(6):508–
722 14.
- 723 103. Bown MJ, Jones GT, Harrison SC, et al. Abdominal aortic aneurysm is associated with
724 a variant in low-density lipoprotein receptor-related protein 1. *Am J Hum Genet*
725 2011;89(5):619–27.
- 726 104. Gretarsdottir S, Baas AF, Thorleifsson G, et al. Genome-wide association study
727 identifies a sequence variant within the *DAB2IP* gene conferring susceptibility to
728 abdominal aortic aneurysm. *Nat Genet* 2010;42(8):692–7.
- 729 105. Jones GT, Bown MJ, Gretarsdottir S, et al. A sequence variant associated with sortilin-
730 1 (*SORT1*) on 1p13.3 is independently associated with abdominal aortic aneurysm.
731 *Hum Mol Genet* 2013;22(14):2941–7.
- 732 106. Harrison SC, Smith AJP, Jones GT, et al. Interleukin-6 receptor pathways in
733 abdominal aortic aneurysm. *Eur Heart J* 2013;34(48):3707–16.
- 734 107. Elmore JR, Obmann MA, Kuivaniemi H, et al. Identification of a genetic variant
735 associated with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide
736 association. *J Vasc Surg* 2009;49(6):1525–31.
- 737 108. Borthwick K, Smelser D, Bock J, et al. Ephenotyping for Abdominal Aortic Aneurysm
738 in the Electronic Medical Records and Genomics (eMERGE) Network: Algorithm
739 Development and Konstanz Information Miner Workflow. *Int J Biomed Data Min*
740 2015;4(1).

- 741 109. Schunkert H, König IR, Kathiresan S, et al. Large-scale association analysis identifies
742 13 new susceptibility loci for coronary artery disease. *Nat Genet* 2011;43(4):333–8.
- 743 110. Smith NL, Felix JF, Morrison AC, et al. Association of genome-wide variation with
744 the risk of incident heart failure in adults of European and African ancestry: a
745 prospective meta-analysis from the cohorts for heart and aging research in genomic
746 epidemiology (CHARGE) consortium. *Circ Cardiovasc Genet* 2010;3(3):256–66.
- 747 111. Woo D, Falcone GJ, Devan WJ, et al. Meta-analysis of genome-wide association
748 studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J*
749 *Hum Genet* 2014;94(4):511–21.
- 750 112. Malik R, Freilinger T, Winsvold BS, et al. Shared genetic basis for migraine and
751 ischemic stroke: A genome-wide analysis of common variants. *Neurology*
752 2015;84(21):2132–45.
- 753 113. Traylor M, Farrall M, Holliday EG, et al. Genetic risk factors for ischaemic stroke and
754 its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide
755 association studies. *Lancet Neurol* 2012;11(11):951–62.
- 756 114. Barrett JC, Clayton DG, Concannon P, et al. Genome-wide association study and
757 meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet*
758 2009;41(6):703–7.
- 759 115. Burren OS, Adlem EC, Achuthan P, Christensen M, Coulson RMR, Todd JA.
760 T1DBase: update 2011, organization and presentation of large-scale data sets for type
761 1 diabetes research. *Nucleic Acids Res* 2011;39(Database):D997–1001.
- 762 116. Morris ADPDP, Voight BFB, Teslovich TMT, et al. Large-scale association analysis
763 provides insights into the genetic architecture and pathophysiology of type 2 diabetes.
764 *Nat Genet* 2012;44(9):981–90.
- 765 117. Fritsche LG, Chen W, Schu M, et al. Seven new loci associated with age-related
766 macular degeneration. *Nat Genet* 2013;45(4):433–9, 439–2.
- 767 118. Jensen RA, Sim X, Li X, et al. Genome-wide association study of retinopathy in
768 individuals without diabetes. *PLoS One* 2013;8(2):e54232.
- 769 119. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3
770 expression contribute to the risk of childhood asthma. *Nature* 2007;448(7152):470–3.
- 771 120. Ferreira MAR, Matheson MC, Duffy DL, et al. Identification of IL6R and
772 chromosome 11q13.5 as risk loci for asthma. *Lancet (London, England)*
773 2011;378(9795):1006–14.
- 774 121. Cho MH, McDonald M-LN, Zhou X, et al. Risk loci for chronic obstructive pulmonary
775 disease: a genome-wide association study and meta-analysis. *Lancet Respir Med*
776 2014;2(3):214–25.
- 777 122. Fingerlin TE, Murphy E, Zhang W, et al. Genome-wide association study identifies
778 multiple susceptibility loci for pulmonary fibrosis. *Nat Genet* 2013;45(6):613–20.
- 779 123. Fogh I, Ratti A, Gellera C, et al. A genome-wide association meta-analysis identifies a
780 novel locus at 17q11.2 associated with sporadic amyotrophic lateral sclerosis. *Hum*
781 *Mol Genet* 2014;23(8):2220–31.

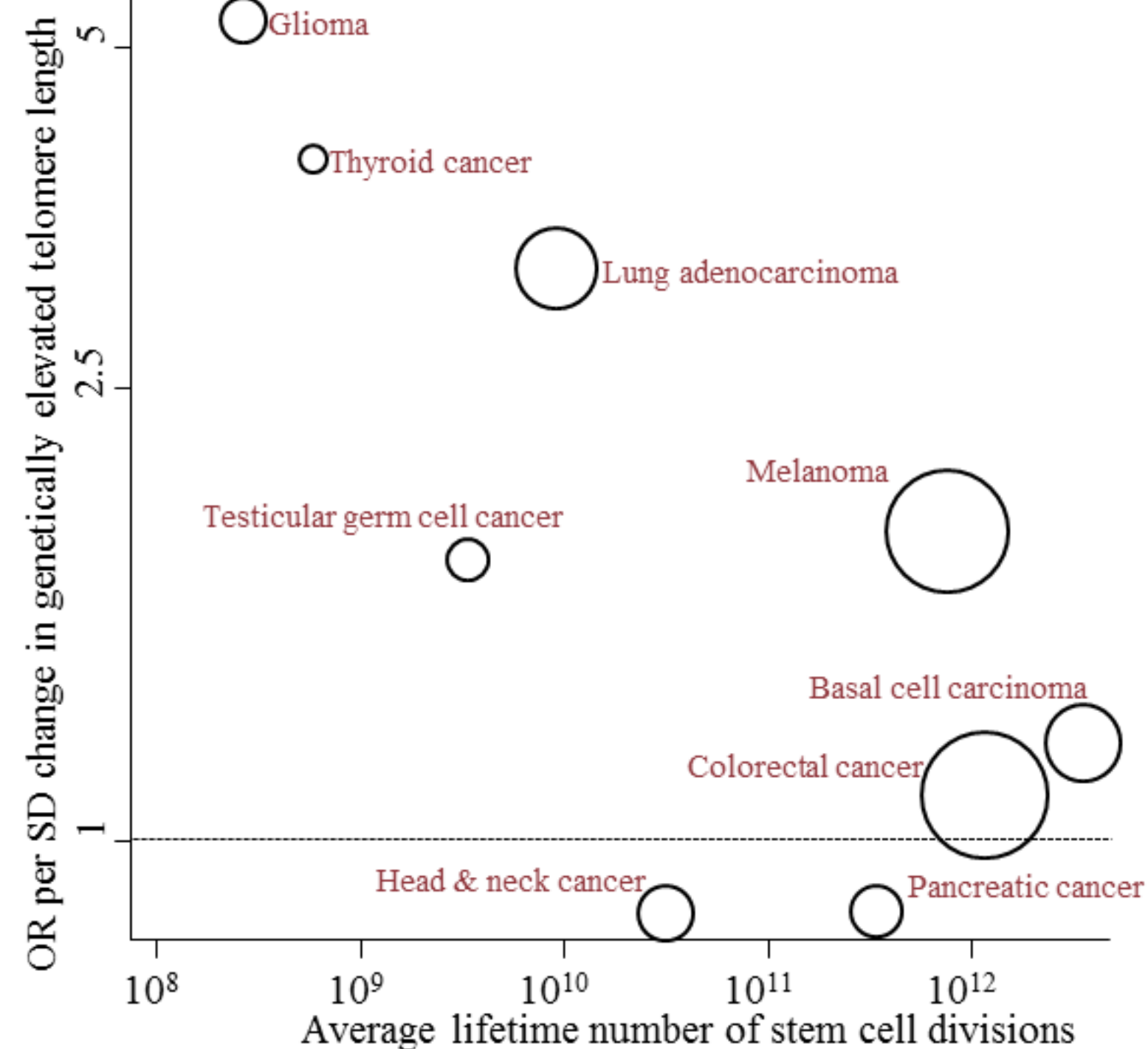
- 782 124. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals
783 identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*
784 2013;45(12):1452–8.
- 785 125. Boraska V, Franklin CS, Floyd JAB, et al. A genome-wide association study of
786 anorexia nervosa. *Mol Psychiatry* 2014;19(10):1085–94.
- 787 126. Smoller JW, Hospital MG. Identification of risk loci with shared effects on five major
788 psychiatric disorders: a genome-wide analysis. *Lancet* 2013;381(9875):1371–9.
- 789 127. Sklar P, Ripke S, Scott LJ, et al. Large-scale genome-wide association analysis of
790 bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet*
791 2011;43(10):977–83.
- 792 128. Ripke S, Wray NR, Lewis CM, et al. A mega-analysis of genome-wide association
793 studies for major depressive disorder. *Mol Psychiatry* 2013;18(4):497–511.
- 794 129. Ripke S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-
795 associated genetic loci. *Nature* 2014;511(7510):421–7.
- 796 130. Scharf JM, Yu D, Mathews CA, et al. Genome-wide association study of Tourette's
797 syndrome. *Mol Psychiatry* 2013;18(6):721–8.
- 798 131. Köttgen A, Pattaro C, Böger C a, et al. New loci associated with kidney function and
799 chronic kidney disease. *Nat Genet* 2010;42(5):376–84.
- 800 132. Nyholt DR, Low S-K, Anderson CA, et al. Genome-wide association meta-analysis
801 identifies new endometriosis risk loci. *Nat Genet* 2012;44(12):1355–9.
- 802



Average lifetime number of stem cell divisions

Adjusted R²=52.63%

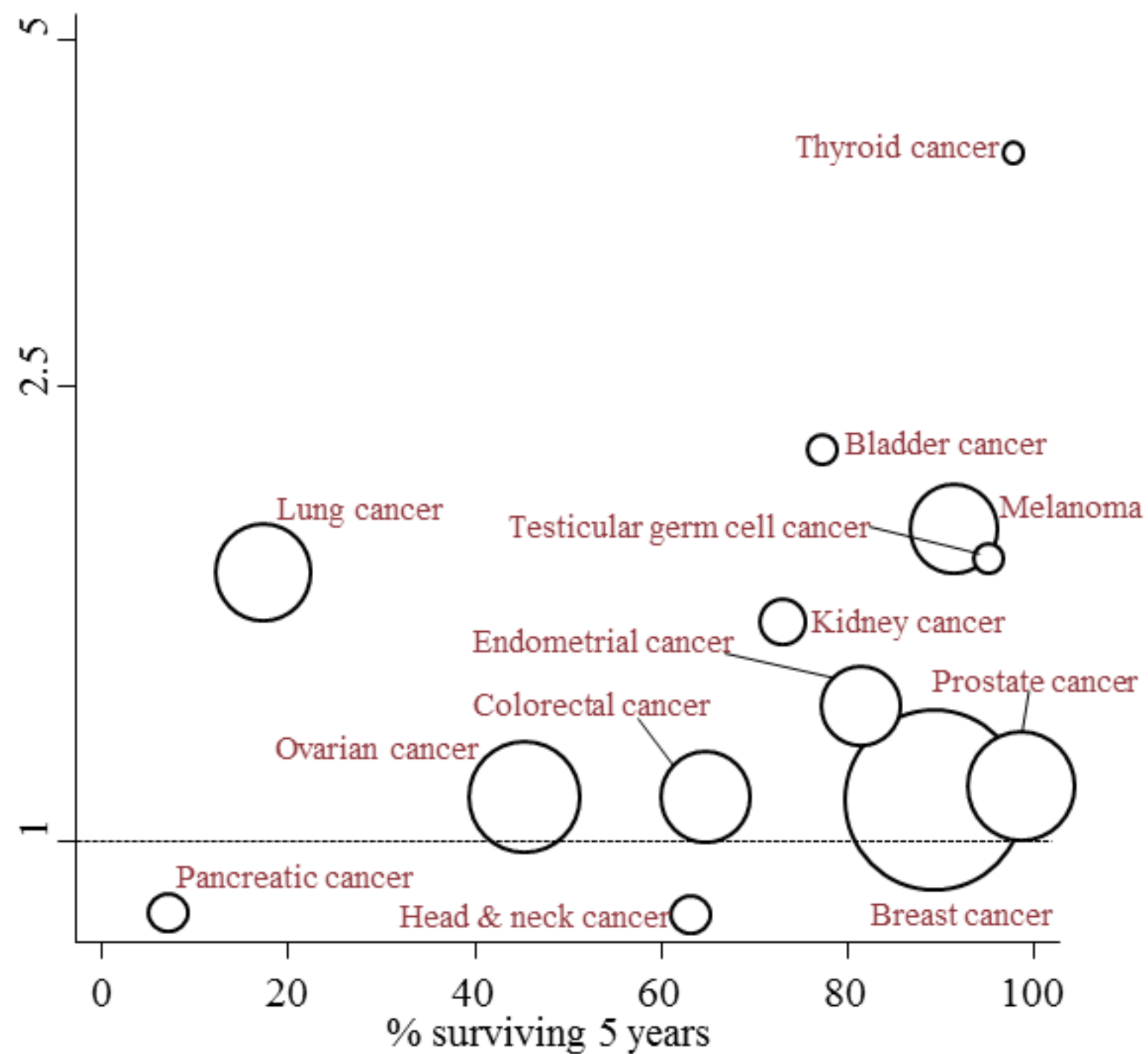
P=0.02



% surviving 5 years

Adjusted R²=-19.49%

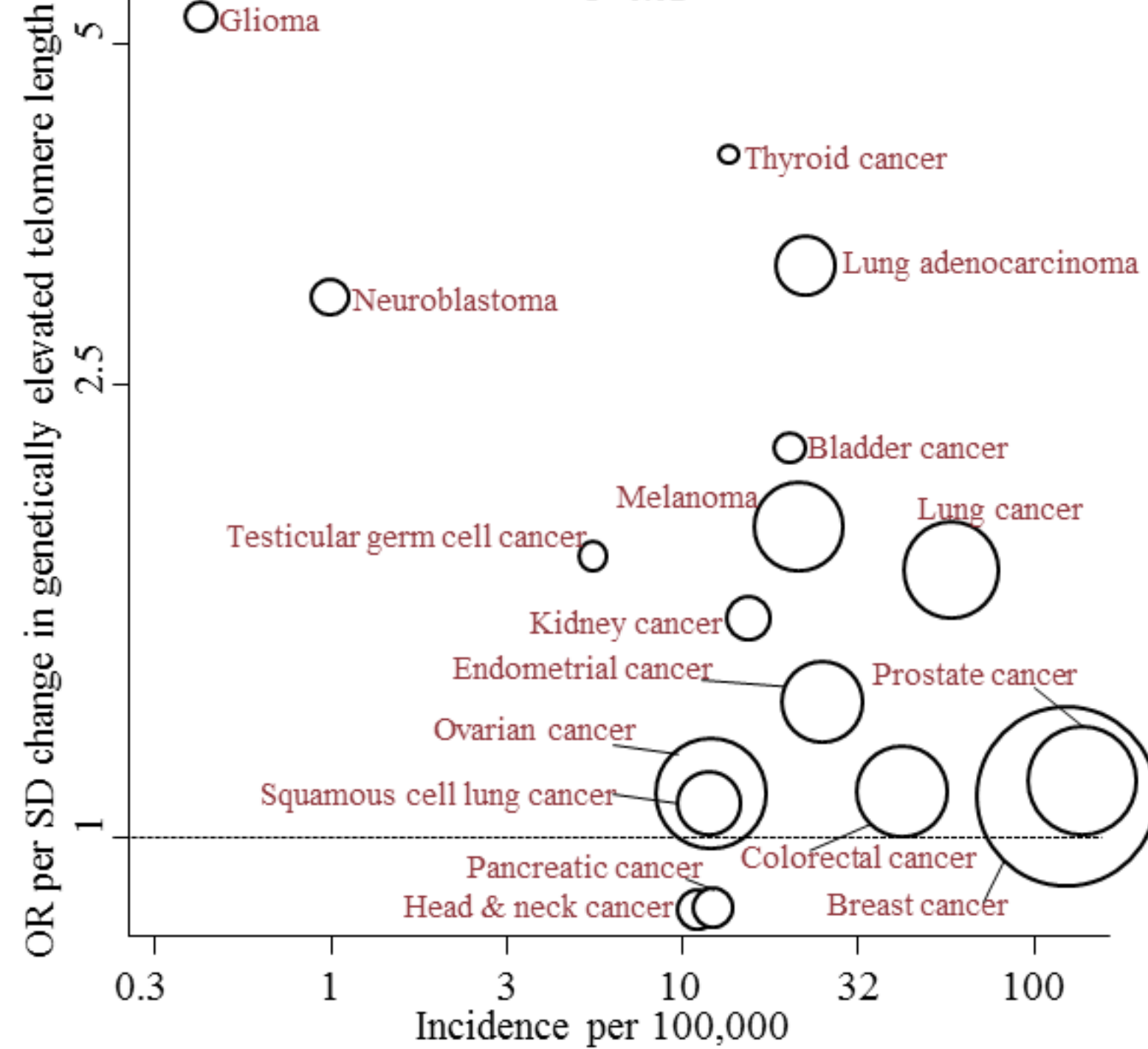
P=0.37



Cancer incidence

Adjusted R²=32.12%

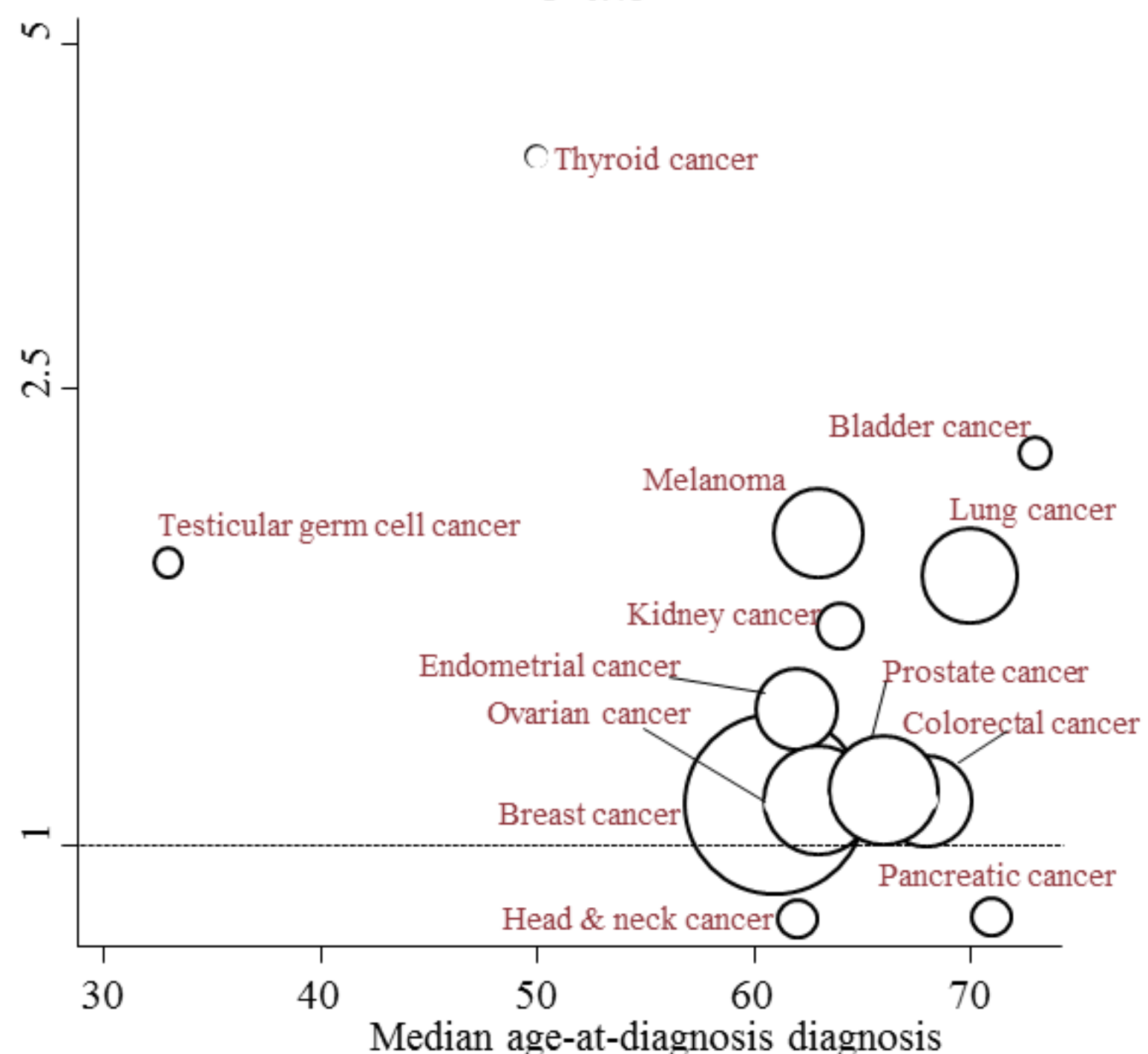
P=0.02

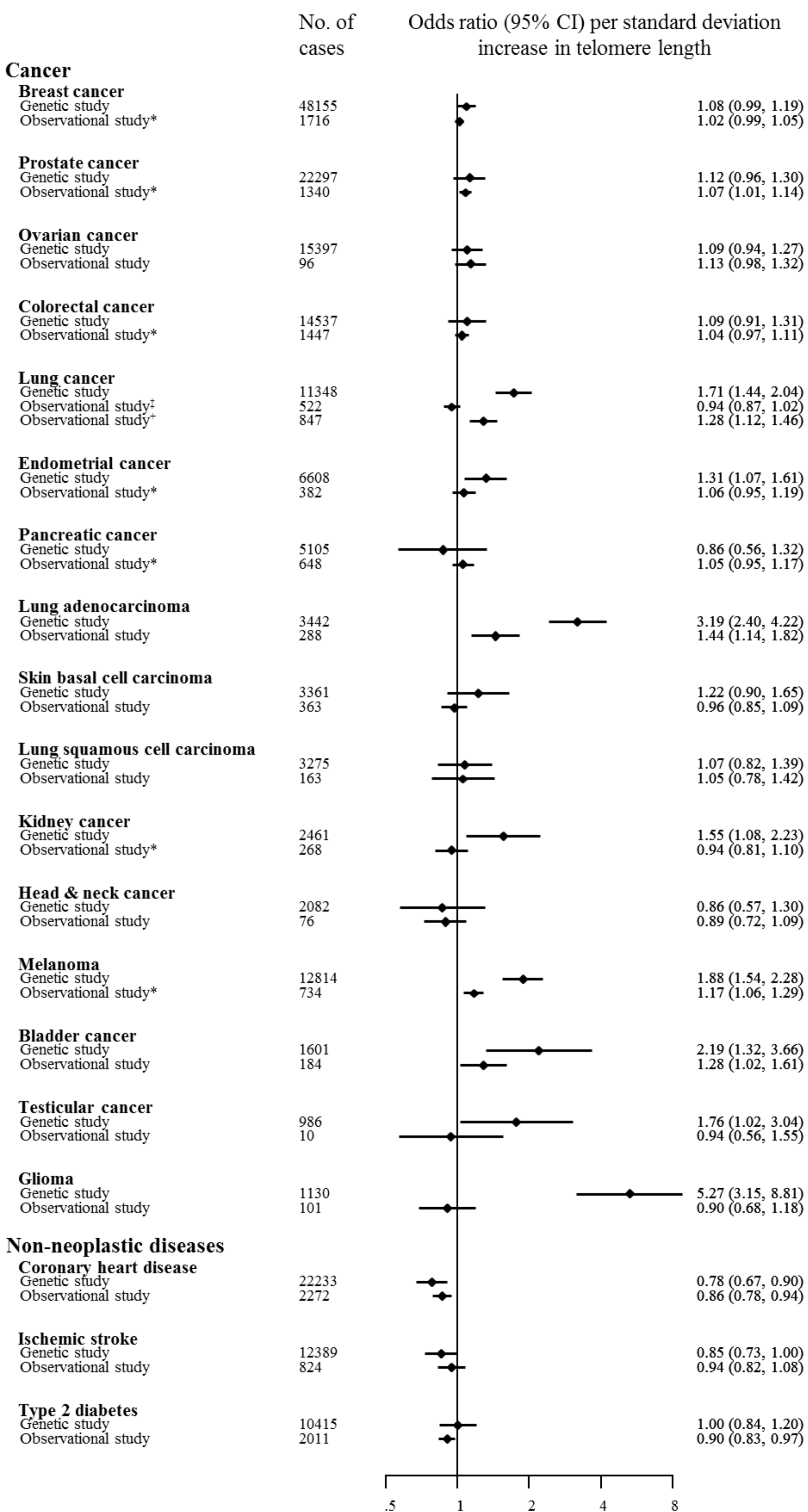


Median age-at-diagnosis diagnosis

Adjusted R²=-8.86%

P=0.41





1 **Supplementary material**

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

4

5 The Telomeres Mendelian Randomization Collaboration

6

7 Correspondence: Philip Haycock

8 MRC Integrative Epidemiology Unit

9 University of Bristol

10 Bristol

11 UK

12

13 philip.haycock@bristol.ac.uk

14 Tel: +44 1173 310 088

15

16

17

18

19 7 supplementary figures / 6 supplementary tables

20

21

22

23

24

25

26

27

28	Contents	
29	SUPPLEMENTARY METHODS	4
30	Additional details on the design strategy.....	4
31	<i>Identification of genetic instruments for telomere length</i>	4
32	<i>Acquisition of summary data from disease and risk factor studies</i>	5
33	<i>Power calculations</i>	5
34	Estimating the association between genetically increased telomere length and outcome traits.....	6
35	<i>Likelihood approach</i>	7
36	<i>The weighted median approach</i> ¹⁴	8
37	<i>The MR-Egger approach</i>	8
38	SUPPLEMENTARY RESULTS	9
39	SUPPLEMENTARY DISCUSSION	10
40	Mechanisms of association between SNPs and telomere length.....	10
41	Bias from sample overlap and strength of the association between SNPs and telomere length.....	10
42	Misconceptions about Mendelian randomization.....	10
43	Potential for confounding by population stratification, ancestry and age.....	11
44	Associations with non-neoplastic diseases.....	12
45	Supplementary Table S1. Study characteristics for secondary non-communicable diseases and diseases	
46	from independent studies for replication analyses.....	13
47	Supplementary Table S2. Study characteristics of 44 risk factors for non-communicable diseases.....	14
48	Supplementary Table S3. Selected prospective observational studies of the association between leukocyte	
49	telomere length and disease.....	16
50	Supplementary Table S4. PubMed search strategy for prospective observational studies of association	
51	between telomere length* and disease.....	19
52	Supplementary Table S6. Glossary of terms.....	20
53	Supplementary Figure S1. Study design.....	21
54	Supplementary Figure S3. Replication of association between genetically increased telomere length and	
55	odds of non-communicable diseases in independent datasets.....	23
56	Supplementary Figure S4. Sensitivity analyses of association between genetically increased telomere	
57	length and odds of non-communicable diseases.....	24
58	Supplementary Figure S5. Association between genetically increased telomere length and risk factors for	
59	non-communicable diseases.....	25
60	Supplementary Figure S6. Association between genetically increased telomere length and smoking.....	26
61	Supplementary Figure S7. Causal diagram illustrating the assumptions of Mendelian randomization.....	27
62	ACKNOWLEDGEMENTS OF THE CONTRIBUTING STUDIES AND CONSORTIA	28
63	Amyotrophic lateral sclerosis GWAS consortium.....	28
64	The Aneurysm Consortium.....	29
65	Australian Asthma Genetics Consortium.....	32

66	Coronary ARtery Disease Genome wide Replication and Meta-analysis (CARDIoGRAM) consortium and	
67	The Coronary Artery Disease (C4D) Genetics consortium.....	33
68	The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) – Heart Failure	
69	Working Group.....	34
70	CHARGE - Sudden Cardiac Arrest Working Group.....	34
71	The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene).....	35
72	Early Growth Genetics (EGG) Consortium.....	38
73	The EARly Genetics and Lifecourse Epidemiology (EAGLE) consortium	38
74	Endometrial Cancer Association Consortium (ECAC)	47
75	Glioma GWAS	49
76	Endometriosis GWA meta-analysis.....	50
77	European Periodontitis Genetics Group (EPG).....	52
78	The International Genomics of Alzheimer's Project (IGAP).....	55
79	The Japanese Collaboration Team for GWAS of Panic Disorder	56
80	Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC).....	57
81	Melanoma meta-analysis consortium (MC)	57
82	The Multi-Ethnic Study of Atherosclerosis (MESA)	69
83	The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS)	70
84	GWAS of non-alcoholic fatty liver disease (hepatic steatosis)	70
85	Pancreatic cancer case-control consortium (PanC4)	70
86	Pancreatic Cancer Cohort Consortium (PanScan).....	71
87	The European Prospective Investigation into Cancer and Nutrition (EPIC) study	71
88	The PRACTICAL Consortium.....	72
89	Sarcoidosis GWAS.....	75
90	The Singapore Epidemiology of Eye Diseases Study (SEED).....	75
91	Acknowledgements of studies that contributed to the GWAS meta-analysis of telomere length ⁴	76
92	<i>The Framingham Heart Study</i>	76
93	<i>TwinsUK</i>	76
94	References	77
95		

96

97 **SUPPLEMENTARY METHODS**

98

99 **Additional details on the design strategy**

100

101 *Identification of genetic instruments for telomere length*

102 To identify genetic variants to serve as instruments for telomere length, we searched the genome-
103 wide association study (GWAS) catalog^{1,2} on the 15 January 2015, to identify reported single
104 nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with
105 additional potential instruments, we also searched the original study reports curated by the GWAS
106 catalog.³⁻¹¹ We included all ‘telomere length’ SNPs in the GWAS catalog as potential proxies,
107 regardless of their reported P-value, but used a P-value threshold of $<5 \times 10^{-8}$ (the conventional
108 threshold for declaring association in GWAS) for SNPs identified from original study reports (if
109 these were not already curated by the GWAS catalog). We acquired summary data for all SNPs
110 identified by the above strategy from a meta-analysis of six GWASs of leukocyte telomere length,
111 conducted in 9,190 participants of European ancestry.⁴ Telomere length in the six studies was
112 measured by Southern blotting. GWAS analyses in the 6 studies were adjusted for age, sex, body
113 mass index and smoking history. The genomic control inflation factor (λ_{GC}) ranged from 0.995 to
114 1.076 across the six studies, indicating little evidence for confounding by population stratification.⁴
115 The following summary data were acquired for each SNP from each of the six studies: the
116 regression coefficient (beta) and its standard error, where the beta reflects the change in telomere
117 length (in base pair units) per copy of the effect allele; the effect allele; the non-effect allele; and
118 effect allele frequency. We combined the effect estimates from the six separate studies by fixed
119 effects meta-analysis. We then excluded SNPs if they lacked strong evidence of association with
120 telomere length. We defined strong evidence of association as a P value $<5 \times 10^{-8}$ in: i) the discovery
121 stage of at least one published GWAS of telomere length³⁻¹⁰ or ii) a meta-analysis of summary data

122 from Mangino et al⁴ and other GWASs of telomere length,^{3,5-10} with any overlapping studies
123 excluded from Mangino et al.⁴ We also excluded SNPs with a minor allele frequency <0.05 or
124 showing strong evidence of between-study heterogeneity in associations with telomere length
125 ($P \leq 0.001$).

126

127 *Acquisition of summary data from disease and risk factor studies*

128 We extracted the following summary data for each genetic instrument for telomere length from
129 GWASs of diseases and risk factors: the regression coefficient (beta) and its standard error, the
130 effect allele, the non-effect allele and effect allele frequency. For binary traits, the beta
131 corresponded to the log odds ratio per copy of the effect allele. For quantitative traits, the beta
132 corresponded to the unit change in the trait per copy of the effect allele. We harmonized the
133 summary data for diseases and risk factors so that the effect allele reflected the allele associated
134 with longer telomeres. When SNPs were palindromic, i.e. A/T or G/C, we used information on
135 allele frequency to resolve strand ambiguity. We also requested the following metrics of SNP
136 genotype quality: P-values for Hardy-Weinberg equilibrium (HWE), imputation quality scores and
137 P-values for between-study heterogeneity. We also estimated the percentage overlap in participants
138 amongst the telomere length and disease and risk factor GWASs. When reported, statistics on
139 between-study heterogeneity, Hardy-Weinberg equilibrium and imputation quality were used to
140 exclude low quality SNPs from disease and risk factor studies, using the following criteria: strong
141 evidence of between-study heterogeneity in the SNP-phenotype association ($P \leq 0.001$), Hardy-
142 Weinberg disequilibrium ($P \leq 0.001$) or imputation quality metric (info or r^2) ≤ 0.90 .

143

144 *Power calculations*

145 Power calculations for disease outcomes were implemented using the method described by
146 Burgess¹² and assumed an odds ratio of ≥ 2.0 per standard deviation higher telomere length and an
147 alpha of 0.01. Power calculations for risk factors for non-communicable diseases were similar,

148 except that a ≥ 0.5 standard deviation change in quantitative risk factors and an odds ratio of ≥ 1.5
149 for binary risk factors was assumed for each standard deviation change in telomere length. When
150 more than one study was available for the same outcome trait, priority was given to the study with
151 the higher statistical power. Power calculations took into account the variance explained in telomere
152 length by each SNP, inferred from published reports,³⁻¹⁰ and the sample size available for each
153 outcome.

154

155 **Estimating the association between genetically increased telomere length and outcome traits**

156 We employed three general approaches for estimating the association between genetically increased
157 telomere length and outcome traits. Our main results are based on a likelihood-approach.¹³
158 Sensitivity analyses were based on two approaches: the weighted median¹⁴ and MR-Egger
159 regression.¹⁵ The technical details of these approaches are described below.

160

161 Prior to calculating the associations of genetically increased telomere length with diseases and risk
162 factors, we estimated the pairwise r^2 for all telomere-associated SNPs residing on the same
163 chromosome using PLINK¹⁶ and 1000 Genomes phase 3 data for European samples.¹⁷ SNPs
164 residing on separate chromosomes or separated by more than 50 megabases on the same
165 chromosome were assumed to be in linkage equilibrium. The genetic instruments for telomere
166 length were pruned so that no SNP pair had an $r^2 > 0.9$ (strong linkage disequilibrium), using the
167 ‘indep’ command in PLINK.¹⁶ The base pair position and chromosome id for each SNP, in
168 GCRCh38 format, was extracted from Ensembl through the R biomart package.¹⁸⁻²⁰ Linkage
169 disequilibrium between the remaining SNPs was taken into account using a variance-covariance
170 matrix (described below). For analyses in which SNP-disease associations were derived from East
171 Asian populations, genetic instruments were further pruned so that no SNP pair had an $r^2 > 0.1$
172 (because the variance-covariance matrix used to model the correlation between SNPs was based on
173 a European population).

174

175 *Likelihood approach*

176 We combined summary data across SNPs into a single instrument, using maximum likelihood to
177 estimate the slope of the relationship between β_{GD} and β_{GP} and a variance-covariance matrix to make
178 allowance for linkage disequilibrium between SNPs, where β_{GD} is the change in the outcome trait
179 per copy of the effect allele and β_{GP} is the standard deviation change in telomere length per copy of
180 the effect allele.¹³ The standard deviation of telomere length corresponds to approximately 650 base
181 pairs.⁴ The variance-covariance matrix was estimated using 1000 Genomes phase 3 data for
182 Europeans.¹³ The model that is fitted is:

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

183 where $\boldsymbol{\beta}_{GP}$ is a vector of the SNP-telomere-length associations, $\boldsymbol{\beta}_{GD}$ is a vector of the SNP-disease
184 associations, β_{IV} is the causal effect parameter, K is the number of SNPs, Σ_{PP} is a variance-
185 covariance matrix with elements $(\Sigma_{PP})_{ij} = se(\beta_{GPi})se(\beta_{GPj})\rho_{ij}$ where $se(\beta_{GPi})$ is the standard
186 error of the SNP-telomere-length association for the i th genetic variant, and ρ_{ij} is the correlation
187 between the i th and j th variants due to linkage disequilibrium. Components of Σ_{DD} are similarly
188 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
189 (sensitivity analyses in a previous study¹³ suggested results were robust to some correlation between
190 the gene-phenotype and gene-outcome associations that may arise due to sample overlap). The
191 slope estimated by maximum likelihood can be interpreted as the log odds ratio for disease per
192 standard deviation change in genetically increased telomere length. The slope can further be
193 interpreted as the causal effect of telomere length on disease if Mendelian randomization
194 assumptions hold. The assumptions are: the SNPs are associated with telomere length (IV1); the
195 SNPs are independent of confounders (IV2); and the SNPs are independent of disease adjusted for
196 telomere length and confounders (IV3). See Supplementary Figure S7 for further details of the
197 Mendelian randomization assumptions and Supplementary Table S6 for a glossary of terms.

198

199 *The weighted median approach*¹⁴

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

201 Now define

202 $w_{(j)}^* = \frac{w_j}{S_j}$, where $S_j = \sum_j w_j$,

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

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

205
$$p_{(j)}^w = \frac{100}{S_j} \left(S_{(j)} - \frac{w_{(j)}}{2} \right).$$

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

207 estimates $\hat{\beta}_{(1)}, \dots, \hat{\beta}_{(J)}$. 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 method¹⁵ 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
$$\frac{\hat{\Gamma}_j}{\sigma_{y_j}} = \frac{\beta_{0E}}{\sigma_{y_j}} + \beta_{1E} \frac{\hat{\gamma}_j}{\sigma_{y_j}}$$

220 where Γ corresponds to the SNP-disease coefficients, γ corresponds to the SNP-exposure
221 coefficients and σ_{y_j} is the standard error of $\hat{\Gamma}_j$. If all SNPs are valid instruments, then $\beta_{0E} = 0$. The
222 value of $\hat{\beta}_{0E}$ can be interpreted as an estimate of the average pleiotropic effect across the SNPs. An
223 intercept term that differs from zero is indicative of overall directional pleiotropy. The MR-Egger
224 estimate for β , $\hat{\beta}_{1E}$, is consistent even if *all* SNPs are invalid, provided that

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

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

231 SUPPLEMENTARY RESULTS

232 In analyses of secondary cancer outcomes, genetically increased telomere length was associated
233 with thyroid cancer, chronic lymphocytic leukemia and multiple myeloma ($P < 0.05$) (Supplementary
234 Figure S2). In analyses of secondary non-neoplastic diseases, genetically increased telomere length
235 was associated with reduced odds of panic disorder ($P < 0.05$) (Supplementary Figure S2). In
236 secondary analyses of 44 risk factors for non-communicable diseases (Supplementary Table S2),
237 genetically increased telomere length was associated with increased pulse pressure, systolic blood
238 pressure, diastolic blood pressure, mean arterial pressure, triglycerides, uric acid and education and
239 with decreased HDL cholesterol, mean corpuscular haemoglobin and mean corpuscular volume
240 ($P < 0.05$) (Supplementary Figure S5). There was some evidence for an association between
241 genetically increased telomere length and ever smoking status ($P = 0.03$, Supplementary Figure S6)
242 but this association is unlikely to be reliable given that the SNP-telomere-length associations were
243 adjusted for smoking history; the association may therefore reflect collider bias.²¹

244
245

246 **SUPPLEMENTARY DISCUSSION**

247 **Mechanisms of association between SNPs and telomere length**

248 The mechanisms of the underlying associations between the selected SNPs and telomere length are
249 generally unknown. Some of the SNPs are located in or near the *TERC* or *TERT* genes, suggesting
250 that the mechanism could involve the telomerase enzyme, as well as the *OBFC1* and *CTCI* genes,
251 which have known roles in regulation of telomere length biology (Table 1). *OBFC1* is an enzyme
252 involved in initiating DNA replication and is involved in the telomere-associated CST complex.²²
253 *CTCI* encodes a component of the CST complex, which plays a role in protecting telomeres from
254 degradation.

255

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

257 The selected genetic instruments for telomere length correspond to 10 independent genomic loci
258 and collectively account for 2-3% of the variance in leukocyte telomere length. The corresponding
259 F statistic is around 18, which means that bias due to weak instruments is unlikely to be substantial
260 even if there were considerable overlap amongst the telomere length and disease and risk factor
261 GWASs.²³ The estimated overlap in participants amongst the telomere length and outcome GWASs
262 was less than 11% for all diseases and risk factors, except for hepatic steatosis, for which overlap
263 was around 51%, indicating that the vast majority of our results should be robust to weak
264 instrument bias.

265

266 **Misconceptions about Mendelian randomization**

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

271 Supplementary Figure S7), the variation explained by the instrument only affects statistical power
272 and does not generally affect validity of the causal inference. In this sense, genotype assignment in
273 a Mendelian randomization study is analogous to treatment assignment in a randomized controlled
274 trial, e.g. of blood pressure lowering drugs.²⁴ Although experimental interventions to reduce blood
275 pressure may only explain a small fraction of the total variation in blood pressure in a typical RCT,
276 we can still make causal inferences about blood pressure as a whole (and not just the proportion of
277 variation in blood pressure due to the experimental intervention). Moreover, the aim of Mendelian
278 randomization studies is to make inferences at the population level and not the individual level (for
279 which genetic proxies of substantial explanatory power would be required).²⁴ If Mendelian
280 randomization assumptions were violated, however, then the limited variation explained by our
281 genetic instruments might not behave in similar manner to other sources of variation in telomere
282 length, which would undermine our ability to draw causal inferences. See the above section
283 ‘Estimating the association between genetically increased telomere length and outcome traits’ and
284 Supplementary Figure S7 for details on the assumptions. See Supplementary Table S6 for an
285 explanation of Mendelian randomization terminology. See Haycock et al²⁵ and Davey Smith and
286 Hemani²⁶ for reviews on Mendelian randomization.

287

288 **Potential for confounding by population stratification, ancestry and age**

289 It is unlikely that confounding by population stratification, ancestry or age (an important
290 confounder of observational studies of telomere length) can account for our results. The 15 primary
291 diseases showing some evidence of association with telomere length (defined as a P value<0.05)
292 were 100% European, on the basis of self reported ancestry or genetic analyses (individuals
293 showing genetic evidence of non-European ancestry were excluded).^{3,27-44} In addition, these studies
294 all made some allowance for population stratification in their analyses: 12 adjusted for principal
295 component scores of genetic variation in their models or applied genomic control corrections to
296 their results; and 3 concluded there was little evidence for population stratification, on the basis of

297 visual inspection of Quantile-Quantile plots of GWAS results (i.e. lambdas for genomic inflation
298 were close to 1). The GWAS we used to defined genetic instruments for telomere length⁴ also
299 adjusted for principal component scores; and lambdas for genomic inflation were close to 1. Since
300 our MR analyses will have inherited any adjustments made in the original analyses, it is therefore
301 unlikely that confounding by ancestry or population stratification can explain our results.

302 Confounding by age is also unlikely, given the random distribution of genotypes in the general
303 population with respect to lifestyle and other environmental factors, as well as the fixed nature of
304 germline genotypes. Consistent with this expectation, we did not observe an association between
305 subject age and their genetically predicted telomere length values in our previous studies.^{44,45}

306

307 **Associations with non-neoplastic diseases**

308 The inverse associations observed for coronary heart disease, abdominal aortic aneurysm, celiac
309 disease and interstitial lung disease are compatible with findings based on observational and
310 Mendelian randomization studies of telomere length as well as dyskeratosis congenita (a congenital
311 disease characterized by chronically short telomeres).⁴⁶⁻⁵⁰

312

313

314

315

316

317

318

319

320
321
322
323
324
325
326
327
328

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						
<i>Cardia adenocarcinoma</i>	1126	2111	11	0.47	EA	Abnet ⁵⁶
<i>Noncardia adenocarcinoma</i>	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 al³¹ 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
Glycated 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
Hematological							
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 ¹⁰ ₃
Serum creatinine	67093	0.24	log _e ml/min/1.73m ²	13	1.00	EUR	CKDGen ¹⁰ ₃
Serum cystatin	20957	0.23	log _e ml/min/1.73m ²	13	1.00	EUR	CKDGen ¹⁰ ₃
Urinary albumin-to-creatinine ratio	31580	1.0	log _e mg/g	13	1.00	EUR	CKDGen ¹⁰ ₃
Other							
Grade of nuclear cataract	7140	0.8	grade	11	1.00	ASN	SEEDS ¹⁰⁴ Speliotes ¹⁰ ₅
Hepatic steatosis	7176	5.6	Hounsfield units	12	1.00	EUR	
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		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
WHL, 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		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		1

<0.001

0.03

0.05

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 ¹¹²⁵	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

329

330

331

332

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

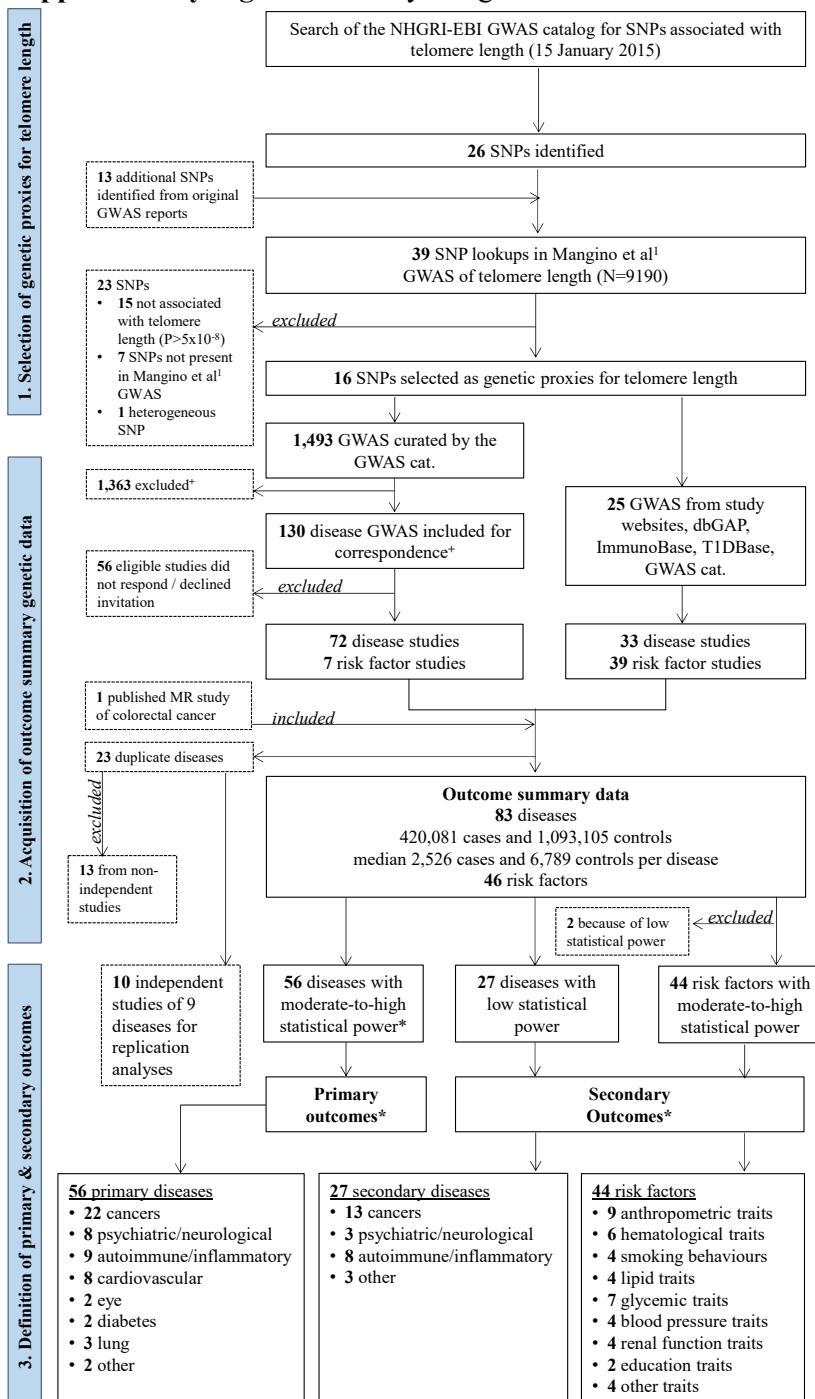
Search strategy	Search terms or meta-analysis	No. of studies identified	No. meeting inclusion criteria	Reasons for further exclusions	No. of studies included
<i>Inclusion criteria: prospective study of primary cancer outcome and telomere length†</i>					
Strategy 1	25 February 2015: cancer[TIAB] AND telomere length[TIAB] AND (meta analysis[TIAB] OR prospective[TIAB] OR meta-analysis[TIAB]) 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])	54	11	NA	11 [‡]
Strategy 2	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
<i>Inclusion criteria: prospective study of primary disease outcome and telomere length†</i>					
Strategy 4	8 January 2016: (meta-analysis OR "meta analysis") AND "telomere length"	42	7	2 did not report relative risks [§] ; 3 duplicates	2

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

Supplementary Table S6. Glossary of terms

Formatted: Numbering: Continuous

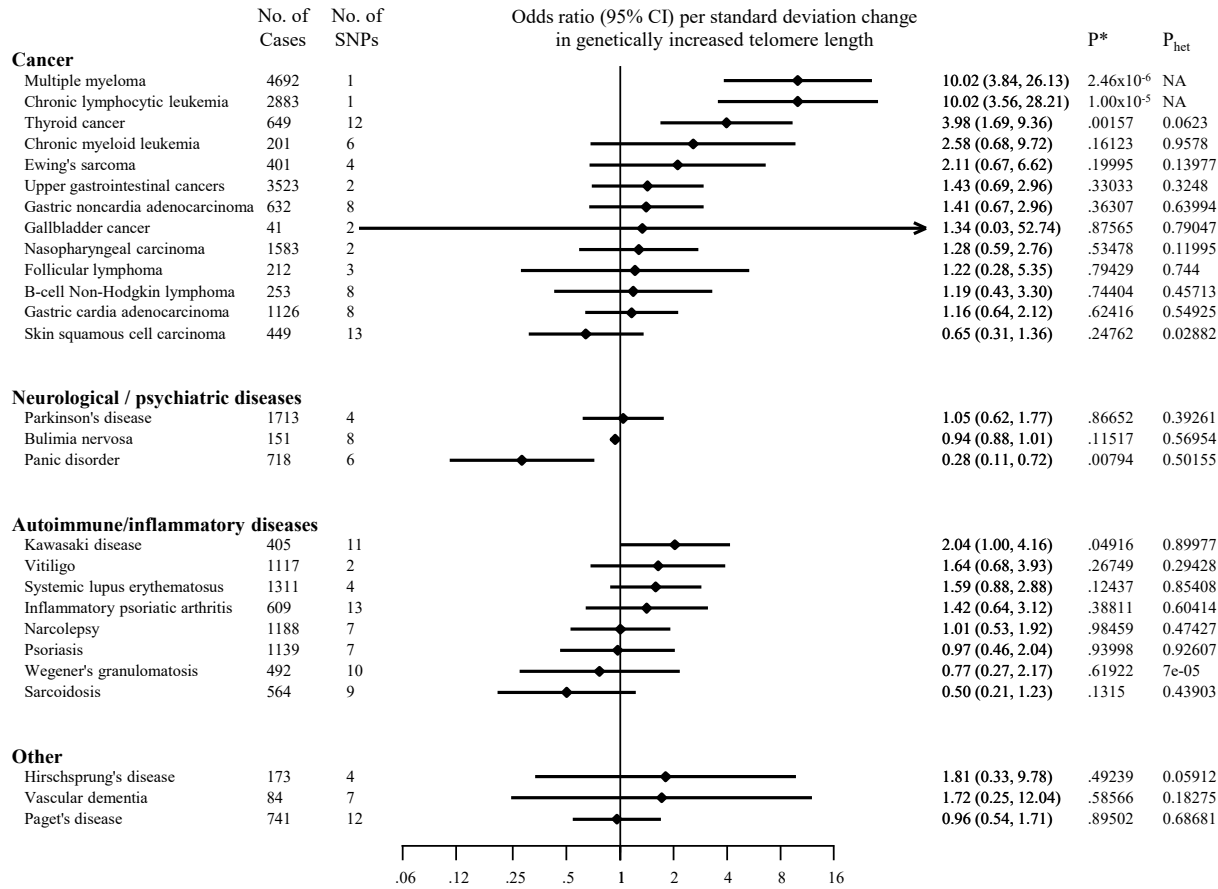
Mendelian randomization	A technique to appraise causality in observational studies using genetic variants as ‘unconfounded’ instruments for risk factors or modifiable exposures of interest.
Instrumental variable	A ‘proxy’ variable used in place of the hypothesized risk factor or exposure in a Mendelian 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 <i>vice versa</i> .
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.



+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 catalog; **SNP**, single nucleotide polymorphism; **NHGRI**, National Human Genome Research Institute; **EBI**, European Bioinformatics Institute

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



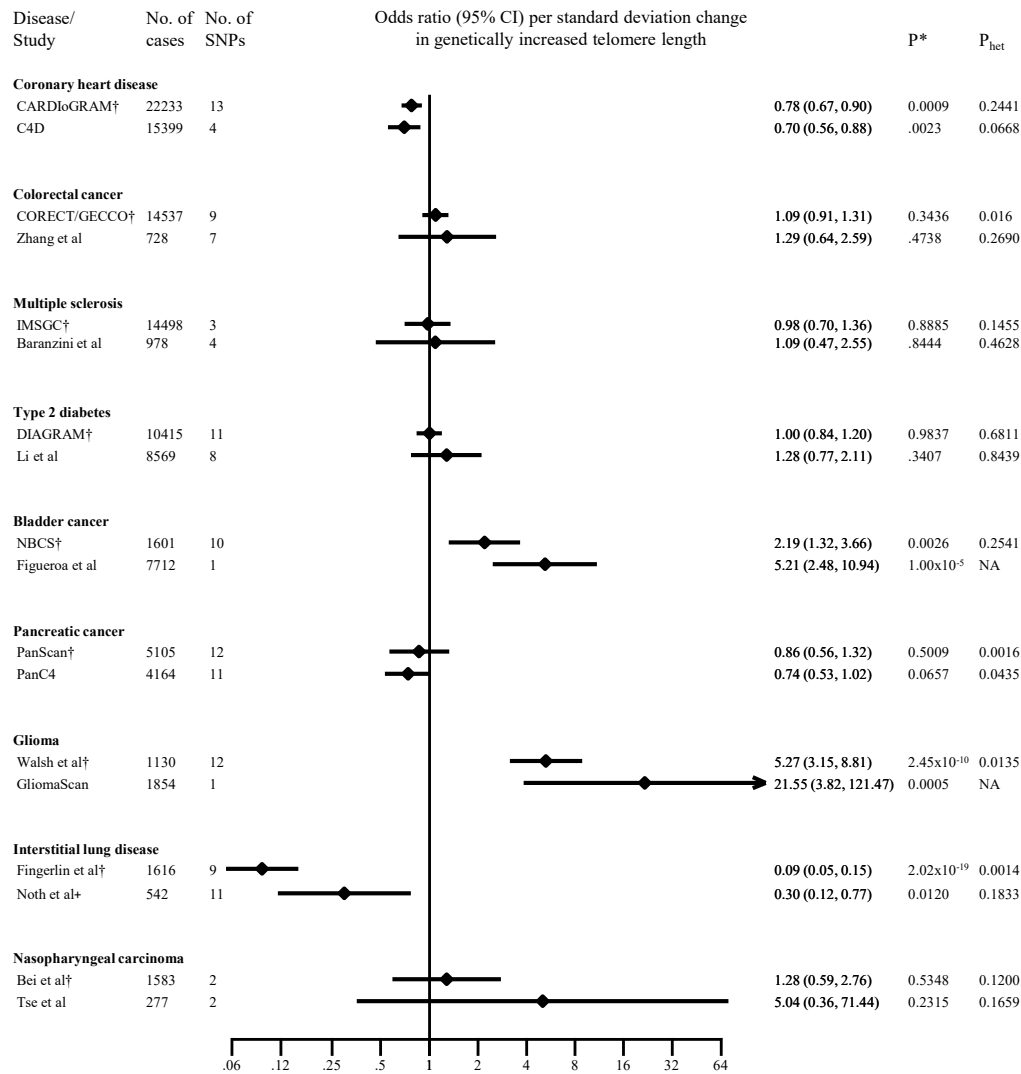
*P value for association between genetically increased telomere length and disease from maximum likelihood; P_{het}, P value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval

Formatted: Numbering: Continuous

337
338
339

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

Formatted: Numbering: Continuous



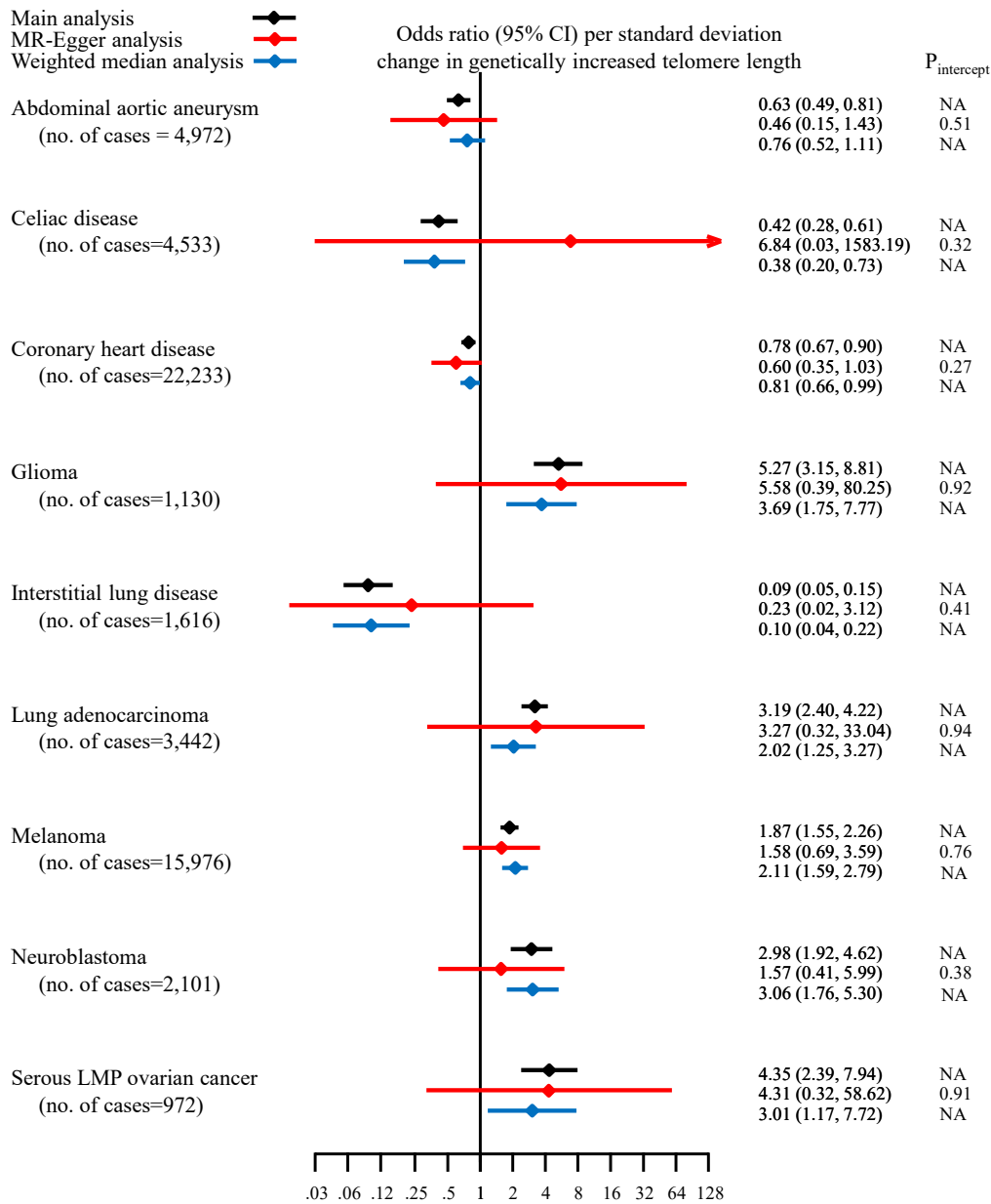
342 *P value for association between genetically increased telomere length and disease from maximum likelihood. †Primary or secondary study from Fig.
 343 1 or Fig. S2. ‡Noth et al³¹: ≤17% of the cases overlapped with cases from Fingerlin et al³¹ and 77% of cases had idiopathic pulmonary fibrosis; ‡An
 344 inverse association was also observed in Mushiroda et al³². P_{het}, p value for heterogeneity amongst SNPs in the genetic risk score (NA when only a
 345 single SNP available); SNP, single nucleotide polymorphism; CI, confidence interval. **Study abbreviations:** C4D, Coronary Artery Disease Genetics
 346 Consortium; CARDIoGRAM, Coronary ARtery Disease Genome wide Replication and Meta-analysis; CORECT, ColoRectal Transdisciplinary
 347 Study; GECCO, Genetics and Epidemiology of Colorectal Cancer Consortium; IMSGC, International Multiple Sclerosis Genetic Consortium;
 348 NBCS, Nijmegen Bladder Cancer Study; IMSGC, International Multiple Sclerosis Genetic Consortium.
 349
 350
 351

352

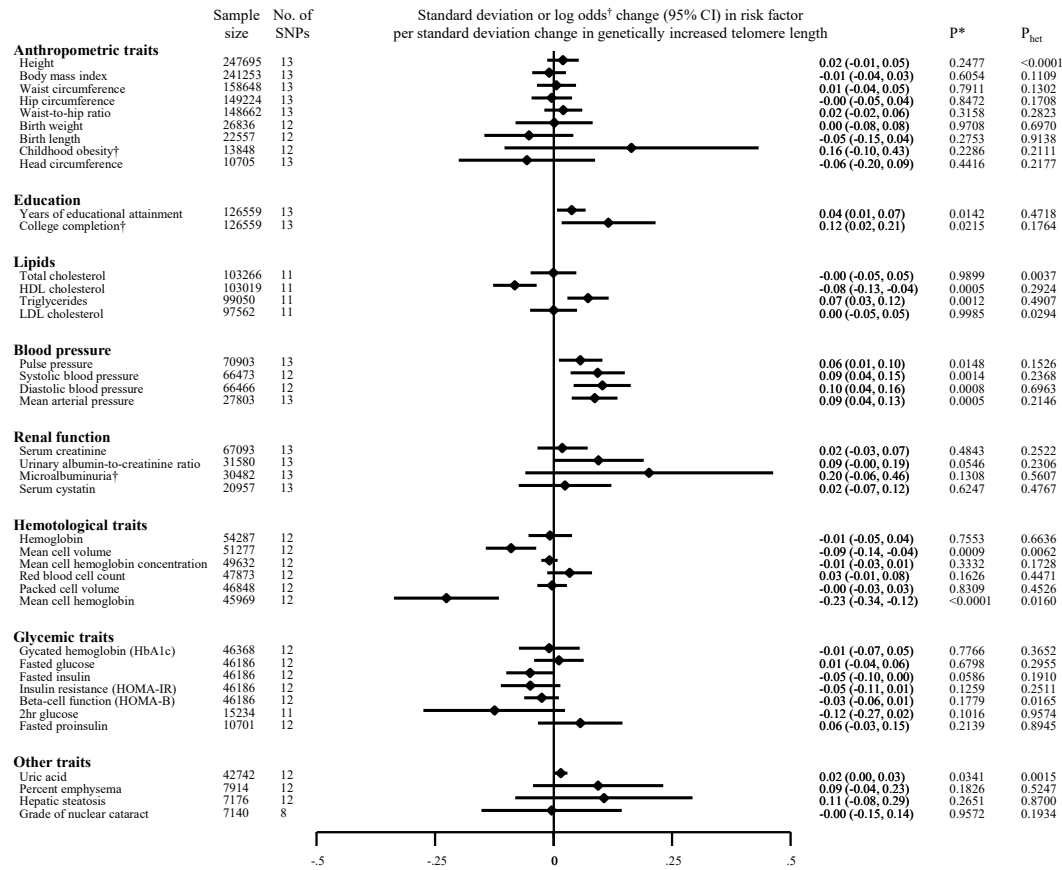
353

354

355 **Supplementary Figure S4.** Sensitivity analyses of association between genetically increased
 356 telomere length and odds of non-communicable diseases
 357



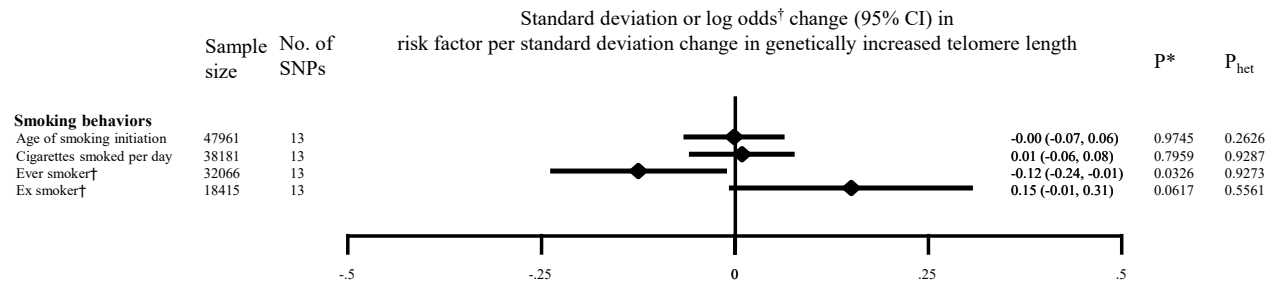
358 LMP, low malignancy potential; CI, confidence interval. The $P_{intercept}$ from MR-Egger regression tests the null hypothesis that the
 359 intercept is zero and can be interpreted as a statistical test for the presence of directional (bias inducing) pleiotropy; the smaller the
 360 $P_{intercept}$ value the stronger the evidence for directional pleiotropy.
 361

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

Formatted: Numbering: Continuous

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

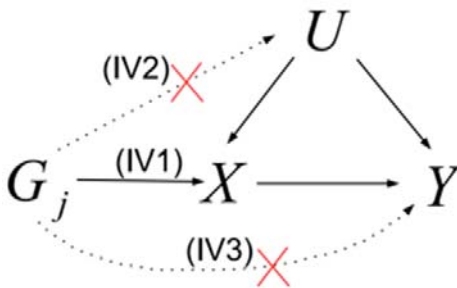


*P value for association between genetically increased telomere length and risk factor from maximum likelihood; P_{het}, P value for heterogeneity amongst SNPs within the genetic risk score; SNP, single nucleotide polymorphism; CI, confidence interval; [†]for binary risk factors results reflect the log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

364

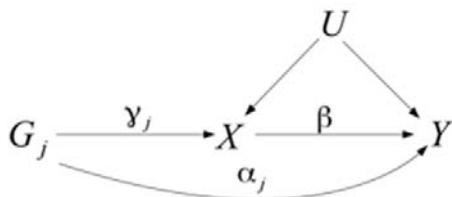
365

366 | **Supplementary Figure S7.** Causal diagram illustrating the assumptions of Mendelian
 367 randomization
 368 a)



369

370 b)



371

372 IV, instrumental variable assumption; G_j , single nucleotide polymorphism j ; X , telomere length; Y ,
 373 outcome (disease or risk factor); U , confounder; α , G - Y association not mediated by telomere
 374 length (often described as a horizontal pleiotropic or direct effect); γ , SNP-telomere-length
 375 association.

376 **a)** Key assumptions of Mendelian randomization. G_j is associated with X (IV1); G_j is independent
 377 of confounders (IV2); G_j is independent of Y given X and U (IV3). The weighted median approach
 378 assumes that IV1-IV3 hold for genetic variants making up at least 50% of the weight in the
 379 analysis; MR-Egger relaxes assumption IV3 (see InSIDE assumption below).

380 **b)** Assumptions underlying the MR-Egger approach. IV3 is replaced with the InSIDE assumption
 381 (Instrument Strength Independent of Direct Effect): the strength of the pleiotropic effect (α_j) does
 382 not correlate with the strength of the G - X association (γ_j). Under the InSIDE assumption, MR-
 383 Egger can consistently estimate the causal effect of X on Y , represented by the parameter β in (b).
 384

385

386

387

388

389

390

391

Formatted: Numbering: Continuous

392 **ACKNOWLEDGEMENTS OF THE CONTRIBUTING STUDIES AND CONSORTIA**

393

394 **Amyotrophic lateral sclerosis GWAS consortium**

395 Isabella Fogh¹, Kuang Lin¹, John F. Powell¹, the SLAGEN Consortium, Vincenzo Silani², the
396 ALSGEN consortium, Orla Hardiman³, Robert H. Brown⁴, Ammar Al-Chalabi¹, Jan H. Veldink⁵.

397

398 1. Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute,
399 Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United
400 Kingdom

401 2. Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano,
402 Milano, Italy

403 3. Population Genetics Laboratory, Smurfit Institute of Genetics, Trinity College Dublin, Dublin,
404 Republic of Ireland

405 4. Department of Neurology, University of Massachusetts Medical School, Worcester,
406 Massachusetts, United States of America

407 5. Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical
408 Center Utrecht, The Netherlands

409

410 *Funding/Support*

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

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

417 070122/A/02/Z) and the NIHR Dementias and Neurodegenerative Diseases Research Network
418 (DeNDRoN).

419 V. Silani was supported by Agenzia Italiana per la Ricerca sulla SLA-AriSLA (grant NOVALS
420 2012 cofinanced with the contribution of 5 x 1000, Healthcare Research support of the Ministry of
421 Health), the Italian Ministry of Health (Grant ALS-FTD, Ric. Finalizzata 2009 no.276) and
422 Associazione Amici “Centro Dino Ferrari”.

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

424

425 **The Aneurysm Consortium**

426 *GWAS data on abdominal aortic aneurysm (AAA) studies*

427 All known studies with AAA genome-wide genotyping were invited to join the International
428 Aneurysm Consortium. All studies agreed to participate in the meta-GWAS, with cohort case
429 control descriptions and inclusion/exclusion criteria having been previously reported.^{28,129,130} All
430 AAA cases shared a common definition of infra-renal aortic diameter >30 mm.

431

432 *Descriptions of AAA cohorts*

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

436 Original Aneurysm Consortium (1846 cases and 5605 controls): The original Aneurysm
437 Consortium recruited cases of AAA from centres across the United Kingdom and Western
438 Australia. Cases were defined as an infra-renal aortic diameter ≥ 30 mm proven on ultrasound or
439 computerized tomography (CT) scan. Controls were taken from the WTCCC2 common control
440 group^{28,131} and were therefore unscreened for AAA.

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

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

450

451 Geisinger Vascular Clinic AAA Study, Pennsylvania, USA: AAA patients (n=724) were enrolled
452 through the Department of Vascular Surgery at Geisinger Medical Center, Danville, PA. Details of
453 this case-control set have been reported previously, and the samples have been used in previous
454 association studies.^{129,132} To identify cases and controls from the electronic medical records, an
455 ePhenotyping algorithm was developed²⁹. AAA cases were defined as infrarenal aortic diameter \geq
456 30 mm as revealed by abdominal imaging. Approximately 20% of individuals with AAA had a
457 family history of AAA. A control group (n=1231) was obtained through the Geisinger MyCode®
458 Project, a cohort of Geisinger Clinic patients recruited for genomic studies. The MyCode® controls
459 were matched for age distribution and sex to the Geisinger Vascular Clinic AAA cases. Based on
460 electronic medical records, controls had no ICD-9 codes for AAA in their records, but they were
461 not screened by ultrasonography for AAA. Both cases and controls from the Geisinger Clinic were
462 of European descent. The eMERGE Network Imputed GWAS for 41 Phenotypes (the dbGaP
463 eMERGE Phase 1 and 2 Merged data Submission) accession number is: phs000888.v1.p1 which
464 includes the Geisinger AAA data.

465

466 Iceland, deCODE Genetics: Icelandic individuals with AAA (defined as infra-renal aortic diameter
467 \geq 30 mm) were recruited from a registry of individuals who were admitted at Landspítali University
468 Hospital, in Reykjavik, Iceland, 1980 – 2006. AAA patients were either followed up or treated by

469 intervention for emergency repair of symptomatic or ruptured AAA or for an elective repair by
470 surgery or endovascular intervention. In total, whole genome data from 557 subjects with AAA,
471 enrolled as part of the CVD genetics program at deCODE, were included in the metaGWAS. The
472 Icelandic controls used (n=89,235) were selected from among individuals who have participated in
473 various GWA studies and who were recruited as part of genetic programs at deCODE. Individuals
474 with known cardiovascular disease were excluded as controls¹²⁹ but controls were unscreened for
475 AAA.

476

477 The Netherlands: The AAA sample set from Utrecht was recruited in 2007-2009 from eight centres
478 in The Netherlands¹²⁹, mainly when individuals visited their vascular surgeon in the polyclinic or, in
479 rare cases, during hospital admission for elective or emergency AAA surgery. An AAA was defined
480 as an infrarenal aorta ≥ 30 mm. The sample set (n=840) comprised 89.9% males, with a mean AAA
481 diameter of 58.4 mm, 61.7% had received surgery, of which 8.1 % was after rupture. The Dutch
482 controls (n=2791) used in the AAA GWAS were recruited as part of the Nijmegen Biomedical
483 Study and the Nijmegen Bladder Cancer Study (see <http://dceg.cancer.gov/icbc/membership.html>).

484

485 *Meta-analysis of AAA GWASs*

486 Data from the six cohorts detailed above, comprising 4972 AAA cases and 99,858 controls, that
487 were genotyped with a variety of genome-wide SNP arrays. All cohorts underwent quality control
488 filtering using the manufacturers' array-specific guidelines but with consistently applied inclusion
489 criteria of SNP or sample call rates $>95\%$ and Hardy-Weinberg equilibrium $P > 5 \times 10^{-5}$ in
490 controls.^{28,129,130,132} Each cohort then underwent imputation (Impute 2.2) to a shared reference panel
491 from the 1000 Genomes project (Phase I integrated variant set release (v3), March 2012, NCBI
492 build 37(hg19) Following imputation SNPs were quality controlled by quality score ($Q > 0.9$) and
493 minor allele frequency ($MAF > 0.05$ in controls) filtering, resulting in a common set of 5331120
494 SNPs across all discovery phase participants.

495 The metaGWAS analysis was conducted using the METAL software package¹³³ on the
496 BCISNPmax database platform (version 3.5, BCI Platforms, Espoo, Finland). METAL was
497 implemented using the sample size scheme with weighting for each cohort being two times the case
498 number. The analysis was adjusted for genomic inflation (λ) in each cohort.

499

500 *Acknowledgements on AAA GWAS studies:*

501 Data provided by the original Aneurysm Consortium was funded by the Wellcome Trust (award
502 number 084695) and made use of data generated by the WTCCC. A full list of the investigators
503 who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the
504 WTCCC project was provided by the Wellcome Trust under award 076113 and 085475. Funding
505 for the New Zealand project was provided by the Health Research Council of New Zealand (08-75,
506 14-155). The Geisinger sample collection was funded in part by the Pennsylvania Commonwealth
507 Universal Research Enhancement program, the Geisinger Clinical Research Fund, the American
508 Heart Association, and the Ben Franklin Technology Development Fund of Pennsylvania. The
509 generation and management of GWAS genotype data for the Rotterdam Study (control samples for
510 the Dutch GWAS) is supported by the Netherlands Organization of Scientific Research NWO
511 Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for
512 Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/NWO
513 project nr. 050-060-810.

514

515

516 **Australian Asthma Genetics Consortium**

517 David L. Duffy^a, Dale R. Nyholt^a, John Beilby^{b-d}, Svetlana Baltic^e, Loren Price^e, Faang Cheah^e,
518 Desiree Mészáros^f, Scott D. Gordon^a, Melissa C. Southey^g, Margaret J. Wright^a, James Markos^h, Li
519 P. Chung^e, Anjali K. Henders^a, Graham Gilesⁱ, Suzanna Temple^e, John Whitfield^a, Brad Shelton^e,
520 Chalermchai Mitrpan^e, Minh Bui, PhD,^j Mark Jenkins^j, Haydn Walters^f, Michael J. Abramson^k,

521 Michael Hunter^{l,d}, Bill Musk^{l,d,m,n}, Peter Le Souëf,^o Shyamali C. Dharmage^j, Grant W.
522 Montgomery,^a Alan James,^{c,m,d}, Nicholas G. Martin^a, Melanie C. Matheson^j

523

524 ^a QIMR Berghofer Medical Research, Brisbane, Australia.

525 ^b PathWest Laboratory Medicine of Western Australia (WA), Nedlands, Australia.

526 ^c School of Pathology and Laboratory Medicine, The University of WA, Nedlands, Australia.

527 ^d Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Perth,
528 Australia.

529 ^e Institute of Respiratory Health, University of WA, Perth, Australia.

530 ^f Menzies Research Institute, Hobart, Australia.

531 ^g Department of Pathology, The University of Melbourne, Melbourne, Australia.

532 ^h Launceston General Hospital, Launceston, Australia.

533 ⁱ Cancer Epidemiology Centre, The Cancer Council Victoria, Melbourne, Australia.

534 ^j Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, University of
535 Melbourne, Melbourne, Australia.

536 ^k Department of Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia

537 ^l School of Population Health, The University of WA, Nedlands, Australia

538 ^m School of Medicine and Pharmacology, University of Western Australia, Nedlands, Australia

539 ⁿ Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Australia

540 ^o School of Paediatrics and Child Health, Princess Margaret Hospital for Children, Perth, Australia

541

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

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

549

550 **The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) – Heart**
551 **Failure Working Group**

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

554

555 **CHARGE - Sudden Cardiac Arrest Working Group**

556 Aravinda Chakravarti¹, Anna Moes¹, Dan E. Arking¹, Foram N. Ashar¹, Georg Ehret¹, Josef
557 Coresh², Man Li², Ronald Prineas³, Angel Mak⁴, Pui-Yan Kwok⁴, Catherine O. Johnson⁵, Nona
558 Sotoodehnia⁵, David S. Siscovick⁶, Oscar H. Franco⁷, Thomas Lumley⁸, Florence Dumaso⁹, Xavier
559 Jouven⁹, Martina Muller-Nurasyid¹⁰, Stefan Kaab¹⁰, Barbara M. McKnight⁵, Bruce M. Psaty⁵,
560 Jennifer A. Brody⁵, Jerome I. Rotter¹¹, Ken Rice⁵, Rozenn N. Lemaitre⁵, Christopher J.
561 O'Donnell¹², Christopher Newton-Cheh¹³, Shih-Jen Hwang¹², Heikki Huikuri¹⁴, Marja-Leena
562 Kortelainen¹⁴, M Juhani Junttila¹⁴, Jean-Claude Tardif¹⁵, John D. Rioux¹⁵, Philippe Goyette¹⁵,
563 Christine M. Albert¹⁶, Martin VanDenBurgh¹⁶, Sara Pulit¹⁷, Andre G Uitterlinden², Albert
564 Hofman², Bruno H Stricker², Mark Eijgelsheim²

565

566 1. Institute of Genetic Medicine, Johns Hopkins, Baltimore, USA, 21205

567 2. Department of Epidemiology, Johns Hopkins University, Baltimore, USA, 21205

568 3. Public Health Sciences, Wake Forest University, Winston-Salem, USA, 27157

569 4. Cardiovascular Research Institute and Institute for Human Genetics, University of California,
570 San Francisco, San Francisco, USA,

571 5. Cardiovascular Health Research Unit, Department of Biostatistics, University of

572 Washington, Seattle, USA, 98101

- 573 6. New York Academy of Medicine, New York, USA,
- 574 7. Department of Epidemiology, Erasmus MC, Erasmus, The Netherlands,
- 575 8. Department of Statistics, University of Auckland, Auckland, NZ,
- 576 9. Paris sudden Death Expertise Center, University Paris Sorbonne cité, Paris, France,
- 577 10. Department of Medicine I, Ludwig-Maximilians University, Munich, Germany,
- 578 11. Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical
- 579 Research Institute, Departments of Pediatrics and Medicine, Harbor-UCLA Medical Center, Los
- 580 Angeles, USA
- 581 12. NHLBI Framingham Heart Study, Boston, USA,
- 582 13. Center for Human Genetic Research & Cardiovascular Research Center, Massachusetts General
- 583 Hospital, Boston, USA,
- 584 14. Internal Medicine, University of Oulu, Oulu, Finland,
- 585 15. Montreal Heart Institute, University of Montreal, Quebec, Canada,
- 586 16. Divisions of Preventive Medicine and Cardiovascular Medicine, Department of
- 587 Medicine, Brigham and Women's Hospital, Boston, USA,
- 588 17. Department of Genetics, University Medical Centre Utrecht, Utrecht, The Netherlands,
- 589

590 **The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene)**

591 The COPDGene project was supported by Award Number R01HL089897 and Award Number

592 R01HL089856 from the National Heart, Lung, and Blood Institute. The content is solely the

593 responsibility of the authors and does not necessarily represent the official views of the National

594 Heart, Lung, and Blood Institute or the National Institutes of Health. The COPDGene project is

595 also supported by the COPD Foundation through contributions made to an Industry Advisory Board

596 comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovion, and

597 GlaxoSmithKline.

598 *COPDGene Administrative Core*: James Crapo, MD (PI), Edwin Silverman, MD, PhD (PI), Barry
599 Make, MD, Elizabeth Regan, MD, PhD
600
601 *COPDGene Genetic Analysis Core*: Terri Beaty, PhD, Nan Laird, PhD, Christoph Lange, PhD,
602 Michael Cho, MD, Stephanie Santorico, PhD, John Hokanson, MPH, PhD, Dawn DeMeo, MD,
603 MPH, Nadia Hansel, MD, MPH, Craig Hersh, MD, MPH, Peter Castaldi, MD, MSc, Merry-Lynn
604 McDonald, PhD, Emily Wan, MD, Megan Hardin, MD, Jacqueline Hetmanski, MS, Margaret
605 Parker, MS, Marilyn Foreman, MD, Brian Hobbs, MD, Robert Busch, MD, Adel El-Boueiz, MD,
606 Peter Castaldi, MD, Megan Hardin, MD, Dandi Qiao, PhD, Elizabeth Regan, MD, Eitan Halper-
607 Stromberg, Ferdouse Begum, Sungho Won, Sharon Lutz, PhD
608 *COPDGene Imaging Core*: David A Lynch, MB, Harvey O Coxson, PhD, MeiLan K Han, MD,
609 MS, MD, Eric A Hoffman, PhD, Stephen Humphries MS, Francine L Jacobson, MD, Philip F Judy,
610 PhD, Ella A Kazerooni, MD, John D Newell, Jr., MD, Elizabeth Regan, MD, James C Ross, PhD,
611 Raul San Jose Estepar, PhD, Berend C Stoel, PhD, Juerg Tschirren, PhD, Eva van Rikxoort, PhD,
612 Bram van Ginneken, PhD, George Washko, MD, Carla G Wilson, MS, Mustafa Al Qaisi, MD,
613 Teresa Gray, Alex Kluiber, Tanya Mann, Jered Sieren, Douglas Stinson, Joyce Schroeder, MD,
614 Edwin Van Beek, MD, PhD
615 *COPDGene PFT QA Core, Salt Lake City, UT*: Robert Jensen, PhD
616 *COPDGene Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO*:
617 Douglas Everett, PhD, Anna Faino, MS, Matt Strand, PhD, Carla Wilson, MS
618 *COPDGene Epidemiology Core, University of Colorado Anschutz Medical Campus, Aurora, CO*:
619 John E. Hokanson, MPH, PhD, Gregory Kinney, MPH, PhD, Sharon Lutz, PhD, Kendra Young
620 PhD, Katherine Pratte, MSPH, Lindsey Duca, MS
621
622 *COPDGene Clinical Centers*
623 *Ann Arbor VA*: Jeffrey L. Curtis, MD, Carlos H. Martinez, MD, MPH, Perry G. Pernicano, MD

624 *Baylor College of Medicine, Houston, TX:* Nicola Hanania, MD, MS, Philip Alapat, MD, Venkata
625 Bandi, MD, Mustafa Atik, MD, Aladin Boriek, PhD, Kalpatha Guntupalli, MD, Elizabeth Guy,
626 MD, Amit Parulekar, MD, Arun Nachiappan, MD
627 *Brigham and Women's Hospital, Boston, MA:* Dawn DeMeo, MD, MPH, Craig Hersh, MD, MPH,
628 George Washko, MD, Francine Jacobson, MD, MPH
629 *Columbia University, New York, NY:* R. Graham Barr, MD, DrPH, Byron Thomashow, MD, John
630 Austin, MD, Belinda D'Souza, MD, Gregory D.N. Pearson, MD, Anna Rozenshtein, MD, MPH,
631 FACR
632 *Duke University Medical Center, Durham, NC:* Neil MacIntyre, Jr., MD, Lacey Washington, MD,
633 H. Page McAdams, MD
634 *Health Partners Research Foundation, Minneapolis, MN:* Charlene McEvoy, MD, MPH, Joseph
635 Tashjian, MD
636 *Johns Hopkins University, Baltimore, MD:* Robert Wise, MD, Nadia Hansel, MD, MPH, Robert
637 Brown, MD, Karen Horton, MD, Nirupama Putcha, MD, MHS,
638 *Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Torrance, CA:*
639 Richard Casaburi, PhD, MD, Alessandra Adami, PhD, Janos Porszasz, MD, PhD, Hans Fischer,
640 MD, PhD, Matthew Budoff, MD, Harry Rossiter, PhD
641 *Michael E. DeBakey VAMC, Houston, TX:* Amir Sharafkhaneh, MD, PhD, Charlie Lan, DO
642 *Minneapolis VA:* Christine Wendt, MD, Brian Bell, MD
643 *Morehouse School of Medicine, Atlanta, GA:* Marilyn Foreman, MD, MS, Gloria Westney, MD,
644 MS, Eugene Berkowitz, MD, PhD
645 *National Jewish Health, Denver, CO:* Russell Bowler, MD, PhD, David Lynch, MD
646 *Reliant Medical Group, Worcester, MA:* Richard Rosiello, MD, David Pace, MD
647 *Temple University, Philadelphia, PA:* Gerard Criner, MD, David Ciccolella, MD, Francis Cordova,
648 MD, Chandra Dass, MD, Gilbert D'Alonzo, DO, Parag Desai, MD, Michael Jacobs, PharmD,
649 Steven Kelsen, MD, PhD, Victor Kim, MD, A. James Mamary, MD, Nathaniel Marchetti, DO,

650 Aditi Satti, MD, Kartik Shenoy, MD, Robert M. Steiner, MD, Alex Swift, MD, Irene Swift, MD,
651 Maria Elena Vega-Sanchez, MD
652 *University of Alabama, Birmingham, AL:* Mark Dransfield, MD, William Bailey, MD, J. Michael
653 Wells, MD, Surya Bhatt, MD, Hrudaya Nath, MD
654 *University of California, San Diego, CA:* Joe Ramsdell, MD, Paul Friedman, MD, Xavier Soler,
655 MD, PhD, Andrew Yen, MD
656 *University of Iowa, Iowa City, IA:* Alejandro Cornellias, MD, John Newell, Jr., MD, Brad
657 Thompson, MD
658 *University of Michigan, Ann Arbor, MI:* MeiLan Han, MD, Ella Kazerooni, MD, Carlos Martinez,
659 MD
660 *University of Minnesota, Minneapolis, MN:* Joanne Billings, MD, Tadashi Allen, MD
661 *University of Pittsburgh, Pittsburgh, PA:* Frank Scurba, MD, Divay Chandra, MD, MSc, Joel
662 Weissfeld, MD, MPH, Carl Fuhrman, MD, Jessica Bon, MD
663 *University of Texas Health Science Center at San Antonio, San Antonio, TX:* Antonio Anzueto, MD,
664 Sandra Adams, MD, Diego Maselli-Caceres, MD, Mario E. Ruiz, MD

665

666 **Early Growth Genetics (EGG) Consortium**

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

670

671 **The EARly Genetics and Lifecourse Epidemiology (EAGLE) consortium**

672 Lavinia Paternoster ^{1,2,112}, Marie Standl ^{3,112}, Johannes Waage ⁴, Hansjörg Baurecht ⁵, Melanie
673 Hotze ⁵, David P Strachan ⁶, John A Curtin ⁷, Klaus Bønnelykke ⁴, Chao Tian ⁸, Atsushi
674 Takahashi ⁹, Jorge Esparza-Gordillo ^{10,11}, Alexessander Couto Alves ¹², Jacob P Thyssen ¹³,
675 Herman T den Dekker ^{14,15,16}, Manuel A Ferreira ¹⁷, Elisabeth Altmaier ^{18,19,20}, Patrick MA

676 Sleiman ^{21, 22}, Feng Li Xiao ²³, Juan R Gonzalez ²⁴, Ingo Marenholz ^{10, 11}, Birgit Kalb ^{10, 25}, Maria
677 Pino-Yanes ^{26, 27, 28}, Cheng-Jian Xu ^{29, 30}, Lisbeth Carstensen ³¹, Maria M Groen-Blokhuis ³²,
678 Cristina Venturini ³³, Craig E Pennell ³⁴, Sheila J Barton ³⁵, Albert M Levin ³⁶, Ivan Curjurić ^{37, 38},
679 Mariona Bustamante ^{24, 39, 40, 41}, Eskil Kreiner-Møller ⁴, Gabrielle A Lockett ⁴², Jonas Bacelis ⁴³,
680 Supinda Bunyavanich ⁴⁴, Rachel A Myers ⁴⁵, Anja Matanovic ^{10, 11}, Ashish Kumar ^{37, 38, 46, 47}, Joyce
681 Y Tung ⁸, Tomomitsu Hirota ⁴⁸, Michiaki Kubo ⁴⁹, Wendy L McArdle ², A J Henderson ², John P
682 Kemp ^{1, 2, 50}, Jie Zheng ^{1, 2}, George Davey Smith ^{1, 2}, Franz Rüschenhoff ¹⁰, Anja Bauerfeind ¹⁰, Min
683 Ae Lee-Kirsch ⁵¹, Andreas Arnold ⁵², Georg Homuth ⁵³, Carsten O Schmidt ⁵⁴, Elisabeth
684 Mangold ⁵⁵, Sven Cichon ^{55, 56, 57, 58, 59}, Thomas Keil ^{60, 61}, Elke Rodríguez ⁵, Annette Peters ^{19, 62},
685 Andre Franke ⁶³, Wolfgang Lieb ⁶⁴, Natalija Novak ⁶⁵, Regina Fölster-Holst ⁵, Momoko
686 Horikoshi ⁴⁷, Juha Pekkanen ^{66, 67}, Sylvain Sebert ^{68, 69}, Lise L Husemoen ⁷⁰, Niels Grarup ⁷¹, Johan
687 C de Jongste ¹⁴, Fernando Rivadeneira ^{15, 16, 72}, Albert Hofman ¹⁵, Vincent WV Jaddoe ^{14, 15, 16},
688 Suzanne GMA Pasmans ⁷³, Niels J Elbert ^{16, 73}, André G Uitterlinden ^{15, 72}, Guy B Marks ⁷⁴, Philip J
689 Thompson ^{75, 76}, Melanie C Matheson ⁷⁷, Colin F Robertson ⁷⁸, Australian Asthma Genetics
690 Consortium (AAGC) ⁷⁹, Janina S Ried ²⁰, Jin Li ²¹, Xian Bo Zuo ²³, Xiao Dong Zheng ²³, Xian
691 Yong Yin ²³, Liang Dan Sun ²³, Maeve A McAleer ^{80, 81}, Grainne M O'Regan ⁸¹, Caoimhe MR
692 Fahy ⁸², Linda E Campbell ⁸³, Milan Macek ⁸⁴, Michael Kurek ⁸⁵, Donglei Hu ²⁶, Celeste Eng ²⁶,
693 Dirkje S Postma ²⁹, Bjarke Feenstra ³¹, Frank Geller ³¹, Jouke Jan Hottenga ³², Christel M
694 Middeldorp ³², Pirro Hysi ³³, Veronique Bataille ³³, Tim Spector ³³, Carla MT Tiesler ^{3, 86}, Elisabeth
695 Thiering ^{3, 86}, Badri Pahukasahasram ⁸⁷, James J Yang ⁸⁸, Medea Imboden ^{37, 38}, Scott Huntsman ²⁶,
696 Natàlia Vilor-Tejedor ^{24, 40, 41}, Caroline L Relton ^{1, 89}, Ronny Myhre ⁹⁰, Wenche Nystad ⁹⁰, Adnan
697 Custovic ⁷, Scott T Weiss ⁹¹, Deborah A Meyers ⁹², Cilla Söderhäll ^{93, 94}, Erik Melén ^{46, 95}, Carole
698 Ober ⁴⁵, Benjamin A Raby ⁹¹, Angela Simpson ⁷, Bo Jacobsson ^{43, 90}, John W Holloway ^{42, 96}, Hans
699 Bisgaard ⁴, Jordi Sunyer ^{24, 40, 41, 97}, Nicole M Probst-Hensch ^{37, 38}, L Keoki Williams ^{87, 98}, Keith M
700 Godfrey ^{35, 99}, Carol A Wang ³⁴, Dorret I Boomsma ^{32, 100}, Mads Melbye ^{31, 101, 102}, Gerard H
701 Koppelman ¹⁰³, Deborah Jarvis ^{104, 105}, WH Irwin McLean ⁸³, Alan D Irvine ^{80, 81, 82}, Xue Jun

702 Zhang²³, Hakon Hakonarson^{21, 22}, Christian Gieger^{18, 19, 20}, Esteban G Burchard^{26, 106}, Nicholas G
703 Martin¹⁷, Liesbeth Duijts^{14, 15, 16}, Allan Linneberg^{70, 101, 107}, Marjo-Riitta Jarvelin^{69, 108, 109, 110},
704 Markus M Noethen^{55, 56}, Susanne Lau²⁵, Norbert Hübner¹⁰, Young-Ae Lee^{10, 11}, Mayumi
705 Tamari⁴⁸, David A Hinds⁸, Daniel Glass³³, Sara J Brown^{83, 111}, Joachim Heinrich³, David M
706 Evans^{1, 2, 50, 113}, Stephan Weidinger^{5, 113} for the EARly Genetics & Lifecourse Epidemiology
707 (EAGLE) eczema consortium¹¹⁴.

708

709 1 Medical Research Council (MRC) Integrative Epidemiology Unit, University of Bristol, Bristol,
710 UK.

711 2 School of Social and Community Medicine, University of Bristol, Bristol, UK.

712 3 Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for
713 Environmental Health, Neuherberg, Germany.

714 4 Copenhagen Prospective Studies on Asthma in Childhood (COPSAC), Herlev and Gentofte
715 Hospital, University of Copenhagen, Copenhagen, Denmark.

716 5 Department of Dermatology, Allergology and Venereology, University Hospital Schleswig-
717 Holstein, Campus Kiel, Kiel, Germany.

718 6 Population Health Research Institute, St George's, University of London, London, UK.

719 7 Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, Manchester
720 Academic Health Science Centre, The University of Manchester and University Hospital of South
721 Manchester National Health Service (NHS) Foundation Trust, Manchester, United Kingdom.

722 8 23andMe, Inc., Mountain View, CA, USA.

723 9 Laboratory for Statistical Analysis, Center for Integrative Medical Sciences, Institute of Physical
724 and Chemical Research (RIKEN), Yokohama, Japan.

725 10 Max-Delbrück-Center (MDC) for Molecular Medicine, Berlin, Germany.

726 11 Clinic for Pediatric Allergy, Experimental and Clinical Research Center, Charité -
727 Universitätsmedizin Berlin, Berlin, Germany.

728 12 Department of Epidemiology and Biostatistics, School of Public Health, Imperial College
729 London, London, UK.

730 13 National Allergy Research Centre, Department of Dermatology and Allergology, Herlev and
731 Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark.

732 14 Department of Pediatrics, Erasmus MC, Rotterdam, the Netherlands.

733 15 Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands.

734 16 The Generation R Study Group, Erasmus MC, Rotterdam, the Netherlands.

735 17 QIMR Berghofer Medical Research Institute, Brisbane, Australia.

736 18 Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research
737 Center for Environmental Health, Neuherberg, Germany.

738 19 Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for
739 Environmental Health, Neuherberg, Germany.

740 20 Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for
741 Environmental Health, Neuherberg, Germany.

742 21 The Center for Applied Genomics, The Children's Hospital of Philadelphia, PA, USA.

743 22 Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania,
744 Philadelphia, PA, USA.

745 23 Institute of Dermatology, Anhui Medical University, Hefei, Anhui, China.

746 24 Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.

747 25 Pediatric Pneumology and Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany.

748 26 Department of Medicine, University of California, San Francisco, CA, USA.

749 27 Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Respiratorias, Instituto de
750 Salud Carlos III, Madrid, Spain.

751 28 Research Unit, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife,
752 Spain.

753 29 University of Groningen, University Medical Center Groningen, Department of Pulmonology,
754 Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands.
755 30 University of Groningen, University Medical Center Groningen, Department of Genetics,
756 Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, the Netherlands.
757 31 Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark.
758 32 Dept Biological Psychology, Netherlands Twin Register, VU University, Amsterdam, the
759 Netherlands.
760 33 KCL Department of Twin Research and Genetic Epidemiology, King's College London,
761 London, UK.
762 34 School of Women's and Infants' Health, The University of Western Australia (UWA), Perth,
763 Australia.
764 35 Medical Research Council (MRC) Lifecourse Epidemiology Unit, University of Southampton,
765 Southampton, UK.
766 36 Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA.
767 37 Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute,
768 Basel, Switzerland.
769 38 University of Basel, Basel, Switzerland.
770 39 Centre for Genomic Regulation (CRG), Barcelona, Spain.
771 40 Pompeu Fabra University (UPF), Barcelona, Spain.
772 41 Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP),
773 Barcelona, Spain.
774 42 Human Development and Health, Faculty of Medicine, University of Southampton,
775 Southampton, UK.
776 43 Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy,
777 Sahlgrenska University Hospital, Gothenburg, Sweden.

778 44 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New
779 York, NY, USA.

780 45 Department of Human Genetics, University of Chicago, Chicago, IL, USA.

781 46 Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

782 47 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.

783 48 Laboratory for Respiratory and Allergic Diseases, Center for Integrative Medical Sciences,
784 Institute of Physical and Chemical Research (RIKEN), Yokohama, Japan.

785 49 Laboratory for Genotyping Development, Center for Integrative Medical Sciences, Institute of
786 Physical and Chemical Research (RIKEN), Yokohama, Japan.

787 50 University of Queensland Diamantina Institute, Translational Research Institute, University of
788 Queensland, Brisbane, Australia.

789 51 Klinik für Kinder- und Jugendmedizin, Technical University Dresden, Dresden, Germany.

790 52 Clinic and Polyclinic of Dermatology, University Medicine Greifswald, Greifswald, Germany.

791 53 Department of Functional Genomics, Interfaculty Institute for Genetics and Functional
792 Genomics, University Medicine and Ernst-Moritz-Arndt-University Greifswald, Greifswald,
793 Germany.

794 54 Institute for Community Medicine, Study of Health in Pomerania/KEF, University Medicine
795 Greifswald, Greifswald, Germany.

796 55 Institute of Human Genetics, University of Bonn, Bonn, Germany.

797 56 Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany.

798 57 Division of Medical Genetics, University Hospital Basel, Basel, Switzerland.

799 58 Department of Biomedicine, University of Basel, Basel, Switzerland.

800 59 Institute of Neuroscience and Medicine (INM-1), Structural and Functional Organisation of the
801 Brain, Genomic Imaging, Research Centre Jülich, Jülich, Germany.

802 60 Institute of Social Medicine, Epidemiology and Health Economics, Charité -
803 Universitätsmedizin Berlin, Berlin, Germany.

804 61 Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany.
805 62 Deutsches Forschungszentrum für Herz-Kreislaferkrankungen (DZHK) (German Research
806 Centre for Cardiovascular Research), Munich Heart Alliance, Munich, Germany.
807 63 Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany.
808 64 Institute of Epidemiology, Christian-Albrechts University Kiel, Kiel, Germany.
809 65 Department of Dermatology and Allergy, University of Bonn Medical Center, Bonn, Germany.
810 66 Unit of Living Environment and Health, National Institute for Health and Welfare, Kuopio,
811 Finland.
812 67 Department of Public Health, University of Helsinki, Helsinki, Finland.
813 68 Center for Life-course and Systems Epidemiology, Faculty of Medicine, University of Oulu,
814 Finland.
815 69 Biocenter Oulu, University of Oulu, Finland.
816 70 Research Centre for Prevention and Health, Capital Region of Denmark, Copenhagen, Denmark.
817 71 The Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and
818 Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
819 72 Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands.
820 73 Department of Dermatology, Erasmus MC, Rotterdam, the Netherlands.
821 74 Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia.
822 75 Lung Institute of Western Australia, QE II Medical Centre Nedlands , Western Australia,
823 Australia.
824 76 School of Medicine and Pharmacology, University of Western Australia, Perth, Australia.
825 77 Melbourne School of Population and Global Health, University of Melbourne, Melbourne,
826 Australia.
827 78 Murdoch Children's Research Institute, Melbourne, Australia.
828 79 A full list of consortium members is provided in Supplementary Note 1, page 4.
829 80 National Children's Research Centre, Crumlin, Dublin, Ireland.

830 81 Our Lady's Children's Hospital, Crumlin, Dublin, Ireland.

831 82 Clinical Medicine, Trinity College Dublin, Dublin, Ireland.

832 83 Centre for Dermatology and Genetic Medicine, University of Dundee, Dundee, UK.

833 84 Department of Biology and Medical Genetics, University Hospital Motol and 2nd Faculty of
834 Medicine of Charles University, Prague, Czech Republic.

835 85 Department of Clinical Allergology, Pomeranian, Pomeranian Medical University, Szczecin,
836 Poland.

837 86 Ludwig-Maximilians-University of Munich, Dr. von Hauner Children's Hospital, Division of
838 Metabolic Diseases and Nutritional Medicine, Munich, Germany.

839 87 Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI,
840 USA.

841 88 School of Nursing, University of Michigan, Ann Arbor, MI, USA.

842 89 Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK.

843 90 Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway.

844 91 Channing Division of Network Medicine, Brigham & Women's Hospital and Harvard Medical
845 School, Boston, MA, USA.

846 92 Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine,
847 Winston-Salem, NC, USA.

848 93 Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden.

849 94 Center for Innovative Medicine (CIMED), Karolinska Institutet, Stockholm, Sweden.

850 95 Sachs' Children's Hospital, Stockholm, Sweden.

851 96 Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton,
852 Southampton, UK.

853 97 Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain.

854 98 Department of Internal Medicine, Henry Ford Health System, Detroit, MI, USA.

855 99 National Institute for Health Research (NIHR) Southampton Biomedical Research Centre,
856 University of Southampton and University Hospital Southampton National Health Service (NHS)
857 Foundation Trust, Southampton, UK.

858 100 Institute for Health and Care Research (EMGO), VU University, Amsterdam, the Netherlands.

859 101 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of
860 Copenhagen, Copenhagen, Denmark.

861 102 Department of Medicine, Stanford School of Medicine, Stanford, California, USA.

862 103 University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital,
863 Department of Pediatric Pulmonology and Pediatric Allergology, Groningen Research Institute for
864 Asthma and COPD (GRIAC), Groningen, the Netherlands.

865 104 Respiratory Epidemiology, Occupational Medicine and Public Health; National Heart and Lung
866 Institute; Imperial College; London, UK.

867 105 Medical Research Council-Public Health England Centre for Environment and Health, School
868 of Public Health, Imperial College London, London, UK.

869 106 Department of Bioengineering and Therapeutic Sciences, University of California, San
870 Francisco, CA, USA.

871 107 Department of Clinical Experimental Research, Rigshospitalet, Glostrup, Denmark.

872 108 Department of Epidemiology and Biostatistics, Medical Research Council (MRC) Health
873 Protection Agency (HPE) Centre for Environment and Health, School of Public Health, Imperial
874 College London, London, UK.

875 109 Center for Life Course Epidemiology, Faculty of Medicine, University of Oulu, Oulu, Finland.

876 110 Unit of Primary Care, Oulu University Hospital,
877 Oulu, Finland.

878 111 Department of Dermatology, Ninewells Hospital and Medical School, Dundee, UK.

879 112 These authors contributed equally to this work.

880 113 These authors jointly directed this work.

881 114 All authors.

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

883

884 **Endometrial Cancer Association Consortium (ECAC)**

885 Amanda B Spurdle¹, Tracy A O'Mara¹, Jodie N Painter¹, The Australian National Endometrial
886 Cancer Study Group (ANECs)¹, Mark McEvoy², John Attia^{2, 3}, Elizabeth G Holliday^{2, 3}, Rodney J
887 Scott³⁻⁶, Deborah J Thompson⁷, Douglas F Easton^{7, 8}, Alison M Dunning⁸, Paul D P Pharoah⁸, Mitul
888 Shah⁸, Shahana Ahmed⁸, Catherine S Healey⁸, Ian Tomlinson⁹, Timothy HT Cheng⁹, Lynn Martin⁹,
889 Maggie Gorman⁹, Shirley Hodgson¹⁰, National Study of Endometrial Cancer Genetics Group
890 (NSECG)⁹, Peter A Fasching^{11, 12}, Alexander Hein¹², Matthias W Beckmann¹², Arif B Ekici¹³,
891 Matthias Rübner¹², Per Hall¹⁴, Kamila Czene¹⁴, Jingmei Li¹⁴, Hatef Darabi¹⁴, Thilo Dörk¹⁵, Ingo
892 Runnebaum¹⁶, Matthias Dürst¹⁶, Peter Hillemanns¹⁷, Diether Lambrechts^{18, 19}, Frederic Amant²⁰,
893 Stefanie Schrauwen²⁰, Jeroen Depreuw¹⁸⁻²⁰, Ellen L Goode²¹, Sean C Dowdy²², Stacey J
894 Winham²¹, Brooke L Fridley²³, Helga B Salvesen^{24, 25}, Henrica MJ Werner^{24, 25}, Tormund S
895 Njølstad^{24, 25}, Jone Trovik^{24, 25}, Katie Ashton^{3, 5, 6}, Tony Proietto²⁶, Geoffrey Otton²⁶, Emma Tham²⁷,
896 Miriam Mints²⁸, RENDOCAS²⁷

897

898 ¹ Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute,
899 Brisbane, QLD, 4006, Australia. ² Centre for Clinical Epidemiology and Biostatistics, School of
900 Medicine and Public Health, University of Newcastle, NSW, 2305, Australia. ³ Hunter Medical
901 Research Institute, John Hunter Hospital, Newcastle, NSW, 2305, Australia. ⁴ Hunter Area
902 Pathology Service, John Hunter Hospital, Newcastle, NSW, 2305, Australia. ⁵ Centre for
903 Information Based Medicine, University of Newcastle, NSW, 2308, Australia. ⁶ School of
904 Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, NSW, 2308, Australia. ⁷
905 Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care,
906 University of Cambridge, Cambridge, CB1 8RN, UK. ⁸ Centre for Cancer Genetic Epidemiology,

907 Department of Oncology, University of Cambridge, Cambridge, CB1 8RN, UK. ⁹ Wellcome Trust
908 Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK. ¹⁰ Department of
909 Clinical Genetics, St George's, University of London, London, SW17 0RE, UK. ¹¹ University of
910 California at Los Angeles, Department of Medicine, Division of Hematology/Oncology, David
911 Geffen School of Medicine, Los Angeles, CA, 90095, USA.

912 ¹² Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander
913 University Erlangen-Nuremberg, Erlangen, 91054, Germany. ¹³ Institute of Human Genetics,
914 University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen,
915 91054, Germany. ¹⁴ Department of Medical Epidemiology and Biostatistics, Karolinska Institutet,
916 Stockholm, SE-171 77, Sweden. ¹⁵ Hannover Medical School, Gynaecology Research Unit,
917 Hannover, 30625, Germany. ¹⁶ Department of Gynaecology, Jena University Hospital - Friedrich
918 Schiller University, Jena, 07743, Germany. ¹⁷ Hannover Medical School, Clinics of Gynaecology
919 and Obstetrics, Hannover, 30625, Germany. ¹⁸ Vesalius Research Center, Leuven, 3000, Belgium.
920 ¹⁹ Laboratory for Translational Genetics, Department of Oncology, University Hospitals Leuven,
921 Leuven, 3000, Belgium. ²⁰ Department of Obstetrics and Gynecology, Division of Gynecologic
922 Oncology, University Hospitals, KU Leuven - University of Leuven, 3000, Belgium. ²¹ Department
923 of Health Sciences Research, Mayo Clinic, Rochester, MN, 55905, USA. ²² Department of
924 Obstetrics and Gynecology, Division of Gynecologic Oncology, Mayo Clinic, Rochester, MN,
925 55905, USA. ²³ Department of Biostatistics, University of Kansas Medical Center, Kansas City,
926 KS, 66160, USA. ²⁴ Centre for Cancerbiomarkers, Department of Clinical Science, The University
927 of Bergen, 5020, Norway.

928 ²⁵ Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, 5021,
929 Norway.

930 ²⁶ School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, 2308,
931 Australia.

932 ²⁷ Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, SE-171 77,
933 Sweden. ²⁸ Department of Women's and Children's Health, Karolinska Institutet, Karolinska
934 University Hospital, Stockholm, SE-171 77, Sweden.

935

936 **Glioma GWAS**

937

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

944

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

957

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 at <http://cancergenome.nih.gov>

961

962 **Endometriosis GWA meta-analysis**

963 Dale R Nyholt^{1,16}, Siew-Kee Low^{2,16}, Carl A Anderson³, Jodie N Painter¹, Satoko Uno^{2,4}, Andrew P
964 Morris⁵, Stuart MacGregor¹, Scott D Gordon¹, Anjali K Henders¹, Nicholas G Martin¹, John
965 Attia^{6,7}, Elizabeth G Holliday^{6,7}, Mark McEvoy^{6,8,9}, Rodney J Scott^{7,10,11}, Stephen H Kennedy¹²,
966 Susan A Treloar¹³, Stacey A Missmer¹⁴, Sosuke Adachi¹⁵, Kenichi Tanaka¹⁵, Yusuke Nakamura²,
967 Krina T Zondervan^{5,12,17}, Hitoshi Zembutsu^{2,17} & Grant W Montgomery^{1,17}

968

969 ¹Queensland Institute of Medical Research, Brisbane, Queensland, Australia. ²Laboratory of
970 Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo,
971 Tokyo, Japan.

972 ³Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK.

973 ⁴First Department of Surgery, Sapporo Medical University, School of Medicine, Sapporo, Japan.

974 ⁵Genetic and Genomic Epidemiology Unit, Wellcome Trust Centre for Human Genetics, University
975 of Oxford, Oxford, UK.

976 ⁶Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health,
977 University of Newcastle, Newcastle, New South Wales, Australia.

978 ⁷Centre for Bioinformatics, Biomarker Discovery and Information-Based Medicine, Hunter Medical
979 Research Institute, Newcastle, New South Wales, Australia.

980 ⁸School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales,
981 Australia.

982 ⁹Public Health Research Program, Hunter Medical Research Institute, Newcastle, New South
983 Wales, Australia.

984 ¹⁰School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, New South
985 Wales, Australia.

986 ¹¹Division of Genetics, Hunter Area Pathology Service, Newcastle, New South Wales, Australia.

987 ¹²Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe
988 Hospital, Oxford, UK.

989 ¹³Centre for Military and Veterans' Health, University of Queensland, Mayne Medical School,
990 Brisbane, Queensland, Australia.

991 ¹⁴Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's
992 Hospital and Harvard Medical School, Boston, Massachusetts, USA. ¹⁵Department of Obstetrics
993 and Gynecology, Niigata University Graduate School of Medical and Dental Sciences, Niigata,
994 Japan.

995 ¹⁶These authors contributed equally to this work. ¹⁷These authors jointly directed this work.

996

997 *Funding*

998 *QIMR*: The QIMR study was supported by grants from the National Health and Medical Research
999 Council (NHMRC) of Australia (241944, 339462, 389927, 389875, 389891, 389892, 389938,
1000 443036, 442915, 442981, 496610, 496739, 552485 and 552498), the Cooperative Research Centre
1001 for Discovery of Genes for Common Human Diseases (CRC), Cerylid Biosciences (Melbourne) and
1002 donations from N. Hawkins and S. Hawkins. D.R.N. was supported by the NHMRC Fellowship
1003 (339462 and 613674) and Australian Research Council (ARC) Future Fellowship (FT0991022)
1004 schemes. S.M. was supported by NHMRC Career Development Awards (496674 and 613705).
1005 E.G.H. (631096) and G.W.M. (339446 and 619667) were supported by the NHMRC Fellowship
1006 scheme. The HCS was funded by the University of Newcastle, the Gladys M Brawn Fellowship
1007 scheme and the Vincent Fairfax Family Foundation in Australia. *OX*: The work presented here was

1008 supported by a grant from the Wellcome Trust (WT084766/Z/08/Z) and makes use of Wellcome
1009 Trust Case Control Consortium 2 (WTCCC2) control data generated by the WTCCC. A full list of
1010 the investigators who contributed to the generation of these data is available at the Wellcome Trust
1011 website (<http://www.wtccc.org.uk/>). Funding for the WTCCC project was provided by the
1012 Wellcome Trust under awards 076113 and 085475. C.A.A. was supported by a grant from the
1013 Wellcome Trust (098051). A.P.M. was supported by a Wellcome Trust Senior Research
1014 Fellowship. S.H.K. is supported by the Oxford Partnership Comprehensive Biomedical Research
1015 Centre, with funding from the Department of Health National Institute for Health Research (NIHR)
1016 Biomedical Research Centres funding scheme. K.T.Z. is supported by a Wellcome Trust Research
1017 Career Development Fellowship (WT085235/Z/08/Z). **BBJ**: We thank the members of the Rotary
1018 Club of Osaka-Midosuji District 2660 Rotary International in Japan for supporting our study. This
1019 work was conducted as part of the BioBank Japan Project that was supported by the Ministry of
1020 Education, Culture, Sports, Science and Technology of the Japanese government.

1021

1022 **European Periodontitis Genetics Group (EPG)**

1023 The GWAS of aggressive periodontitis (AgP) was supported by a research grant of the Deutsche
1024 Forschungsgemeinschaft DFG (GZ: SCHA 1582/3-1). The cohort case description has been
1025 previously reported in Schaefer A.S. *et al.* Genetic evidence for PLASMINOGEN as a shared
1026 genetic risk factor of coronary artery disease and periodontitis. *Circ Cardiovasc Genet* **8**, 159-67
1027 (2015). The investigators who contributed to the generation of this case sample are: Henrik
1028 Dommisch¹, Christian Graetz², Inga Harks³, Yvonne Jockel-Schneider⁴, Jörg Eberhardt⁵, Joerg
1029 Meyle⁶, Peter Eickholz⁷, Mathias Folwaczny⁸, Barbara Noack⁹, Wolfgang Lieb¹⁰, Christof Doerfer²,
1030 Corinna Bruckmann¹¹, Søren Jepsen¹²

1031 *Author affiliations*

1032 ¹Charité – University Medicine Berlin, Institute of Dental, Oral and Maxillary Medicine,
1033 Department of Periodontology, Berlin, Germany

1034 ²Department of Operative Dentistry and Periodontology, University Medical Center Schleswig-
1035 Holstein, Kiel, Germany

1036 ³Center of Periodontology, Operative and Preventive Dentistry, University Medical Center Münster,
1037 Germany

1038 ⁴Department of Periodontology, Clinic of Preventive Dentistry and Periodontology, University
1039 Medical Center of the Julius-Maximilians-University, Würzburg, Germany

1040 ⁵Department of Conservative Dentistry, Periodontology and Preventive Dentistry, Hannover
1041 Medical School, Hannover, Germany

1042 ⁶Department of Periodontology, University Medical Center Giessen and Marburg, Germany

1043 ⁷Department of Periodontology, Centre for Dental, Oral, and Maxillofacial Medicine (Carolinum),
1044 Johann Wolfgang Goethe-University, Frankfurt am Main, Germany

1045 ⁸Department of Preventive Dentistry and Periodontology, University of Munich, Germany

1046 ⁹Center of Periodontology, Operative and Preventive Dentistry, Clinic of Preventive Dentistry,
1047 University Medical Center Carl Gustav Carus der Technischen Universität Dresden, Germany

1048 ¹⁰Biobank popgen, University Medical Center Schleswig-Holstein, Campus Kiel, Germany

1049 ¹¹Department of Conservative Dentistry and Periodontology, Clinic of Dentistry, Bernhard Gottlieb
1050 University, Vienna, Austria

1051 ¹²Department of Periodontology, Operative and Preventive Dentistry, University of Bonn, Bonn,
1052 Germany

1053

1054 Genotyping of the AgP cases was performed on an IScan system with HumanOmni BeadChips
1055 (Illumina) at the Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel,
1056 Germany. We specially thank Andre Franke and Stefan Schreiber.

1057 The aggressive periodontitis control sample consists of three independent studies:

1058 1. The Heinz-Nixdorff-Recall (HNR) was described in Schermund, A., *et al.* Assessment of
1059 clinically silent atherosclerotic disease and established and novel risk factors for predicting

1060 myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the
1061 Heinz Nixdorf RECALL Study. Risk Factors, Evaluation of Coronary Calcium and Lifestyle. *Am*
1062 *Heart J* **144**, 212-18 (2002). The HNR study was supported by the Heinz Nixdorf Foundation
1063 (Germany). Additionally, the study was funded by the German Ministry of Education and Science
1064 and the German Research Council (DFG; Project SI 236/8-1, SI236/9-1, ER 155/6-1). The
1065 genotyping of the Illumina HumanOmni-1 Quad BeadChips of the HNR subjects was financed by
1066 the German Centre for Neurodegenerative Disorders (DZNE), Bonn. We are extremely grateful to
1067 all investigators who contributed to the generation of this dataset.

1068 The HNR study is represented by Per Hoffmann^{1,2} and Bastian Krone³

1069 *Authors Affiliations*

1070 ¹Institute of Human Genetics, University of Bonn, Germany

1071 ²Human Genomics Research Group, Department of Biomedicine, University Hospital of Basel,

1072 Switzerland

1073 ³Bastian Krone, Institute of Medical Informatics, Biometry and Epidemiology, University Clinic

1074 Essen, Germany.

1075 2. The Dortmund Health Study (DOGS) is described in Berger, K. *et. al.* DHS: The Dortmund
1076 health study. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* **55**, 816-21 (2012).

1077 DOGS is supported by the German Migraine & Headache Society (DMKG) and by unrestricted
1078 grants of equal share from Almirall, Astra Zeneca, Berlin Chemie, Boehringer, Boots Health Care,
1079 Glaxo-Smith-Kline, Janssen Cilag, McNeil Pharma, MSD Sharp & Dohme and Pfizer to the
1080 University of Muenster (collection of sociodemographic and clinical data). Blood collection in the
1081 Dortmund Health Study was done through funds from the Institute of Epidemiology and Social
1082 Medicine University of Muenster.

1083 DOGS is represented by Klaus Berger¹ and Jürgen Wellmann¹

1084 *Authors Affiliations*

1085 ¹Institute of Epidemiology and Social Medicine, University Münster, Germany.

1086 3. The FOCUS (Food chain plus) control sample is described in Muller, N., *et al.* IL-6 blockade by
1087 monoclonal antibodies inhibits apolipoprotein (a) expression and lipoprotein (a) synthesis in
1088 humans. *J Lipid Res* **56**, 1034-42 (2015). FOCUS was supported by the Federal Ministry of
1089 Education and Research BMBF (FKZ 0315540A). FOCUS is represented by Matthias Laudes¹
1090 ¹Clinic of Internal Medicine I, University Medical Center Schleswig-Holstein, Kiel, Germany
1091

1092 **The International Genomics of Alzheimer's Project (IGAP)**

1093 We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results
1094 data for these analyses. The investigators within IGAP contributed to the design and
1095 implementation of IGAP and/or provided data but did not participate in analysis or writing of this
1096 report. IGAP was made possible by the generous participation of the control subjects, the patients,
1097 and their families. The i-Select chips was funded by the French National Foundation on
1098 Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of
1099 excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille,
1100 Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical
1101 Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome
1102 Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF):
1103 Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was
1104 partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES
1105 contract N01-AG-12100, the NHLBI grant R01 HL105756, the Icelandic Heart Association, and
1106 the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA
1107 grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant
1108 ADGC-10-196728.

1109

1110 *Material and methods*

1111 International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon
1112 genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP
1113 used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-
1114 analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases
1115 and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease
1116 Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic
1117 Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium –
1118 GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set
1119 of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed
1120 combining results from stages 1 & 2.

1121

1122 **The Japanese Collaboration Team for GWAS of Panic Disorder**

1123 Tsukasa Sasaki¹, Yoshiya Kawamura², Takeshi Otowa^{3,4}, Mamoru Tochigi⁵, Fumichika
1124 Nishimura⁴, Hisashi Tani, Katsushi Tokunaga⁷, Hisanobu Kaiya⁸, Yuji Okazaki⁹

1125

1126 1 Department of Physical and Health Education, Graduate School of Education, The University of
1127 Tokyo, Japan

1128 2 Department of Psychiatry, Shonan Kamakura General Hospital, Kanagawa, Japan

1129 3 Major of Professional Clinical Psychology, Graduate School of Clinical Psychology, Teikyo
1130 Heisei University, Tokyo, Japan

1131 4 Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Japan

1132 5 Department of Psychiatry, Teikyo University School of Medicine, Tokyo, Japan

1133 6 Department of Psychiatry, Graduate School of Medicine, Mie University, Tsu, Japan

1134 7 Department of Human Genetics, Graduate School of Medicine, The University of Tokyo, Japan

1135 8 Anxiety Disorder Research Center, Warakukai Medical Cooperation, Tokyo, Japan

1136 9 Metropolitan Matsuzawa Hospital, Tokyo, Japan

1137

1138 **Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)**

1139 Data on glycaemic traits have been contributed by MAGIC investigators and have been downloaded
1140 from www.magicinvestigators.org. The investigators within MAGIC did not participate in the
1141 analysis, writing or interpretation of this paper.

1142

1143 **Melanoma meta-analysis consortium (MC)**

1144 Matthew H. Law¹, D. Timothy Bishop², Jeffrey E. Lee³, Myriam Brossard^{4,5,66}, Nicholas G.
1145 Martin⁶, Eric K. Moses⁷, Fengju Song⁸, Jennifer H. Barrett², Rajiv Kumar⁹, Douglas F. Easton¹⁰,
1146 Paul D. P. Pharoah¹¹, Anthony J. Swerdlow^{12,13}, Katerina P. Kypreou¹⁴, , Lisa Bowdler⁴², Leanne
1147 Wallace⁴², Anjali Henders⁴², John C. Taylor², Mark Harland², Juliette Randerson-Moor², Lars A.
1148 Akslen^{15,16}, Per A. Andresen¹⁷, Marie-Françoise Avril¹⁸, Esther Azizi^{19,20}, Giovanna Bianchi
1149 Scarrà^{21,22}, Kevin M. Brown²³, Tadeusz Dębniak²⁴, David L. Duffy⁶, David E. Elder²⁵, Shenyang
1150 Fang³, Eitan Friedman²⁰, Pilar Galan²⁶, Paola Ghiorzo^{21,22}, Elizabeth M. Gillanders²⁷, Alisa M.
1151 Goldstein²³, Nelleke A. Gruis²⁸, Johan Hansson²⁹, Per Helsing³⁰, Marko Hočevár³¹, Veronica
1152 Höiom²⁹, Christian Ingvar³², Peter A. Kanetsky³³, Wei V. Chen³⁴, GenoMEL Consortium³⁵, Essen-
1153 Heidelberg Investigators³⁵, The SDH Study Group³⁵, Q-MEGA and QTWIN Investigators³⁵, AMFS
1154 Investigators³⁵, ATHENS Melanoma Study Group³⁵, Maria Teresa Landi²³, Julie Lang³⁶, G. Mark
1155 Lathrop³⁷, Jan Lubiński²⁴, Rona M. Mackie^{38,39}, Graham J. Mann⁴⁰, Anders Molven^{16,41}, Grant W.
1156 Montgomery⁴², Srdjan Novaković⁴³, Håkan Olsson^{44,45}, Susana Puig^{46,47}, Joan Anton Puig-
1157 Butille^{46,47}, Abrar A. Qureshi⁴⁸, Graham L. Radford-Smith^{49,50,51}, Nienke van der Stoep⁵², Remco
1158 van Doorn²⁸, David C. Whiteman⁵³, Jamie E. Craig⁵⁴, Dirk Schadendorf^{55,56}, Lisa A. Simms⁴⁹,
1159 Kathryn P. Burdon⁵⁷, Dale R. Nyholt^{58,42}, Karen A. Pooley¹⁰, Nicholas Orr⁵⁹, Alexander J.
1160 Stratigos¹⁴, Anne E. Cust⁶⁰, Sarah V. Ward⁷, Nicholas K. Hayward⁶¹, Jiali Han^{62,63}, Hans-Joachim
1161 Schulze⁶⁴, Alison M. Dunning¹¹, Julia A. Newton Bishop², Florence Demenais⁶⁶, Christopher I.
1162 Amos^{65,66}, Stuart MacGregor^{1,67}, Mark M. Iles^{2,67}

1163

1164 ¹ Statistical Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia

1165 ² Section of Epidemiology and Biostatistics, Leeds Institute of Cancer and Pathology, University of
1166 Leeds, Leeds, UK

1167 ³ Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center,
1168 Houston, Texas, USA

1169 ⁴ Institut National de la Santé et de la Recherche Médicale (INSERM), UMR-946, Genetic
1170 Variation and Human Diseases Unit, Paris, France

1171 ⁵ Institut Universitaire d'Hématologie, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

1172 ⁶ Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Australia

1173 ⁷ Centre for Genetic Origins of Health and Disease, Faculty of Medicine, Dentistry and Health
1174 Sciences, The University of Western Australia, Western Australia, Australia

1175 ⁸ Departments of Epidemiology and Biostatistics, Key Laboratory of Cancer Prevention and
1176 Therapy, Tianjin, National Clinical Research Center of Cancer, Tianjin Medical University Cancer
1177 Institute and Hospital, Tianjin, P. R. China

1178 ⁹ Division of Molecular Genetic Epidemiology, German Cancer Research Center, Im Neuenheimer
1179 Feld 580, Heidelberg Germany

1180 ¹⁰ Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care,
1181 University of Cambridge, Cambridge, UK

1182 ¹¹ Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge,
1183 Cambridge, UK

1184 ¹² Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK

1185 ¹³ Division of Breast Cancer Research, The Institute of Cancer Research, London, UK

1186 ¹⁴ Department of Dermatology, University of Athens School of Medicine, Andreas Sygros Hospital,
1187 Athens, Greece

1188 ¹⁵ Centre for Cancer Biomarkers CCBIO, Department of Clinical Medicine, University of Bergen,
1189 Bergen, Norway

1190 ¹⁶ Department of Pathology, Haukeland University Hospital, Bergen, Norway

1191 ¹⁷ Department of Pathology, Molecular Pathology, Oslo University Hospital, Rikshospitalet, Oslo,
1192 Norway

1193 ¹⁸ Assistance Publique–Hôpitaux de Paris, Hôpital Cochin, Service de Dermatologie, Université
1194 Paris Descartes, Paris, France

1195 ¹⁹ Department of Dermatology, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine,
1196 Tel Aviv, Israel

1197 ²⁰ Oncogenetics Unit, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv
1198 University, Tel Aviv, Israel

1199 ²¹ Department of Internal Medicine and Medical Specialties, University of Genoa, Genoa, Italy

1200 ²² Laboratory of Genetics of Rare Cancers, Istituto di ricovero e cura a carattere scientifico Azienda
1201 Ospedaliera Universitaria (IRCCS AOU) San Martino-IST Istituto Nazionale per la Ricerca sul
1202 Cancro, Genoa, Italy

1203 ²³ Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of
1204 Health, Bethesda, Maryland, USA

1205 ²⁴ International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland

1206 ²⁵ Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the
1207 University of Pennsylvania, Philadelphia, Pennsylvania, USA

1208 ²⁶ Université Paris 13, Equipe de Recherche en Epidémiologie Nutritionnelle (EREN), Centre de
1209 Recherche en Epidémiologie et Statistiques, Institut National de la Santé et de la Recherche
1210 Médicale (INSERM U1153), Institut National de la Recherche Agronomique (INRA U1125),
1211 Conservatoire National des Arts et Métiers, Communauté d'Université Sorbonne Paris Cité, F-
1212 93017 Bobigny, France

1213 ²⁷ Inherited Disease Research Branch, National Human Genome Research Institute, National
1214 Institutes of Health, Baltimore, Maryland, USA

1215 ²⁸ Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands

1216 ²⁹ Department of Oncology-Pathology, Karolinska Institutet, Karolinska University Hospital,
1217 Stockholm, Sweden

1218 ³⁰ Department of Dermatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

1219 ³¹ Department of Surgical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia

1220 ³² Department of Surgery, Clinical Sciences, Lund University, Lund, Sweden

1221 ³³ Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute,
1222 Tampa, Florida, USA

1223 ³⁴ Department of Genetics, The University of Texas MD Anderson Cancer Center, Houston, Texas,
1224 USA

1225 ³⁵ A full list of members and affiliations appears in the Supplementary Note.

1226 ³⁶ Department of Medical Genetics, University of Glasgow, Glasgow, UK

1227 ³⁷ McGill University and Genome Quebec Innovation Centre, Montreal, Canada

1228 ³⁸ Department of Public Health, University of Glasgow, Glasgow UK

1229 ³⁹ Department of Medical Genetics, University of Glasgow, Glasgow, UK

1230 ⁴⁰ Centre for Cancer Research, University of Sydney at Westmead, Millennium Institute for Medical
1231 Research and Melanoma Institute Australia, Sydney, Australia

1232 ⁴¹ Gade Laboratory for Pathology, Department of Clinical Medicine, University of Bergen, Bergen,
1233 Norway

1234 ⁴² Molecular Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Australia

1235 ⁴³ Department of Molecular Diagnostics, Institute of Oncology Ljubljana, Ljubljana, Slovenia

1236 ⁴⁴ Department of Oncology/Pathology, Clinical Sciences, Lund University, Lund; Sweden

1237 ⁴⁵ Department of Cancer Epidemiology, Clinical Sciences, Lund University, Lund, Sweden

1238 ⁴⁶ Melanoma Unit, Dermatology Department & Biochemistry and Molecular Genetics Departments,
1239 Hospital Clinic, Institut de Investigació Biomèdica August Pi Suñe, Universitat de Barcelona,
1240 Barcelona, Spain
1241 ⁴⁷ Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Raras, Instituto de Salud
1242 Carlos III, Barcelona, Spain
1243 ⁴⁸ Department of Dermatology, The Warren Alpert Medical School of Brown University, Rhode
1244 Island, USA
1245 ⁴⁹ Inflammatory Bowel Diseases, QIMR Berghofer Medical Research Institute, Brisbane, Australia
1246 ⁵⁰ Department of Gastroenterology and Hepatology, Royal Brisbane & Women's Hospital,
1247 Brisbane, Australia
1248 ⁵¹ University of Queensland School of Medicine, Herston Campus, Brisbane, Australia
1249 ⁵² Department of Clinical Genetics, Center of Human and Clinical Genetics, Leiden University
1250 Medical Center, Leiden, The Netherlands
1251 ⁵³ Cancer Control Group, QIMR Berghofer Medical Research Institute, Brisbane, Australia
1252 ⁵⁴ Department of Ophthalmology, Flinders University, Adelaide, Australia
1253 ⁵⁵ Department of Dermatology, University Hospital Essen, Essen, Germany
1254 ⁵⁶ German Consortium Translational Cancer Research (DKTK), Heidelberg, Germany
1255 ⁵⁷ Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
1256 ⁵⁸ Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane,
1257 Queensland, Australia
1258 ⁵⁹ Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, London, UK
1259 ⁶⁰ Cancer Epidemiology and Services Research, Sydney School of Public Health, The University of
1260 Sydney, Australia
1261 ⁶¹ Oncogenomics, QIMR Berghofer Medical Research Institute, Brisbane, Australia
1262 ⁶² Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University,
1263 Indianapolis, Indiana, USA

1264 ⁶³ Melvin and Bren Simon Cancer Center, Indiana University, Indianapolis, Indiana, USA

1265 ⁶⁴ Department of Dermatology, Fachklinik Hornheide, Institute for Tumors of the Skin at the
1266 University of Münster, Münster, Germany

1267 ⁶⁵ Department of Community and Family Medicine, Geisel School of Medicine, Dartmouth College,
1268 Hanover, New Hampshire, USA

1269 ⁶⁶ These authors contributed equally to this work

1270 ⁶⁷ These authors jointly supervised this work

1271

1272 The melanoma meta-analysis consortium was supported by CRUK Programme grants
1273 (C588/A19167 C8197/A10123, C8197/A10865), NIH grant (R01CA083115, RO1CA001833) NIH
1274 NCI (CA88363, CA83115, CA122838, CA87969, CA055075, CA100264, CA133996 and
1275 CA49449), the NHMRC (200071, 241944, 339462, 380385, 389927, 389875, 389891, 389892,
1276 389938, 443036, 442915, 442981, 496610, 496675, 496739, 552485, 552498, 66946, 107359,
1277 211172, 402761, 535074, 1023911).

1278

1279 *Groups contributing to the melanoma meta-analysis*

1280

1281 *GenoMEL Consortium*

1282 *Australian Melanoma Family Study: see below.*

1283 *Barcelona:* Paula Aguilera, Beatriz Alejo, Celia Badenas, Abel Caño, Cristina Carrera, Francisco
1284 Cuellar, Mireia Dominguez, Daniel Gabriel, Pol Gimenez-Xavier, Pablo Iglesias, Josep Malvehy,
1285 Rosa Marti-Laborda, Montse Mila, Zighe Ogbah, Miriam Potrony, Joan-Anton Puig Butille, Susana
1286 Puig, Gemma Tell and Other members of the Melanoma Unit: Llúcia Alós, Ana Arance, Pedro
1287 Arguís, Antonio Bennassar, Oscar Chirife, Carlos Conill, Ramon Rull, Marcelo Sánchez, Sergi
1288 Vidal-Sicart, Antonio Vilalta.

1289 *Brisbane:* See Q-MEGA authorship below.

1290 *Emilia-Romagna*: Maria Teresa Landi, Donato Calista, Giorgio Landi, Paola Minghetti, Fabio
1291 Arcangeli, Pier Alberto Bertazzi.

1292 *Genoa*: Department of Internal Medicine and Medical Specialties, Laboratory of Genetics of Rare
1293 Cancers, University of Genoa/ IRCCS AOU San Martino-IST Istituto Nazionale per la Ricerca sul
1294 Cancro: Giovanna Bianchi Scarrà, Paola Ghiorzo, Lorenza Pastorino, William Bruno, Virginia
1295 Andreotti, Claudia Martinuzzi, Linda Battistuzzi, Paola Origone. Medical Oncology Unit, IRCCS
1296 AOU San Martino-IST Istituto Nazionale per la Ricerca sul Cancro, Genoa :Paola Queirolo.

1297 *Glasgow*: Rona Mackie, Julie Lang.

1298 *Leeds*: Julia A Newton Bishop, Paul Affleck, Jennifer H Barrett, D Timothy Bishop, Jane Harrison,
1299 Mark M Iles, Juliette Randerson-Moor, Mark Harland, John C Taylor, Linda Whittaker, Kairen
1300 Kukulizch, Susan Leake, Birute Karpavicius, Sue Haynes, Tricia Mack, May Chan, Yvonne Taylor,
1301 John Davies, Paul King.

1302 *Leiden: Department of Dermatology, Leiden University Medical Centre*: Nelleke A Gruis, Frans A
1303 van Nieuwpoort, Coby Out, Clasine van der Drift, Wilma Bergman, Nicole Kukutsch, Jan Nico
1304 Bouwes Bavinck. *Department of Clinical Genetics, Centre of Human and Clinical Genetics, Leiden*
1305 *University Medical Centre*: Bert Bakker, Nienke van der Stoep, Jeanet ter Huurne. *Department of*
1306 *Dermatology, Haga Hospital, The Hague*: Han van der Rhee. *Department of Dermatology, Reinier*
1307 *de Graaf Groep, Delft*: Marcel Bekkenk. *Department of Dermatology, Sint Franciscus Gasthuis,*
1308 *Rotterdam*: Dyon Snels, Marinus van Praag. *Department of Dermatology, Ghent University*
1309 *Hospital, Ghent, Belgium*: Lieve Brochez and colleagues. *Department of Dermatology, St. Radboud*
1310 *University Medical Centre, Nijmegen*: Rianne Gerritsen and colleagues. *Department of*
1311 *Dermatology, Rijnland Hospital, Leiderdorp*: Marianne Crijns and colleagues. *Dutch patient*
1312 *organisation, Stichting Melanoom, Purmerend. The Netherlands Foundation for the detection of*
1313 *Hereditary Tumors, Leiden*: Hans Vasen. *ServiceXS*: Wilbert van Workum, Bart Janssen, Marjolein
1314 Janssen and Suzanne Mulder

1315 *Lund*: Lund Melanoma Study Group: Håkan Olsson, Christian Ingvar, Göran Jönsson, Åke Borg,
1316 Anna Måsbäck, Lotta Lundgren, Katja Baeckenhorn, Kari Nielsen, Anita Schmidt Casslén.
1317 *Norway: Oslo University Hospital*: Per Helsing, Per Arne Andresen, Helge Rootwelt. *University of*
1318 *Bergen*: Lars A. Akslen, Anders Molven.
1319 *Paris (MELARISK study)*: Florence Demenais, Marie-Françoise Avril, Brigitte Bressac-de
1320 Paillerets, Eve Maubec, Myriam Brossard, Amaury Vaysse, Hamida Mohamdi, Patricia Jeannin,
1321 Valérie Chaudru, Nicolas Chateigner, Eve Corda, Fabienne Lesueur, Mahaut de Lichy and the
1322 French Family Study Group including the following oncogeneticists and Dermatologists: Pascale
1323 Andry-Benzaquen, Bertrand Bachollet, Frédéric Bérard, Pascaline Berthet, Françoise Boitier,
1324 Valérie Bonadona, Jean-Louis Bonafé, Jean-Marie Bonnetblanc, Frédéric Cambazard, Olivier
1325 Caron, Frédéric Caux, Jacqueline Chevrant-Breton, Agnès Chompret (deceased), Stéphane Dalle,
1326 Liliane Demange, Olivier Dereure, Martin-Xavier Doré, Marie-Sylvie Doutre, Catherine Dugast,
1327 Laurence Faivre, Florent Grange, Philippe Humbert, Pascal Joly, Delphine Kerob, Christine Lasset,
1328 Marie Thérèse Leccia, Gilbert Lenoir, Dominique Leroux, Julien Levang, Dan Lipsker, Sandrine
1329 Mansard, Ludovic Martin, Tanguy Martin-Denavit, Christine Mateus, Jean-Loïc Michel, Patrice
1330 Morel, Laurence Olivier-Faivre, Jean-Luc Perrot, Caroline Robert, Sandra Ronger-Savle, Bruno
1331 Sassolas, Pierre Souteyrand, Dominique Stoppa-Lyonnet, Luc Thomas, Pierre Vabres, Eva
1332 Wierzbicka.
1333 *Philadelphia*: David Elder, Peter Kanetsky, Jillian Knorr, Michael Ming, Nandita Mitra, Althea
1334 Ruffin, Patricia Van Belle
1335 *Poland*: Tadeusz Dębniak, Jan Lubiński, Aneta Mirecka, Sławomir Ertmański. *Slovenia*: Srdjan
1336 Novakovic, Marko Hocevar, Barbara Peric, Petra Cerkovnik. *Stockholm*: Veronica Höiom, Johan
1337 Hansson. *Sydney*: Graham J. Mann, Richard F. Kefford, Helen Schmid, Elizabeth A. Holland
1338 *Tel Aviv*: Esther Azizi, Gilli Galore-Haskel, Eitan Friedman, Orna Baron-Epel, Alon Scope, Felix
1339 Pavlotsky, Emanuel Yakobson, Irit Cohen-Manheim, Yael Laitman, Roni Milgrom, Iris Shimoni,
1340 Evgeniya Kozlova.

1341 *Australian Melanoma Family Study investigators*

1342 Anne E. Cust¹, Helen Schmid², Elizabeth A. Holland², Joanne F. Aitken³, Bruce K. Armstrong¹,

1343 Graham G. Giles^{3,4}, Richard F. Kefford², John L. Hopper⁵ Mark A. Jenkins⁵, Graham J. Mann²

1344 1) Cancer Epidemiology and Services Research, Sydney School of Public Health, The
1345 University of Sydney, Australia

1346 2) Centre for Cancer Research, University of Sydney at Westmead Millennium Institute for
1347 Medical Research and Melanoma Institute Australia, Sydney, Australia

1348 3) Viertel Centre for Research in Cancer Control, Cancer Council Queensland, Spring Hill,
1349 Brisbane, Australia

1350 4) Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia

1351 5) Centre for Molecular, Environmental, Genetic and Analytic (MEGA) Epidemiology,
1352 Melbourne School of Population Health, University of Melbourne, Melbourne, Australia

1353

1354 *IBD investigators*

1355 Lisa Simms¹, Grant W. Montgomery², Peter Visscher³

1356 1) Inflammatory Bowel Diseases Laboratory, QIMR Berghofer Medical Research Institute,
1357 Brisbane, Australia

1358 2) Molecular Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Australia

1359 3) The Queensland Brain Institute, The University of Queensland, QBI Building, St Lucia,
1360 Queensland 4071, Australia.

1361

1362 *Q-MEGA and QTWIN investigators*

1363 The Queensland study of Melanoma: Environmental and Genetic Associations (Q- MEGA)

1364 Principal Investigators are: Nicholas G. Martin¹, Grant W. Montgomery¹, David Duffy¹, David C.

1365 Whiteman¹, Matthew H. Law¹, Stuart MacGregor¹, Nicholas K. Hayward¹. The Australian Cancer

1366 Study (ACS) Principal Investigators are: David C. Whiteman¹, Penny Webb¹, Adele Green¹, Peter
1367 Parsons¹, David Purdie¹, Nicholas K.Hayward¹.
1368 QTWIN: Zhen Zhen Zhao¹, Joanne F Aitken², Anjali K.Henders¹, Mitchell Stark¹, David L. Duffy¹,
1369 Jodie N. Painter¹
1370 1 QIMR Berghofer, Brisbane, QLD 4029, Australia
1371 2 Viertel Centre for Research in Cancer Control, Cancer Council Queensland, Spring Hill,
1372 Brisbane, Australia
1373
1374 *The SDH Study Group*
1375 Study of Digestive Health (SDH) Team
1376 Chief Investigators
1377 David Whiteman, Adele Green, Nicholas Hayward, Peter Parsons, Sandra Pavey, David Purdie,
1378 Penny Webb (Queensland Institute of Medical Research)
1379 David Gotley, Mark Smithers (University of Queensland / Princess Alexandra Hospital)
1380 Paul Drew, Glyn Jamieson (University of Adelaide)
1381 Paul Drew, David Watson (Flinders University of South Australia)
1382 Andrew Clouston (Mayne Pathology)
1383
1384 *Research Staff*
1385 D Nancarrow
1386 D Hussey
1387 E Smith
1388 G Mayne
1389
1390 *Project Manager* S O'Brien (QIMR)
1391 *Data Manager* T Sadkowsky (QIMR)

1392

1393 Research Nurses

1394 QLD-

1395 A McMurtrie, L Terry, M Connard, L Jackman, S Perry, M Davis

1396

1397 SA-

1398 D Roffe, M Martin, L Smith

1399

1400 *Clinical Collaborators*

1401 QLD-

1402 A Clouston (Envoi Pathology)

1403 I Brown (S&N Pathology)

1404 N Walker (QML Pathology)

1405 SA-

1406 Justin Bessell (Flinders Medical Centre)

1407 William Tam (Royal Adelaide Hospital)

1408 Andrew Ruskowicz (Institute of Medical and Veterinary Science)

1409

1410 *Essen-Heidelberg investigators*

1411 Rajiv Kumar (r.kumar@dkfz.de)

1412 Division of Molecular Genetic Epidemiology, German Cancer Research Center, Im Neuenheimer

1413 Feld 580, 69120 Heidelberg Germany

1414 Dirk Schadendorf (Dirk.Schadendorf@uk-essen.de)

1415 Department of Dermatology, University Hospital Essen, 45122 Essen, Germany

1416 and

1417 German Consortium Translational Cancer Research (DKTK), 69120 Heidelberg, Germany

1418 Hans-Joachim Schulze(Schulze@fachklinik-hornheide.de)
1419 Department of Dermatology, Fachklinik Hornheide, Institute for Tumors of the Skin at the
1420 University of Münster, Germany
1421 Kari Hemminki (k.hemminki@dkfz.de)
1422 Division of Molecular Genetic Epidemiology, German Cancer Research Center, Im Neuenheimer
1423 Feld 580, 69120 Heidelberg, Germany
1424 Antje Sucker (antje.sucker@uk-essen.de)
1425 Department of Dermatology, University Hospital Essen, 45122 Essen, Germany, German
1426 Consortium Translational Cancer Research, 69120 Heidelberg, Germany
1427 Thomas Vogt (thomas.vogt@uks.eu)
1428 University Hospital Saarland, Department of Dermatology, Venerology and Allergology, Building
1429 18, Kirrberger Straße, D - 66424 Homburg/Saar, Germany
1430 Johan Hansson (johan.hansson@ki.se)
1431 Department of Oncology Pathology, Karolinska Institutet, Karolinska University Hospital, Solna S
1432 171 76, Stockholm, Sweden.
1433 Ralf Gutzmer (Gutzmer.Ralf@mh-hannover.de)
1434 Department of Dermatology and Allergy, Skin Cancer Center Hannover, Hannover Medical School,
1435 Carl-Neuberg-Str. 1, 30625 Hannover, Germany
1436 Helen Gogas (hgogas@hol.gr)
1437 1st Department of Medicine, University of Athens Medical School, Laiko Hospital,
1438 PO 14120, 11510, Athens, Greece
1439 Dave Hoon (hoon@jwci.org)
1440 John Wayne Cancer Institute, 2200 Santa Monica Blvd, Santa Monica, CA 90404, USA
1441 Eduardo Nagore (eduardo_nagore@ono.com)
1442 Department of Dermatology, Instituto Valenciano de Oncologia, Valencia 46009, Spain
1443 John Kirkwood (kirkwoodjm@upmc.edu)

1444 Dermatology & Translational Science, Melanoma and Skin Cancer Program, 5117 Centre Avenue,
1445 Suite 1.32, Pittsburgh, PA 15213, USA
1446 Benjamin Weide (benjamin.weide@med.uni-tuebingen.de)
1447 Department of Dermatology, University Medical Center, Liebermeisterstr. 25, 72076 Tübingen,
1448 Germany
1449 Piotr Rutkowski (rutkowski@coi.waw.pl)
1450 Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial
1451 Cancer Center and Institute of Oncology, Roentgena 5, 02-781 Warsaw, Poland
1452 Selma Ugurel (Selma.Ugurel@uk-essen.de)
1453 Department of Dermatology, University Hospital Essen, 45122 Essen, Germany, German
1454 Consortium Translational Cancer Research, 69120 Heidelberg, Germany
1455 *ATHENS Melanoma Study Group - investigators*
1456 Katerina Kypreou, Fani Karagianni, Kyriaki Antonopoulou, Dorothea Polydorou, Vasiliki Hasapi,
1457 Michaela Plaka, Nelli Gousetti, Othon Papadopoulos, Christina Antoniou, Alexander Stratigos
1458 (Department of Dermatology, Andreas Sygros Hospital, Athens, Greece)
1459 Helen Gogas (Department of Internal Medicine, Laikon Hospital, University of Athens, Athens,
1460 Greece)
1461 Vangelis Evangelou (Department of Epidemiology, University of Ioannina, Ioannina, Greece)
1462
1463 **The Multi-Ethnic Study of Atherosclerosis (MESA)**
1464 The MESA and the MESA SHARe project are conducted and supported by the National Heart,
1465 Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA
1466 is provided by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-
1467 HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168,
1468 N01-HC-95169, UL1-TR-001079, UL1-TR-000040, and DK063491. Funding for SHARe
1469 genotyping was provided by NHLBI Contract N02-HL-64278. Genotyping was performed at

1470 Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT (Boston,
1471 Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0. Funding support
1472 for the Lung CT dataset was provided by grants R01-HL077612 and RC1-HL100543.NIH
1473 Intramural award ZIAEY00403 supported the collection of eye-related data in MESA.

1474

1475 **The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS)**

1476 We would like to thank the participants and staff of the Nurses' Health Study, the Health
1477 Professionals Follow-Up Study for their valuable contributions as well as the following state cancer
1478 registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD,
1479 MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The
1480 authors assume full responsibility for analyses and interpretation of these data. This work was
1481 supported by NIH R01 CA49449, P01 CA87969, UM1 CA186107, and UM1 CA167552.

1482

1483 **GWAS of non-alcoholic fatty liver disease (hepatic steatosis)**

1484 Bratati Kahali and Elizabeth K Speliotes were supported by the Doris Duke Medical Foundation,
1485 NIH grant R01DK106621-01, the University of Michigan Internal Medicine Department, Division
1486 of Gastroenterology, the University of Michigan Biological Sciences Scholars Program and The
1487 Central Society for Clinical Research.

1488

1489 **Pancreatic cancer case-control consortium (PanC4)**

1490 The Mayo Clinic Molecular Epidemiology of Pancreatic Cancer study was supported by the Mayo
1491 Clinic SPORE in Pancreatic Cancer (P50CA102701). The Yale University study was supported by
1492 grant number 5R01CA098870 from the NCI. The work at Johns Hopkins University was supported
1493 by NCI Grants P50CA62924 and R01CA97075 and the Lustgarten Foundation for Pancreatic
1494 Cancer Research. The Pancreas Tumor Registry at Memorial Sloan Kettering Cancer Center was
1495 supported by NIH P30CA008748 and the Goldstein Fund for Prevention, Control and Population

1496 Research. The work at MD Anderson was supported by NIH Grant R01CA98380. The UCSF
1497 study was supported in part by NCI Grants CA59706, CA108370, CA109767, CA89726, and
1498 CA98889 and by the Rombauer Pancreatic Cancer Research Fund. The University of Toronto
1499 study was supported by NIH Grant R01CA97075, the Lustgarten Foundation for Pancreatic Cancer
1500 Research, and the Ontario Cancer Research Network.

1501

1502 **Pancreatic Cancer Cohort Consortium (PanScan)**

1503 PanScan is the NCI cohort consortium genome-wide association study for pancreatic cancer. This
1504 research was supported by the Intramural Research Program of the National Institutes of Health,
1505 Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of
1506 Health, Department of Health and Human Services.

1507

1508 **The European Prospective Investigation into Cancer and Nutrition (EPIC) study**

1509 The coordination of EPIC is financially supported by the European Commission (DG-SANCO)
1510 and the International Agency for Research on Cancer. The national cohorts are supported by the
1511 Health Research Fund (FIS) of the Spanish Ministry of Health, Regional Governments of Andalucía,
1512 Asturias, Basque Country, Murcia (no.6236), Navarra and the Catalan Institute of Oncology, La
1513 Caixa (BM 06-130), Red Temática de Investigación Cooperativa en Cáncer (RD12/0036/0018;
1514 RD06/0020/0091; Spain); Danish Cancer Society (Denmark); Ligue contre le Cancer, Institut
1515 Gustave Roussy, Mutuelle Générale de l'Éducation Nationale, Institut National de la Santé et de la
1516 Recherche Médicale (INSERM; France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum
1517 (DKFZ) and Federal Ministry of Education and Research (Germany); the Hellenic Health
1518 Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro (AIRC) and National
1519 Research Council (Italy); Dutch Ministry of Public Health, Welfare, and Sports (VWS),
1520 Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON

1521 (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), and Statistics Netherlands
1522 (The Netherlands); Nordic Center of Excellence in Food, Nutrition, and Health Helga (Norway);
1523 Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skane and
1524 Vasterbotten (Sweden); Cancer Research UK (C570/A16491, R.C. Travis; 14136, K.T. Khaw) and
1525 Medical Research Council (G1000143, K.T. Khaw; United Kingdom).

1526

1527 **The PRACTICAL Consortium**

1528 (<http://practical.ccge.medschl.cam.ac.uk/>)

1529 Rosalind Eeles^{1, 2}, Doug Easton³, Zsofia Kote-Jarai¹, Ali Amin Al Olama³, Sara Benlloch³,
1530 Kenneth Muir⁴, Graham G. Giles^{5, 6}, Fredrik Wiklund⁷, Henrik Gronberg⁷, Christopher A.
1531 Haiman⁸, Johanna Schleutker^{9, 10}, Maren Weischer¹¹, Ruth C. Travis¹², David Neal¹³, Paul
1532 Pharoah¹⁴, Kay-Tee Khaw¹⁵, Janet L. Stanford^{16, 17}, William J. Blot¹⁸, Stephen Thibodeau¹⁹,
1533 Christiane Maier^{20, 21}, Adam S. Kibel^{22, 23}, Cezary Cybulski²⁴, Lisa Cannon-Albright²⁵, Hermann
1534 Brenner^{26, 27}, Jong Park²⁸, Radka Kaneva²⁹, Jyotsna Batra³⁰, Manuel R. Teixeira³¹, Hardev
1535 Pandha³²

1536

1537 ¹ The Institute of Cancer Research, London, SM2 5NG, UK, ² Royal Marsden NHS Foundation
1538 Trust, London, SW3 6JJ, UK, ³ Centre for Cancer Genetic Epidemiology, Department of Public
1539 Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Worts
1540 Causeway, Cambridge, UK, ⁴ University of Warwick, Coventry, UK, ⁵ Cancer Epidemiology
1541 Centre, Cancer Council Victoria, 615 St Kilda Road, Melbourne Victoria, Australia, ⁶ Centre for
1542 Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The
1543 University of Melbourne, Victoria, Australia, ⁷ Department of Medical Epidemiology and
1544 Biostatistics, Karolinska Institute, Stockholm, Sweden, ⁸ Department of Preventive Medicine, Keck
1545 School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los
1546 Angeles, California, USA, ⁹ Department of Medical Biochemistry and Genetics, University of

1547 Turku, Turku, Finland, ¹⁰ Institute of Biomedical Technology/BioMediTech, University of Tampere
1548 and FimLab Laboratories, Tampere, Finland, ¹¹ Department of Clinical Biochemistry, Herlev
1549 Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark, ¹²
1550 Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford,
1551 Oxford, UK, ¹³ Surgical Oncology (Uro-Oncology: S4), University of Cambridge, Box 279,
1552 Addenbrooke's Hospital, Hills Road, Cambridge, UK and Cancer Research UK Cambridge
1553 Research Institute, Li Ka Shing Centre, Cambridge, UK, ¹⁴ Centre for Cancer Genetic
1554 Epidemiology, Department of Oncology, University of Cambridge, Strangeways Research
1555 Laboratory, Worts Causeway, Cambridge, UK, ¹⁵ Cambridge Institute of Public Health, University
1556 of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 0SR, ¹⁶ Division of Public Health
1557 Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA, ¹⁷ Department of
1558 Epidemiology, School of Public Health, University of Washington, Seattle, Washington, USA, ¹⁸
1559 International Epidemiology Institute, 1455 Research Blvd., Suite 550, Rockville, MD 20850, ¹⁹
1560 Mayo Clinic, Rochester, Minnesota, USA, ²⁰ Department of Urology, University Hospital Ulm,
1561 Germany, ²¹ Institute of Human Genetics University Hospital Ulm, Germany, ²² Brigham and
1562 Women's Hospital/Dana-Farber Cancer Institute, 45 Francis Street- ASB II-3, Boston, MA 02115,
1563 ²³ Washington University, St Louis, Missouri, ²⁴ International Hereditary Cancer Center,
1564 Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland, ²⁵
1565 Division of Genetic Epidemiology, Department of Medicine, University of Utah School of
1566 Medicine²⁶ Division of Clinical Epidemiology and Aging Research & Division of Preventive
1567 Oncology, German Cancer Research Center, Heidelberg Germany, ²⁷German Cancer Consortium
1568 (DKTK), German Cancer Research Center (DKFZ), Heidelberg Germany, ²⁸Division of Cancer
1569 Prevention and Control, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, Florida, USA,
1570 ²⁹ Molecular Medicine Center and Department of Medical Chemistry and Biochemistry, Medical
1571 University - Sofia, 2 Zdrave St, 1431, Sofia, Bulgaria, ³⁰ Australian Prostate Cancer Research
1572 Centre-Qld, Institute of Health and Biomedical Innovation and Schools of Life Science and Public

1573 Health, Queensland University of Technology, Brisbane, Australia, ³¹ Department of Genetics,
1574 Portuguese Oncology Institute, Porto, Portugal and Biomedical Sciences Institute (ICBAS), Porto
1575 University, Porto, Portugal, ³²The University of Surrey, Guildford, Surrey, GU2 7XH, UK

1576

1577 *COGS acknowledgement and funding:*

1578 This study would not have been possible without the contributions of the following: Per Hall
1579 (COGS); Douglas F. Easton, Paul Pharoah, Kyriaki Michailidou, Manjeet K. Bolla, Qin Wang
1580 (BCAC), Andrew Berchuck (OCAC), Rosalind A. Eeles, Douglas F. Easton, Ali Amin Al Olama,
1581 Zsofia Kote-Jarai, Sara Benlloch (PRACTICAL), Georgia Chenevix-Trench, Antonis Antoniou,
1582 Lesley McGuffog, Fergus Couch and Ken Offit (CIMBA), Joe Dennis, Alison M. Dunning,
1583 Andrew Lee, and Ed Dicks, Craig Luccarini and the staff of the Centre for Genetic Epidemiology
1584 Laboratory, Javier Benitez, Anna Gonzalez-Neira and the staff of the CNIO genotyping unit,
1585 Jacques Simard and Daniel C. Tessier, Francois Bacot, Daniel Vincent, Sylvie LaBoissière and
1586 Frederic Robidoux and the staff of the McGill University and Génome Québec Innovation Centre,
1587 Stig E. Bojesen, Sune F. Nielsen, Borge G. Nordestgaard, and the staff of the Copenhagen DNA
1588 laboratory, and Julie M. Cunningham, Sharon A. Windebank, Christopher A. Hilker, Jeffrey Meyer
1589 and the staff of Mayo Clinic Genotyping Core Facility

1590

1591 Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework
1592 Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer
1593 Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384,
1594 C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978)
1595 and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 - the
1596 GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes
1597 of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen

1598 Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research
1599 Fund.

1600

1601 **Sarcoidosis GWAS**

1602 This work was supported by the German Federal Ministry of Education and Research (BMBF)
1603 within the framework of the e:Med research and funding concept (SysInflame grant 01ZX1306A).

1604 This project received infrastructure support from the DFG Excellence Cluster No. 306
1605 “Inflammation at Interfaces”. Andre Franke receives an endowment professorship by the
1606 Foundation for Experimental Medicine (Zuerich, Switzerland).

1607

1608 **The Singapore Epidemiology of Eye Diseases Study (SEED)**

1609 Jia Yu Koh,¹ Qiao Fan,¹ Wanting Zhao,¹ Blanche Lim,^{1,2} Jacqueline Chua,^{1,3} Paul Mitchell,⁴ Jie Jin
1610 Wang,^{4,5} Yik-Ying Teo,^{6,7} Tien Yin Wong,^{1,2,3} Ching-Yu Cheng^{1,2,3}

1611

- 1612 1. Singapore Eye Research Institute, Singapore National Eye Center, Singapore
- 1613 2. Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of
1614 Singapore, Singapore
- 1615 3. Duke-NUS Medical School, Singapore
- 1616 4. Department of Ophthalmology, Centre for Vision Research, Westmead Millennium
1617 Institute, University of Sydney, Sydney, New South Wales, Australia
- 1618 5. Centre for Eye Research Australia (CERA), University of Melbourne, Royal Victorian Eye
1619 and Ear Hospital, Melbourne, Victoria, Australia
- 1620 6. Saw Swee Hock School of Public Health, National University Health System, National
1621 University of Singapore, Singapore
- 1622 7. Department of Statistics and Applied Probability, National University of Singapore,
1623 Singapore

1624

1625 **Acknowledgements of studies that contributed to the GWAS meta-analysis of telomere**
1626 **length⁴**

1627 *The Framingham Heart Study*

1628 The Framingham Heart Study is funded by National Institutes of Health contract N01-HC-25195.

1629 The Framingham GWAS component of this project was funded by the Division of Intramural

1630 Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

1631

1632 *TwinsUK*

1633 The study was funded by the Wellcome Trust; European Community's Seventh Framework

1634 Programme (FP7/2007-2013). The study also receives support from the National Institute for Health

1635 Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at

1636 Guy's and St Thomas' NHS Foundation Trust and King's College London.

1637

1638

1639

1640

1641

1642

1643

1644

1645

1646

1647 **References**

- 1648 1. Welter D, MacArthur J, Morales J, et al. The NHGRI GWAS Catalog, a curated resource of
1649 SNP-trait associations. *Nucleic Acids Res* 2014;42(Database issue):D1001-6.
- 1650 2. Hindorff LA LA, MacArthur J, Morales J, et al. A catalog of published genome-wide
1651 association studies [Internet]. [cited 2015 Jan 15];Available from:
1652 www.genome.gov/gwastudies
- 1653 3. Pooley KA, Bojesen SE, Weischer M, et al. A genome-wide association scan (GWAS) for
1654 mean telomere length within the COGS project: identified loci show little association with
1655 hormone-related cancer risk. *Hum Mol Genet* 2013;22(24):5056–64.
- 1656 4. Mangino M, Hwang S-J, Spector TD, et al. Genome-wide meta-analysis points to CTC1 and
1657 ZNF676 as genes regulating telomere homeostasis in humans. *Hum Mol Genet*
1658 2012;21(24):5385–94.
- 1659 5. Prescott J, Kraft P, Chasman DI, et al. Genome-wide association study of relative telomere
1660 length. *PLoS One* 2011;6(5):e19635.
- 1661 6. Gu J, Chen M, Shete S, et al. A genome-wide association study identifies a locus on
1662 chromosome 14q21 as a predictor of leukocyte telomere length and as a marker of
1663 susceptibility for bladder cancer. *Cancer Prev Res (Phila)* 2011;4(4):514–21.
- 1664 7. Codd V, Nelson CP, Albrecht E, et al. Identification of seven loci affecting mean telomere
1665 length and their association with disease. *Nat Genet* 2013;45(4):422–7.
- 1666 8. Codd V, Mangino M, van der Harst P, et al. Common variants near TERC are associated
1667 with mean telomere length. *Nat Genet* 2010;42(3):197–9.
- 1668 9. Liu Y, Cao L, Li Z, et al. A genome-wide association study identifies a locus on TERT for
1669 mean telomere length in Han Chinese. *PLoS One* 2014;9(1):e85043.

- 1670 10. Saxena R, Bjornnes A, Prescott J, et al. Genome-wide association study identifies variants in
1671 casein kinase II (CSNK2A2) to be associated with leukocyte telomere length in a Punjabi
1672 Sikh diabetic cohort. *Circ Cardiovasc Genet* 2014;7(3):287–95.
- 1673 11. Levy D, Neuhausen SL, Hunt SC, et al. Genome-wide association identifies OBFC1 as a
1674 locus involved in human leukocyte telomere biology. *Proc Natl Acad Sci U S A*
1675 2010;107(20):9293–8.
- 1676 12. Burgess S. Sample size and power calculations in Mendelian randomization with a single
1677 instrumental variable and a binary outcome. *Int J Epidemiol* 2014;43(3):922–9.
- 1678 13. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG, EPIC-InterAct
1679 Consortium. Using published data in Mendelian randomization : a blueprint for efficient
1680 identification of causal risk factors. *Eur J Epidemiol* 2015;30(7):543–52.
- 1681 14. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian
1682 randomization with some invalid instruments using a weighted median estimator. *Genet*
1683 *Epidemiol*
- 1684 15. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments:
1685 effect estimation and bias detection through Egger regression. *Int J Epidemiol*
1686 2015;44(2):512–25.
- 1687 16. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association
1688 and population-based linkage analyses. *Am J Hum Genet* 2007;81(3):559–75.
- 1689 17. Abecasis GR, Auton A, Brooks LD, et al. An integrated map of genetic variation from 1,092
1690 human genomes. *Nature* 2012;491(7422):56–65.
- 1691 18. Durinck S, Moreau Y, Kasprzyk A, et al. BioMart and Bioconductor: a powerful link
1692 between biological databases and microarray data analysis. *Bioinformatics*
1693 2005;21(16):3439–40.

- 1694 19. Durinck S, Spellman PT, Birney E, Huber W. Mapping identifiers for the integration of
1695 genomic datasets with the R/Bioconductor package biomaRt. *Nat Protoc* 2009;4(8):1184–91.
- 1696 20. Kinsella RJ, Kahari A, Haider S, et al. Ensembl BioMarts: a hub for data retrieval across
1697 taxonomic space. *Database* 2011;2011:bar030-bar030.
- 1698 21. Aschard H, Vilhjálmsdóttir BJ, Joshi AD, Price AL, Kraft P. Adjusting for heritable covariates
1699 can bias effect estimates in genome-wide association studies. *Am J Hum Genet*
1700 2015;96(2):329–39.
- 1701 22. Miyake Y, Nakamura M, Nabetani A, et al. RPA-like mammalian Ctc1-Stn1-Ten1 complex
1702 binds to single-stranded DNA and protects telomeres independently of the Pot1 pathway.
1703 *Mol Cell* 2009;36(2):193–206.
- 1704 23. Burgess S, Thompson SG. Bias in causal estimates from Mendelian randomization studies
1705 with weak instruments. *Stat Med* 2011;30(11):1312–23.
- 1706 24. Davey Smith G. Use of genetic markers and gene-diet interactions for interrogating
1707 population-level causal influences of diet on health. *Genes Nutr* 2011;6(1):27–43.
- 1708 25. Haycock PC, Burgess S, Wade KH, Bowden J, Relton C, Davey Smith G. Best (but oft-
1709 forgotten) practices: the design, analysis, and interpretation of Mendelian randomization
1710 studies. *Am J Clin Nutr* 2016;103(4):965–78.
- 1711 26. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference
1712 in epidemiological studies. *Hum Mol Genet* 2014;23(R1):R89-98.
- 1713 27. Schunkert H, König IR, Kathiresan S, et al. Large-scale association analysis identifies 13
1714 new susceptibility loci for coronary artery disease. *Nat Genet* 2011;43(4):333–8.
- 1715 28. Bown MJ, Jones GT, Harrison SC, et al. Abdominal aortic aneurysm is associated with a
1716 variant in low-density lipoprotein receptor-related protein 1. *Am J Hum Genet*
1717 2011;89(5):619–27.

- 1718 29. Borthwick K, Smelser D, Bock J, et al. Ephenotyping for Abdominal Aortic Aneurysm in the
1719 Electronic Medical Records and Genomics (eMERGE) Network: Algorithm Development
1720 and Konstanz Information Miner Workflow. *Int J Biomed Data Min* 2015;4(1).
- 1721 30. Dubois PC a, Trynka G, Franke L, et al. Multiple common variants for celiac disease
1722 influencing immune gene expression. *Nat Genet* 2010;42(4):295–302.
- 1723 31. Fingerlin TE, Murphy E, Zhang W, et al. Genome-wide association study identifies multiple
1724 susceptibility loci for pulmonary fibrosis. *Nat Genet* 2013;45(6):613–20.
- 1725 32. Wang Y, McKay JD, Rafnar T, et al. Rare variants of large effect in BRCA2 and CHEK2
1726 affect risk of lung cancer. *Nat Genet* 2014;46(7).
- 1727 33. Diskin SJ, Capasso M, Schnepf RW, et al. Common variation at 6q16 within HACE1 and
1728 LIN28B influences susceptibility to neuroblastoma. *Nat Genet* 2012;44(10):1126–30.
- 1729 34. Pharoah PDP, Tsai Y-Y, Ramus SJ, et al. GWAS meta-analysis and replication identifies
1730 three new susceptibility loci for ovarian cancer. *Nat Genet* 2013;45(4):362–70, 370-2.
- 1731 35. Spurdle AB, Thompson DJ, Ahmed S, et al. Genome-wide association study identifies a
1732 common variant associated with risk of endometrial cancer. *Nat Genet* 2011;43(5):451–4.
- 1733 36. Painter JN, O'Mara TA, Batra J, et al. Fine-mapping of the HNF1B multicancer locus
1734 identifies candidate variants that mediate endometrial cancer risk. *Hum Mol Genet*
1735 2015;24(5):1478–92.
- 1736 37. Purdue MP, Johansson M, Zelenika D, et al. Genome-wide association study of renal cell
1737 carcinoma identifies two susceptibility loci on 2p21 and 11q13.3. *Nat Genet* 2010;43(1):60–
1738 5.
- 1739 38. Turnbull C, Rapley E a, Seal S, et al. Variants near DMRT1, TERT and ATF7IP are
1740 associated with testicular germ cell cancer. *Nat Genet* 2010;42(7):604–7.

- 1741 39. Rapley EA, Turnbull C, Al Olama AA, et al. A genome-wide association study of testicular
1742 germ cell tumor. *Nat Genet* 2009;41(7):807–10.
- 1743 40. Amos CI, Wang L-E, Lee JE, et al. Genome-wide association study identifies novel loci
1744 predisposing to cutaneous melanoma. *Hum Mol Genet* 2011;20(24):5012–23.
- 1745 41. Rafnar T, Sulem P, Thorleifsson G, et al. Genome-wide association study yields variants at
1746 20p12.2 that associate with urinary bladder cancer. *Hum Mol Genet* 2014;23(20):5545–57.
- 1747 42. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals
1748 identifies 11 new susceptibility loci for Alzheimer’s disease. *Nat Genet* 2013;45(12):1452–8.
- 1749 43. Barrett JC, Clayton DG, Concannon P, et al. Genome-wide association study and meta-
1750 analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet* 2009;41(6):703–7.
- 1751 44. Walsh KM, Codd V, Rice T, et al. Longer genotypically-estimated leukocyte telomere length
1752 is associated with increased adult glioma risk. *Oncotarget* 2015;6(40):42468–77.
- 1753 45. Ojha J, Codd V, Nelson CP, et al. Genetic Variation Associated with Longer Telomere
1754 Length Increases Risk of Chronic Lymphocytic Leukemia. *Cancer Epidemiol Biomarkers
1755 Prev* 2016;25(7):1043–9.
- 1756 46. Snetselaar R, van Moorsel CHM, Kazemier KM, et al. Telomere length in interstitial lung
1757 diseases. *Chest* 2015;148(4):1011–8.
- 1758 47. Haycock PC, Heydon EE, Kaptoge S, Butterworth a. S, Thompson A, Willeit P. Leucocyte
1759 telomere length and risk of cardiovascular disease: systematic review and meta-analysis.
1760 *BMJ* 2014;349(jul08 3):g4227–g4227.
- 1761 48. Cottliar A, Palumbo M, La Motta G, et al. Telomere length study in celiac disease. *Am J
1762 Gastroenterol* 2003;98(12):2727–31.
- 1763 49. Atturu G, Brouillette S, Samani NJ, London NJM, Sayers RD, Bown MJ. Short leukocyte

- 1764 telomere length is associated with abdominal aortic aneurysm (AAA). *Eur J Vasc Endovasc*
1765 *Surg* 2010;39(5):559–64.
- 1766 50. Armanios M. Syndromes of telomere shortening. *Annu Rev Genomics Hum Genet*
1767 2009;10(46):45–61.
- 1768 51. Speedy HE, Di Bernardo MC, Sava GP, et al. A genome-wide association study identifies
1769 multiple susceptibility loci for chronic lymphocytic leukemia. *Nat Genet* 2014;46(1):56–60.
- 1770 52. Kim DHD, Lee S-T, Won H-H, et al. A genome-wide association study identifies novel loci
1771 associated with susceptibility to chronic myeloid leukemia. *Blood* 2011;117(25):6906–11.
- 1772 53. Postel-Vinay S, Véron AS, Tirode F, et al. Common variants near TARDBP and EGR2 are
1773 associated with susceptibility to Ewing sarcoma. *Nat Genet* 2012;44(3):323–7.
- 1774 54. Conde L, Halperin E, Akers NK, et al. Genome-wide association study of follicular
1775 lymphoma identifies a risk locus at 6p21.32. *Nat Genet* 2010;42(8):661–4.
- 1776 55. Cha P-CC, Zembutsu H, Takahashi A, Kubo M, Kamatani N, Nakamura Y. A genome-wide
1777 association study identifies SNP in DCC is associated with gallbladder cancer in the Japanese
1778 population. *J Hum Genet* 2012;57(4):235–7.
- 1779 56. Abnet CC, Freedman ND, Hu N, et al. A shared susceptibility locus in PLCE1 at 10q23 for
1780 gastric adenocarcinoma and esophageal squamous cell carcinoma. *Nat Genet*
1781 2010;42(9):764–7.
- 1782 57. Chubb D, Weinhold N, Broderick P, et al. Common variation at 3q26.2, 6p21.33, 17p11.2
1783 and 22q13.1 influences multiple myeloma risk. *Nat Genet* 2013;45(10):1221–5.
- 1784 58. Bei J-X, Li Y, Jia W-H, et al. A genome-wide association study of nasopharyngeal
1785 carcinoma identifies three new susceptibility loci. *Nat Genet* 2010;42(7):599–603.
- 1786 59. Tan DEK, Foo JN, Bei J-X, et al. Genome-wide association study of B cell non-Hodgkin

- 1787 lymphoma identifies 3q27 as a susceptibility locus in the Chinese population. *Nat Genet*
1788 2013;45(7):804–7.
- 1789 60. Zhang M, Song F, Liang L, et al. Genome-wide association studies identify several new loci
1790 associated with pigmentation traits and skin cancer risk in European Americans. *Hum Mol*
1791 *Genet* 2013;22(14):2948–59.
- 1792 61. Köhler A, Chen B, Gemignani F, et al. Genome-wide association study on differentiated
1793 thyroid cancer. *J Clin Endocrinol Metab* 2013;98(10):E1674–81.
- 1794 62. Li W-Q, Hu N, Hyland PL, et al. Genetic variants in DNA repair pathway genes and risk of
1795 esophageal squamous cell carcinoma and gastric adenocarcinoma in a Chinese population.
1796 *Carcinogenesis* 2013;34(7):1536–42.
- 1797 63. Hüffmeier U, Uebe S, Ekici AB, et al. Common variants at TRAF3IP2 are associated with
1798 susceptibility to psoriatic arthritis and psoriasis. *Nat Genet* 2010;42(11):996–9.
- 1799 64. Khor CC, Davila S, Breunis WB, et al. Genome-wide association study identifies FCGR2A
1800 as a susceptibility locus for Kawasaki disease. *Nat Genet* 2011;43(12):1241–6.
- 1801 65. Han F, Faraco J, Dong XS, et al. Genome wide analysis of narcolepsy in China implicates
1802 novel immune loci and reveals changes in association prior to versus after the 2009 H1N1
1803 influenza pandemic. *PLoS Genet* 2013;9(10):e1003880.
- 1804 66. Zhang X-J, Huang W, Yang S, et al. Psoriasis genome-wide association study identifies
1805 susceptibility variants within LCE gene cluster at 1q21. *Nat Genet* 2009;41(2):205–10.
- 1806 67. Fischer A, Schmid B, Ellinghaus D, et al. A novel sarcoidosis risk locus for Europeans on
1807 chromosome 11q13.1. *Am J Respir Crit Care Med* 2012;186(9):877–85.
- 1808 68. Hom G, Graham RR, Modrek B, et al. Association of Systemic Lupus Erythematosus with
1809 C8orf13–BLK and ITGAM–ITGAX. *N Engl J Med* 2008;358(9):900–9.

- 1810 69. Quan C, Ren Y-Q, Xiang L-H, et al. Genome-wide association study for vitiligo identifies
1811 susceptibility loci at 6q27 and the MHC. *Nat Genet* 2010;42(7):614–8.
- 1812 70. Xie G, Roshandel D, Sherva R, et al. Association of granulomatosis with polyangiitis
1813 (Wegener’s) with HLA-DPB1*04 and SEMA6A gene variants: evidence from genome-wide
1814 analysis. *Arthritis Rheum* 2013;65(9):2457–68.
- 1815 71. Wade TD, Gordon S, Medland S, et al. Genetic variants associated with disordered eating.
1816 *Int J Eat Disord* 2013;46(6):594–608.
- 1817 72. Otowa T, Yoshida E, Sugaya N, et al. Genome-wide association study of panic disorder in
1818 the Japanese population. *J Hum Genet* 2009;54(2):122–6.
- 1819 73. Simón-Sánchez J, Schulte C, Bras JM, et al. Genome-wide association study reveals genetic
1820 risk underlying Parkinson’s disease. *Nat Genet* 2009;41(12):1308–12.
- 1821 74. Tang CS, Sribudiani Y, Miao XP, et al. Fine mapping of the 9q31 Hirschsprung’s disease
1822 locus. *Hum Genet* 2010;127(6):675–83.
- 1823 75. Albagha OME, Wani SE, Visconti MR, et al. Genome-wide association identifies three new
1824 susceptibility loci for Paget’s disease of bone. *Nat Genet* 2011;43(7):685–9.
- 1825 76. Kim Y, Kong M, Lee C. Association of intronic sequence variant in the gene encoding
1826 spleen tyrosine kinase with susceptibility to vascular dementia. *World J Biol Psychiatry*
1827 2013;14(3):220–6.
- 1828 77. Figueroa JD, Ye Y, Siddiq A, et al. Genome-wide association study identifies multiple loci
1829 associated with bladder cancer risk. *Hum Mol Genet* 2014;23(5):1387–98.
- 1830 78. Zhang B, Jia W-H, Matsuda K, et al. Large-scale genetic study in East Asians identifies six
1831 new loci associated with colorectal cancer risk. *Nat Genet* 2014;46(6):533–42.
- 1832 79. Coronary Artery Disease (C4D) Genetics Consortium. A genome-wide association study in

- 1833 Europeans and South Asians identifies five new loci for coronary artery disease. *Nat Genet*
1834 2011;43(4):339–44.
- 1835 80. Rajaraman P, Melin BS, Wang Z, et al. Genome-wide association study of glioma and meta-
1836 analysis. *Hum Genet* 2012;131(12):1877–88.
- 1837 81. Noth I, Zhang Y, Ma S-F, et al. Genetic variants associated with idiopathic pulmonary
1838 fibrosis susceptibility and mortality: a genome-wide association study. *Lancet Respir Med*
1839 2013;1(4):309–17.
- 1840 82. Mushiroda T, Wattanapokayakit S, Takahashi a, et al. A genome-wide association study
1841 identifies an association of a common variant in TERT with susceptibility to idiopathic
1842 pulmonary fibrosis. *J Med Genet* 2008;45(10):654–6.
- 1843 83. Childs EJ, Mocci E, Campa D, et al. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1
1844 associated with susceptibility to pancreatic cancer. *Nat Genet* 2015;47(8):911–6.
- 1845 84. Baranzini SE, Wang J, Gibson RA, et al. Genome-wide association analysis of susceptibility
1846 and clinical phenotype in multiple sclerosis. *Hum Mol Genet* 2009;18(4):767–78.
- 1847 85. Tse KP, Su WH, Chang KP, et al. Genome-wide Association Study Reveals Multiple
1848 Nasopharyngeal Carcinoma-Associated Loci within the HLA Region at Chromosome
1849 6p21.3. *Am J Hum Genet* 2009;85(2):194–203.
- 1850 86. Li H, Gan W, Lu L, et al. A genome-wide association study identifies GRK5 and RASGRP1
1851 as type 2 diabetes loci in Chinese Hans. *Diabetes* 2013;62(1):291–8.
- 1852 87. van der Valk RJP, Kreiner-Møller E, Kooijman MN, et al. A novel common variant in
1853 DCST2 is associated with length in early life and height in adulthood. *Hum Mol Genet*
1854 2015;24(4):1155–68.
- 1855 88. Horikoshi M, Yaghooskar H, Mook-Kanamori DO, et al. New loci associated with birth
1856 weight identify genetic links between intrauterine growth and adult height and metabolism.

- 1857 Nat Genet 2013;45(1):76–82.
- 1858 89. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights
1859 for obesity biology. *Nature* 2015;518(7538):197–206.
- 1860 90. Bradfield JP, Taal HR, Timpson NJ, et al. A genome-wide association meta-analysis
1861 identifies new childhood obesity loci. *Nat Genet* 2012;44(5):526–31.
- 1862 91. Taal HR, St Pourcain B, Thiering E, et al. Common variants at 12q15 and 12q24 are
1863 associated with infant head circumference. *Nat Genet* 2012;44(5):532–8.
- 1864 92. Wood AR, Esko T, Yang J, et al. Defining the role of common variation in the genomic and
1865 biological architecture of adult human height. *Nat Genet* 2014;(November).
- 1866 93. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and
1867 insulin biology to body fat distribution. *Nature* 2015;518(7538):187–96.
- 1868 94. Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci
1869 associated with smoking behavior. *Nat Genet* 2010;42(5):441–7.
- 1870 95. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood
1871 pressure and cardiovascular disease risk. *Nature* 2011;478(7367):103–9.
- 1872 96. Wain L V, Verwoert GC, O'Reilly PF, et al. Genome-wide association study identifies six
1873 new loci influencing pulse pressure and mean arterial pressure. *Nat Genet*
1874 2011;43(10):1005–11.
- 1875 97. Rietveld CA, Medland SE, Derringer J, et al. GWAS of 126,559 individuals identifies
1876 genetic variants associated with educational attainment. *Science* 2013;340(6139):1467–71.
- 1877 98. Saxena R, Hivert M-F, Langenberg C, et al. Genetic variation in GIPR influences the glucose
1878 and insulin responses to an oral glucose challenge. *Nat Genet* 2010;42(2):142–8.
- 1879 99. Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose

- 1880 homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 2010;42(2):105–16.
- 1881 100. Soranzo N, Sanna S, Wheeler E, et al. Common variants at 10 genomic loci influence
1882 hemoglobin A₁(C) levels via glyceemic and nonglyceemic pathways. *Diabetes*
1883 2010;59(12):3229–39.
- 1884 101. van der Harst P, Zhang W, Mateo Leach I, et al. Seventy-five genetic loci influencing the
1885 human red blood cell. *Nature* 2012;492(7429):369–75.
- 1886 102. Willer CJ, Schmidt EM, Sengupta S, et al. Discovery and refinement of loci associated with
1887 lipid levels. *Nat Genet* 2013;45(11):1274–83.
- 1888 103. Köttgen A, Pattaro C, Böger C a, et al. New loci associated with kidney function and chronic
1889 kidney disease. *Nat Genet* 2010;42(5):376–84.
- 1890 104. Liao J, Su X, Chen P, et al. Meta-analysis of genome-wide association studies in multiethnic
1891 Asians identifies two loci for age-related nuclear cataract. *Hum Mol Genet*
1892 2014;23(22):6119–28.
- 1893 105. Speliotes EK, Yerges-Armstrong LM, Wu J, et al. Genome-wide association analysis
1894 identifies variants associated with nonalcoholic fatty liver disease that have distinct effects
1895 on metabolic traits. *PLoS Genet* 2011;7(3).
- 1896 106. Manichaikul A, Hoffman E a, Smolonska J, et al. Genome-wide study of percent emphysema
1897 on computed tomography in the general population. The Multi-Ethnic Study of
1898 Atherosclerosis Lung/SNP Health Association Resource Study. *Am J Respir Crit Care Med*
1899 2014;189(4):408–18.
- 1900 107. Huffman JE, Albrecht E, Teumer A, et al. Modulation of genetic associations with serum
1901 urate levels by body-mass-index in humans. *PLoS One* 2015;10(3):e0119752.
- 1902 108. McGrath M, Wong JYY, Michaud D, Hunter DJ, De Vivo I. Telomere length, cigarette

- 1903 smoking, and bladder cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev*
1904 2007;16(4):815–9.
- 1905 109. Weischer M, Nordestgaard BG, Cawthon RM, Freiberg JJ, Tybjærg-Hansen A, Bojesen SE.
1906 Short telomere length, cancer survival, and cancer risk in 47102 individuals. *J Natl Cancer*
1907 *Inst* 2013;105(7):459–68.
- 1908 110. Qu S, Wen W, Shu X-O, et al. Association of leukocyte telomere length with breast cancer
1909 risk: nested case-control findings from the Shanghai Women’s Health Study. *Am J*
1910 *Epidemiol* 2013;177(7):617–24.
- 1911 111. Kim S, Sandler DP, Carswell G, et al. Telomere length in peripheral blood and breast cancer
1912 risk in a prospective case-cohort analysis: results from the Sister Study. *Cancer Causes*
1913 *Control* 2011;22(7):1061–6.
- 1914 112. Pooley KA, Sandhu MS, Tyrer J, et al. Telomere length in prospective and retrospective
1915 cancer case-control studies. *Cancer Res* 2010;70(8):3170–6.
- 1916 113. Lee I-M, Lin J, Castonguay AJ, Barton NS, Buring JE, Zee RYL. Mean leukocyte telomere
1917 length and risk of incident colorectal carcinoma in women: a prospective, nested case-control
1918 study. *Clin Chem Lab Med* 2010;48(2):259–62.
- 1919 114. Zee RYL, Castonguay AJ, Barton NS, Buring JE. Mean telomere length and risk of incident
1920 colorectal carcinoma: a prospective, nested case-control approach. *Cancer Epidemiol*
1921 *Biomarkers Prev* 2009;18(8):2280–2.
- 1922 115. Cui Y, Cai Q, Qu S, et al. Association of leukocyte telomere length with colorectal cancer
1923 risk: nested case-control findings from the Shanghai Women’s Health Study. *Cancer*
1924 *Epidemiol Biomarkers Prev* 2012;21(10):1807–13.
- 1925 116. Prescott J, McGrath M, Lee I-M, Buring JE, De Vivo I. Telomere length and genetic
1926 analyses in population-based studies of endometrial cancer risk. *Cancer* 2010;116(18):4275–

- 1927 82.
- 1928 117. Walcott F, Rajaraman P, Gadalla SM, et al. Telomere length and risk of glioma. *Cancer*
1929 *Epidemiol* 2013;37(6):935–8.
- 1930 118. Hofmann JN, Lan Q, Cawthon R, et al. A prospective study of leukocyte telomere length and
1931 risk of renal cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2013;22(5):997–1000.
- 1932 119. Seow WJ, Cawthon RM, Purdue MP, et al. Telomere length in white blood cell DNA and
1933 lung cancer: a pooled analysis of three prospective cohorts. *Cancer Res* 2014;74(15):4090–8.
- 1934 120. Nan H, Du M, De Vivo I, et al. Shorter telomeres associate with a reduced risk of melanoma
1935 development. *Cancer Res* 2011;71(21):6758–63.
- 1936 121. Lynch SM, Major JM, Cawthon R, et al. A prospective analysis of telomere length and
1937 pancreatic cancer in the alpha-tocopherol beta-carotene cancer (ATBC) prevention study. *Int*
1938 *J Cancer* 2013;133(11):2672–80.
- 1939 122. Campa D, Mergarten B, De Vivo I, et al. Leukocyte telomere length in relation to pancreatic
1940 cancer risk: a prospective study. *Cancer Epidemiol Biomarkers Prev* 2014;23(11):2447–54.
- 1941 123. Julin B, Shui I, Heaphy CM, et al. Circulating leukocyte telomere length and risk of overall
1942 and aggressive prostate cancer. *Br J Cancer* 2015;112(4):769–76.
- 1943 124. Liang G, Qureshi AA, Guo Q, De Vivo I, Han J. No association between telomere length in
1944 peripheral blood leukocytes and the risk of nonmelanoma skin cancer. *Cancer Epidemiol*
1945 *Biomarkers Prev* 2011;20(5):1043–5.
- 1946 125. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. Leucocyte
1947 telomere length and risk of cardiovascular disease: systematic review and meta-analysis.
1948 *BMJ* 2014;349:g4227.
- 1949 126. Willeit P, Raschenberger J, Heydon EE, et al. Leucocyte Telomere Length and Risk of Type

- 1950 2 Diabetes Mellitus: New Prospective Cohort Study and Literature-Based Meta-Analysis.
1951 PLoS One 2014;9(11):e112483.
- 1952 127. Ma H, Zhou Z, Wei S, et al. Shortened telomere length is associated with increased risk of
1953 cancer: a meta-analysis. PLoS One 2011;6(6):e20466.
- 1954 128. Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA. The association of telomere length
1955 and cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2011;20(6):1238–50.
- 1956 129. Gretarsdottir S, Baas AF, Thorleifsson G, et al. Genome-wide association study identifies a
1957 sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic
1958 aneurysm. Nat Genet 2010;42(8):692–7.
- 1959 130. Jones GT, Bown MJ, Gretarsdottir S, et al. A sequence variant associated with sortilin-1
1960 (SORT1) on 1p13.3 is independently associated with abdominal aortic aneurysm. Hum Mol
1961 Genet 2013;22(14):2941–7.
- 1962 131. Harrison SC, Smith AJP, Jones GT, et al. Interleukin-6 receptor pathways in abdominal
1963 aortic aneurysm. Eur Heart J 2013;34(48):3707–16.
- 1964 132. Elmore JR, Obmann MA, Kuivaniemi H, et al. Identification of a genetic variant associated
1965 with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide association. J
1966 Vasc Surg 2009;49(6):1525–31.
- 1967 133. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide
1968 association scans. Bioinformatics 2010;26(17):2190–1.
- 1969