A Mendelian Randomisation Study of telomere length causality in Idiopathic Pulmonary Fibrosis and Chronic Obstructive Pulmonary Disease– Supplementary Material

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Summary of UK Biobank cohort numbers

Different cohorts were used for the genetic risk score analysis and the 2-sample Mendelian randomisation analysis. For the 2 sample Mendelian Randomisation, both unrelated and related participants were included whereas for the initial study using the genetic risk score, only unrelated participants were included. The breakdown of numbers in IPF, COPD and control cohorts is shown here.

Supplementary Table 1: Breakdown of UK Biobank cohort numbers used in analyses.

451 025 European Cases + Controls of which **379708** are unrelated	
Unrelated + Related (for 2 sample MR)	**Unrelated (for genetic risk score analyses)**
1621 (IPF 'broad') (of which 1369 'narrow')	1353 (IPF 'broad') (of which 1133 'narrow')
+ 13538 (COPD)	+ 11413 (COPD)
+ 435866 (controls)	+ 366942 (controls)
= 451025 Total	= **379708**

Selection of telomere length associated SNPs

The single nucleotide polymorphisms associated with telomere length derived from GWAS and chosen for our study are listed in Table 1, together with gene with which they are associated. Those assessed for use in our Mendelian randomisation genetic risk score are highlighted in Table 1b and those not selected are shown to be in linkage disequilibrium with them (ie $R^2>1$ or D'>0.8) and therefore do not qualify as independent variants.

Supplementary Table 2: Telomere length SNPs from Codd *et al* (N is number of individuals meta-analysed for each variant and Explained Variance is the explained percentage variance in leukocyte telomere length, Gene identifiers as supplied[1]).

SNP	Chr	Pos	Gene	N	Effect Allele	Other Allele	EA freq	β	SE	p-value	Explained Variance
rs11125529	2	54329370	ACYP2	37653	C	A	0.858	-0.056	0.010	4.48×10^{-8}	0.08%
rs10936599	3	170974795	TERC	37669	T	C	0.252	-0.097	0.008	2.54×10^{-31}	0.36%
rs7675998	4	164227270	NAF1	34694	A	G	0.217	-0.074	0.009	4.35×10^{-16}	0.19%
rs2736100	5	1339516	TERT	25842	A	C	0.514	-0.078	0.009	4.38×10^{-19}	0.31%
rs9420907	10	105666455	OBFC1	37653	A	C	0.865	-0.069	0.010	1.11×10^{-9}	0.11%
rs8105767	19	22007281	ZNF208	37499	A	G	0.709	-0.048	0.008	1.11×10^{-9}	0.09%
rs755017	20	61892066	RTEL1	37113	A	G	0.869	-0.062	0.011	6.71×10^{-9}	0.09%

Supplementary Table 3: Telomere length SNPs used by The Telomeres Mendelian Randomization Collaboration showing the extent of linkage disequilibrium where SNPs occur within the same chromosome in terms of D' (the normalised coefficient of linkage disequilibrium) and R squared (where R is the correlation coefficient between pairs of loci and depends on the allele frequency) for the sixteen variants identified. The SNPs are considered to have highly co-inherited variants when both D' and R squared are greater than 0.8 (shaded orange and grey respectively). The seven selected variants, which are not in linkage disequilibrium with any other SNP from the list, are highlighted in yellow. Gene identifiers are as supplied by The Telomeres Mendelian Randomization Collaboration [2].

							R squared													
	No	SNP	Chr	Gene	Variance explained %	SNP no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
D'	1	rs11125529	2	ACYP2																		
	2	rs6772228	3	PXK					0.00	0.00	0.00	0.00										
	3	rs12696304	3	TERC	0.319			0.11		0.88	0.88	0.99										
	4	rs10936599	3	TERC	0.319			0.02	0.99		1.00	0.88										
	5	rs1317082	3	TERC	0.319			0.02	0.99	1.00		0.88										
	6	rs10936601	3	TERC	0.319			0.11	1.00	1.00	1.00											
	7	rs7675998	4	NAF1																		
	8	rs2736100	5	TERT																		
	9	rs9419958	10	OBFC1	0.171											1.00	0.82					
	10	rs9420907	10	OBFC1	0.171										1.00		0.82					
	11	rs4387287	10	OBFC1	0.171										1.00	1.00						
	12	rs30277234	17	CTC1																		
	13	rs8105767	19	ZNF208																0.53		
	14	rs412658	19	ZNF676															0.86			
	15	rs6028466	20	DHX35																		0.00
	16	rs755017	20	ZBTB46																	0.03	

Differences between telomere associated SNPs in males and females

Since there is a known gender bias in IPF (it is more prevalent in males than in females [3] and this is replicated in the UK Biobank cohort, we tested the hypothesis that the effects of telomere length on IPF incidence may differ by repeating the one sample analysis separately in each sex. The beta values obtained in the telomere length source GWAS data [3] for males and females were compared using Fisher's z-score method [4] (Equation 3):

$$z = \frac{\beta_1 - \beta_2}{\sqrt{SE_1{}^2 + SE_2{}^2}}$$

Two of the seven beta values were found to differ significantly (see Supplementary Material, Table 3) so we used the gender specific values to create sex specific genetic risk scores for telomere length and repeated the regression analysis accordingly.

Supplementary Table 4: Source GWAS telomere length betas for males and females compared using Fisher's Z-score method. Those variants that are significantly different to P<0.05 are shown highlighted in green.

		Females		Males				
SNP	**Chr**	**Beta**	**SE**	**Beta**	**SE**		**Z score**	**P**
rs11125529	2	-0.068	0.014	-0.04	0.015		-1.364636501	0.086
rs10936599	3	-0.098	0.011	-0.101	0.012		0.184288535	
rs7675998	4	-0.061	0.012	-0.093	0.014		1.735443663	0.0475
rs2736100	5	-0.077	0.011	-0.082	0.014		0.280827978	
rs9420907	10	-0.069	0.014	-0.07	0.016		0.047036043	
rs8105767	19	-0.058	0.011	-0.032	0.011		-1.671343301	0.0475
rs755017	20	-0.05	0.014	-0.073	0.016		1.081828999	0.14

Additional UK Biobank demographics for different groups

In this section are the additional UK Biobank cohort demographics for IPF 'broad' definition in unrelated individuals compared with controls and for all three groupings (IPF 'narrow', IPF 'broad' and COPD) in the larger groups of related individuals compared with the larger group of unrelated controls. The findings in the related groups are very similar to the unrelated groups in all three cases.

Supplementary Table 5: Idiopathic Pulmonary Fibrosis data for the broad definition of IPF in unrelated individuals of European ancestry in UK Biobank (Odds ratios and p values are adjusted for age and sex).

[a] OR for continuous variable computed for a one-unit increase in that variable on the likelihood of disease outcome. Invert OR (1/OR) for the effect of a decrease in the continuous variable

[b] Male to Female OR

[c] OR versus "Never smoker" as the reference value

[d] Average household income in bands: 1 = <£18000; 2 = £18,000 – 30,999; 3 = £31,000 – £51,999; 4 = £52,000 – £100,000; 5 = >£100,000

Demographic	IPF Broad	Controls	OR	95% CI		P
N = 379,708	1,353	366,942				
Mean age at baseline (SD) Mean age at diagnosis (SD)	62.7 (6.02) 66.5 (7.7)	57.1 (8.0)	1.12[a]	1.11	1.13	$<1X10^{-15}$
Male sex, N (%)	817 (60.4%)	167,910 (45.8%)	1.72[b]	1.54	1.92	$<1X10^{-15}$
Female sex, N (%)	536 (39.6%)	199.032 (54.2%)				
Townsend Deprivation Index (SD)	-0.78 (3.2)	-1.53 (2.95)	1.10[a]	1.08	1.12	$<1X10^{-15}$
Pollution (SD), NO_2 µg/m^3	27.3 (8.2)	26.2 (7.4)	1.02[a]	1.02	1.03	$1.6x10^{-12}$
Smoking status						
Never smoker	425 (31.4%)	201,987 (55.1%)				
Former smoker	701 (51.8%)	128,242 (35.0%)	2.06[c]	1.83	2.33	$<1X10^{-15}$
Current smoker	199 (14.7%)	32,022 (8.73%)	3.30[c]	2.78	3.91	$<1X10^{-15}$
Missing	28 (2.1%)	5,104 (1.3%)				
Median Household Income (IQR)[d]	2 (1-3)	3 (2-4)	0.70[a]	0.66	0.74	$<1X10^{-15}$
Mean FEV (SD), L	2.35 (0.69)	2.77 (0.77)	0.36[a]	0.32	0.39	$<1X10^{-15}$
FEV1 percent predicted (SD)	84.4 (23.4)	91.1 (22.6)	0.99[a]	0.98	0.99	$<1X10^{-15}$
Mean FVC (SD), L	3.17 (0.89)	3.66 (1.00)	0.42[a]	0.39	0.46	$<1X10^{-15}$
FVC percent predicted (SD)	114.0 (29.8)	120.2 (29.6)	0.99[a]	0.99	0.99	$<1X10^{-15}$
Physical activity score (SD)	7.07 (1.31)	7.41 (1.13)	0.77[a]	0.73	0.81	$<1X10^{-15}$
Participants deceased, N (%)	*489 (36.1%)*	*10,977 (3.0%)*	*11.1*	*9.85*	*12.4*	$<1X10^{-15}$

Supplementary Table 6: Idiopathic Pulmonary Fibrosis data for the 'narrow' definition of IPF in related individuals of European ancestry in UK Biobank (Odds ratios and p values are adjusted for age and sex).

[a] OR for continuous variable computed for a one-unit increase in that variable on the likelihood of disease outcome. Invert OR (1/OR) for the effect of a decrease in the continuous variable

[b] Male to Female OR

[c] OR versus "Never smoker" as the reference value

[d] Average household income in bands: 1 = <£18000; 2 = £18,000 – 30,999; 3 = £31,000 – £51,999; 4 = £52,000 – £100,000; 5 = >£100,000

Demographic	IPF narrow only	Controls	OR	95% CI		P
N = 437,235	1,369	435,866				
Mean age at baseline (SD) Mean age at diagnosis (SD)	63.3 (5.82) 67.3 (7.6)	57.1 (8.02)	1.13[a]	1.12	1.14	$<1X10^{-15}$
Male sex, N (%)	843 (61.6%)	197,878 (45.4%)	1.83[b]	1.64	2.04	$<1X10^{-15}$
Female sex, N (%)	526 (38.4%)	237,988 (54.6%)				
Townsend Deprivation Index (SD)	-0.78 (3.34)	-1.53 (2.95)	1.10[a]	1.08	1.12	$<1X10^{-15}$
Pollution (SD), NO_2 µg/m^3	27.2 (7.8)	26.2 (7.3)	1.02[a]	1.02	1.03	$2.9x10^{-11}$
Smoking status						
Never smoker	410 (30.0%)	239,982 (55.1%)				
Former smoker	731 (53.4%)	152,597 (35.0%)	2.16[c]	1.91	2.44	$<1X10^{-15}$
Current smoker	200 (14.6%)	37,742 (8.7%)	3.47[c]	2.92	4.12	$<1X10^{-15}$
Missing	28 (2.0%)	5,545 (1.3%)				
Median Household Income (IQR)[d]	2 (1-3)	3 (2-4)	0.69[a]	0.65	0.73	$<1X10^{-15}$
Mean FEV1 (SD), L	2.35 (0.70)	2.77 (0.77)	0.36[a]	0.32	0.40	$<1X10^{-15}$
FEV1 percent predicted (SD)	85.0 (23.8)	91.0 (22.5)	0.97[a]	0.97	0.98	$<1X10^{-15}$
Mean FVC (SD), L	3.05 (0.96)	3.65 (1.00)	0.42[a]	0.39	0.46	$<1X10^{-15}$
FVC percent predicted (SD)	114.8 (30.3)	120.1 (29.6)	0.98[a]	0.97	0.98	$<1X10^{-15}$
Physical activity score (SD)	7.12 (1.32)	7.41 (1.13)	0.77[a]	0.73	0.80	$<1X10^{-15}$

Supplementary Table 7: Idiopathic Pulmonary Fibrosis data for the 'broad' definition of IPF in related individuals of European ancestry in UK Biobank (Odds ratios and p values are adjusted for age and sex).
[a] OR for continuous variable computed for a one-unit increase in that variable on the likelihood of disease outcome. Invert OR (1/OR) for the effect of a decrease in the continuous variable
[b] Male to Female OR
[c] OR versus "Never smoker" as the reference value
[d] Average household income in bands: 1 = <£18000; 2 = £18,000 – 30,999; 3 = £31,000 – £51,999; 4 = £52,000 – £100,000; 5 = >£100,000

Demographic	IPF Broad	Controls	OR	95% CI		P
N = 473,478	1,621	435,866				
Mean age at baseline (SD) Mean age at diagnosis (SD)	62.9 (6.01) 66.8 (7.75)	57.1 (8.02)	1.12[a]	1.11	1.13	$<1X10^{-15}$
Male sex, N (%)	959 (59.2%)	197,878 (45.4%)	1.66[b]	1.51	1.84	$<1X10^{-15}$
Female sex, N (%)	662 (40.8%)	237,988 (54.6%)				
Townsend Deprivation Index (SD)	-0.78 (3.33)	-1.53 (2.95)	1.10[a]	1.08	1.11	$<1X10^{-15}$
Pollution (SD), NO_2 µg/m^3	27.2 (8.0)	26.2 (7.3)	1.02[a]	1.02	1.03	$8.4x10^{-14}$
Smoking status						
Never smoker	506 (31.2%)	239,982 (55.1%)				
Former smoker	844 (52.1%)	152,597 (35.0%)	2.08[c]	1.86	2.32	$<1X10^{-15}$
Current smoker	238 (14.7%)	37,742 (8.7%)	3.37[c]	2.88	3.94	$<1X10^{-15}$
Missing	33 (2.0%)	5,545 (1.3%)				
Median Household Income (IQR)[d]	2 (1-3)	3 (2-4)	0.70[a]	0.66	0.74	$<1X10^{-15}$
Mean FEV (SD), L	2.35 (0.70)	2.77 (0.77)	0.36[a]	0.33	0.40	$<1X10^{-15}$
FEV1 percent predicted (SD)	84.6 (19.3)	91.0 (22.5)	0.97[a]	0.97	0.98	$<1X10^{-15}$
Mean FVC (SD), L	3.17 (0.90)	3.65 (1.00)	0.43[a]	0.40	0.46	$<1X10^{-15}$
FVC percent predicted (SD)	71.8 (24.3)	120.1 (29.6)	0.98[a]	0.97	0.98	$<1X10^{-15}$
Physical activity score (SD)	7.09 (1.29)	7.41 (1.13)	0.78[a]	0.74	0.81	$<1X10^{-15}$

Supplementary Table 8: COPD data in related individuals of European ancestry in UK Biobank (Odds ratios and p values are adjusted for age and sex).
[a] OR for continuous variable computed for a one-unit increase in that variable on the likelihood of disease outcome. Invert OR (1/OR) for the effect of a decrease in the continuous variable
[b] Male to Female OR
[c] OR versus "Never smoker" as the reference value
[d] Average household income in bands: 1 = <£18000; 2 = £18,000 – 30,999; 3 = £31,000 – £51,999; 4 = £52,000 – £100,000; 5 = >£100,000

Demographic	COPD	Controls	OR	95% CI		P
N = 449.404	13,538	435,866				
Mean age at baseline (SD) Mean age at diagnosis (SD)	62.0 (6.2) 65.4 (7.3)	57.1 (8.02)	1.09[a]	1.09	1.10	$<1X10^{-15}$
Male sex, N (%)	7,386 (54.6%)	197,878 (45.4%)	1.39[b]	1.34	1.44	$<1X10^{-15}$
Female sex, N (%)	6,152 (45.4%).	237,988 (54.6%)				
Townsend Deprivation Index (SD)	0.23 (3.54)	-1.53 (2.95)	1.20[a]	1.19	1.20	$<1X10^{-15}$
Pollution (SD), NO_2 µg/m^3	28.0 (7.7)	26.2 (7.3)	1.04[a]	1.03	1.04	$<1X10^{-15}$
Smoking status						
Never smoker	2,173 (16.1%)	239,982 (55.1%)				
Former smoker	6,458 (47.7%)	152,597 (35.0%)	3.86[c]	3.67	4.05	$<1X10^{-15}$
Current smoker	4,396 (32.5%)	37,742 (8.7%)	14.9[c]	14.1	15.7	$<1X10^{-15}$
Missing	511 (3.8%)	5,545 (1.3%)				
Median Household Income (IQR)[d]	1 (1-2)	3 (2-4)	0.53[a]	0.52	0.54	$<1X10^{-15}$
Mean FEV (SD), L	2.02 (0.72)	2.77 (0.77)	0.15[a]	0.15	0.16	$<1X10^{-15}$
FEV1 percent predicted (SD)	71.7 (24.0)	91.0 (22.5)	0.96[a]	0.96	0.96	$<1X10^{-15}$
Mean FVC (SD), L	3.05 (0.96)	3.65 (1.00)	0.34[a]	0.33	0.35	$<1X10^{-15}$
FVC percent predicted (SD)	108.2 (31.7)	120.1 (29.6)	0.97[a]	0.97	0.97	$<1X10^{-15}$
Physical activity score (SD)	7.12 (1.32)	7.41 (1.13)	0.79[a]	0.78	0.81	$<1X10^{-15}$

Evidence from 2-sample MR in UK Biobank and replication cohorts of a causal role for telomere length in IPF but not in COPD. Supplementary Table 9: Results from 2-sample MR for different cohorts using the IVW method and comparison of results with other methods. Results from the IVW model are usually quoted and P values showing significance using several models support those results. Here we see significant estimates for causality in IPF cohorts and not in COPD cohorts.

				2-sample Genetic (IVW) ^					2-sample Genetic (Egger)^^					2-sample Genetic (Median IV)^^				2-sample Genetic (Penalised Median)^^			
Cohort	Disease	Genetic instrument	N cases (controls)	Beta	SE	Odds (95%CI) of IPF per SD shorter telomere length	P	SNP P hetero*	Beta	SE	Odds (95%CI) of IPF per SD shorter telomere length	P	Egger intercept p-value	Beta	SE	Odds (95%CI) of IPF per SD shorter telomere length	P	Beta	SE	Odds (95%CI) of IPF per SD shorter telomere length	P
UK Biobank	IPF 'narrow'	7 SNP	1,369 (435,866)	1.4329	0.3003	4.19 (2.33-7.55)	**0.0031**	0.18	2.5698	1.426	13.06 (0.80-213)	0.1310	0.45	1.5067	0.3576	4.51 (2.24-9.09)	**$2.52x10^{-5}$**	1.2242	0.3658	3.40 (1.66-6.97)	**0.0008**
UK Biobank	IPF 'narrow'	6 SNP - no rs2736100	1,369 (435,866)	1.1454	0.2854	3.14 (1.80-5.500	**0.0102**		2.0033	1.219	7.41 (0.68-80.9)	0.1758	0.51	0.9323	0.3898	2.54 (1.18-5.45)	**0.0168**	0.9324	0.3661	2.54V(1.23-5.21)	**0.0109**
UK Biobank	IPF 'broad'	7 SNP	1,621 (435,866)	1.1876	0.3153	3.28 (1.77-6.08)	**0.0093**	0.072	2.3451	1.503	10.43 (0.55-199)	0.1790	0.47	1.1893	0.3276	3.28 (1.73-6.24)	**0.0003**	1.0479	0.3545	2.85 (1.42-5.71)	0.0031
UK Biobank	IPF 'broad'	6 SNP - no rs2736100	1,621 (435,866)	0.8478	0.2624	2.33 (1.40-3.90)	**0.0231**		1.6685	1.124	5.30(0.59-48.00)	0.2118	0.49	0.6809	0.3562	1.98 (0.98-3.97)	0.0559	0.6809	0.3555	1.98 (0.98-3.97)	0.0554
Replication 1	IPF	7 SNP	2,668 (8,591)	2.5119	0.4556	12.3 (5.05-30.1)	**0.0015**	**$1.5x10^{-4}$**	3.2463	2.278	25.7(0.30-2233)	0.2100	0.75	2.7954	0.3413	16.4 (8.39-32.0)	**$2.63x10^{-16}$**	2.7577	0.3764	15.8 (7.54-33.0)	**$2.37x10^{-13}$**
Replication 1	IPF	6 SNP - no rs2736100	2,668 (8,591)	2.1507	0.483	8.59 (3.33-22.1)	**0.0067**		2.546	2.207	12.8(0.17-965)	0.3129	0.86	2.4647	0.3611	11.8 (5.79-23.9)	**$8.71x10^{-12}$**	2.6752	0.373	14.5 (6.99-30.2)	**$7.36x10^{-13}$**
Replication 1	IPF	6 SNP - no rs7675998	2,668 (8,591)	2.9407	0.2382	18.9 (11.9-30.2)	$6.17x10^{-5}$	0.39	3.6444	1.075	38.3 (4.65-315)	0.027	0.54	2.9761	0.3553	19.6 (9.77-39.3)	$5.56x10^{-17}$	2.9761	0.3495	19.6 (9.89-38.9)	$1.65x10^{-17}$
UK Biobank	COPD	7 SNP	13,538 (435,866)	0.0699	0.0987	1.07 (0.88-1.30)	0.5056	0.15	0.1053	0.499	1.11 (0.42-2.95)	0.8412	0.95	0.0448	0.0988	1.05 (0.86-1.27)	0.6500	0.0429	0.0981	1.04 (0.86-1.27)	0.6617
UK Biobank	COPD	6 SNP	13,538 (435,866)	0.0741	0.1249	1.07 (0.84-1.38)	0.579		0.1156	0.576	1.12 (0.36-3.47)	0.8508	0.94	0.0182	0.1161	1.02 (0.81-1.27)	0.8751	0.0077	0.1087	1.01 (0.81-1.25)	0.9437
Replication 2	COPD	7 SNP	15,256 (47,936)	0.0438	0.1954	1.04 (0.71-1.53)	0.8300	**0.029**	-0.0668	0.966	0.94 (0.14-6.21)	0.9475	0.91	-0.1092	0.1633	0.90(0.65-1.23)	0.5053	-0.1399	0.1644	0.87 (0.63-1.20)	0.3948
Replication 2	COPD	6 SNP	15,256 (47,936)	0.0225	0.2425	1.02 (0.64-1.65)	0.9296		-0.1162	1.109	0.89 (0.10-7.83)	0.9216	0.9	-0.1638	0.1802	0.85 (0.60-1.21)	0.3633	-0.1799	0.1862	0.84 (0.58-1.20)	0.3339

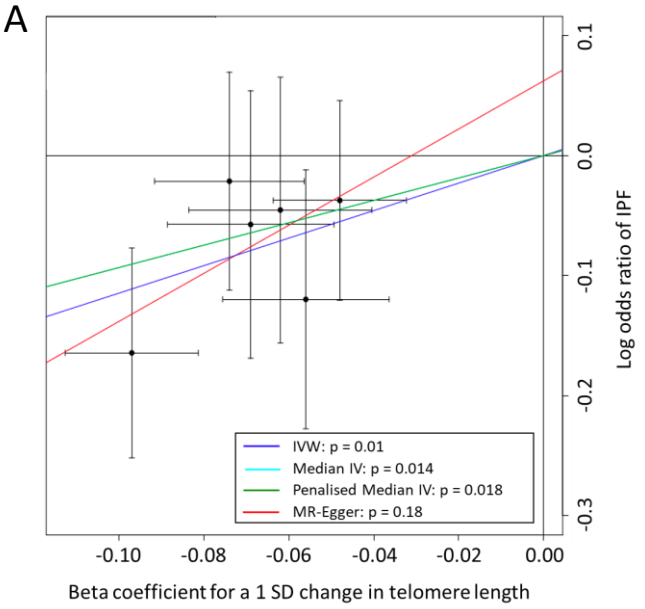
^ 2-sample MR performed using the telomere length associated variants from previous GWAS using BOLT-LMM to account for population stratification. Models adjusted for age, sex, assessment centre and genotyping platform

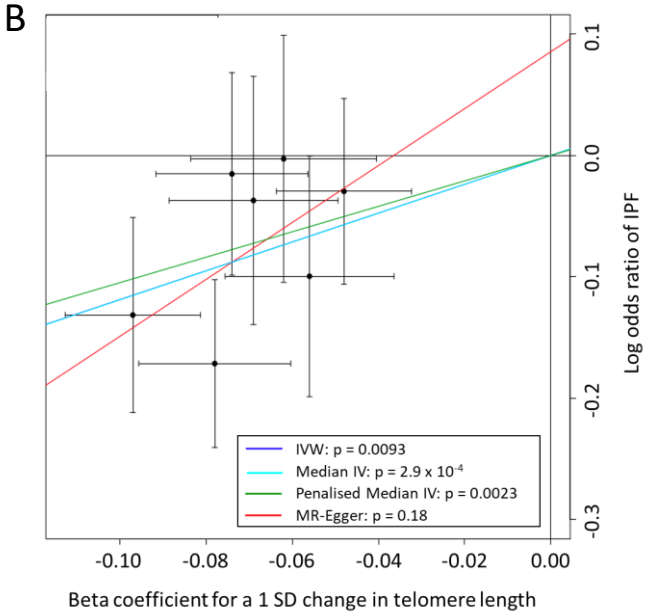
^^ 2-sample MR as above using different methods to account for pleiotropy as detailed in Bowden et al., 2015 and Bowden et al., 2016 (see main paper)

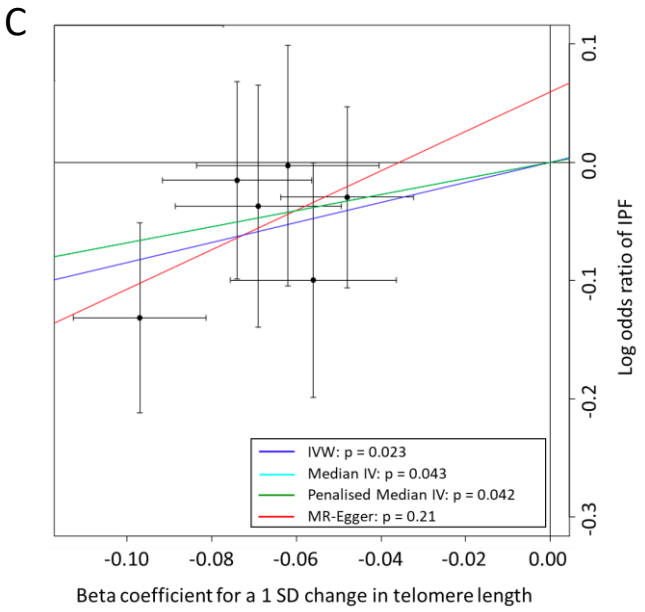
* P value for heterogeneity between SNPs

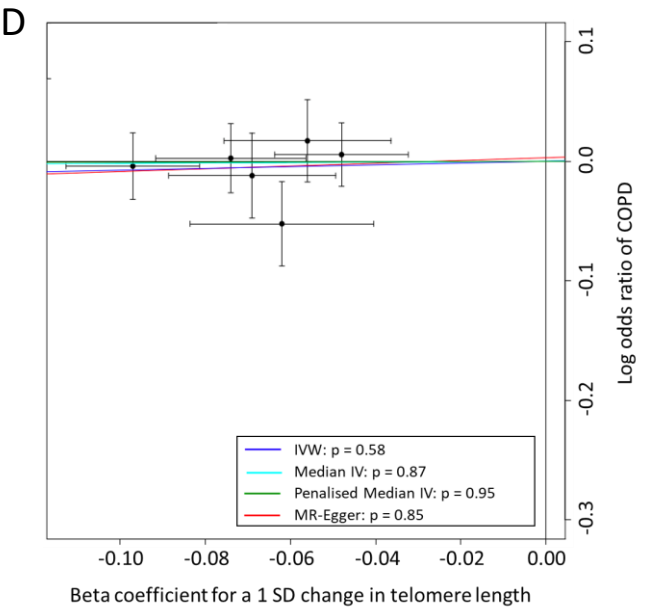
Results of sensitivity studies
In this section are the additional two-sample MR results showing sensitivity analyses for broader IPF category in UK Biobank and reduced numbers of variants.

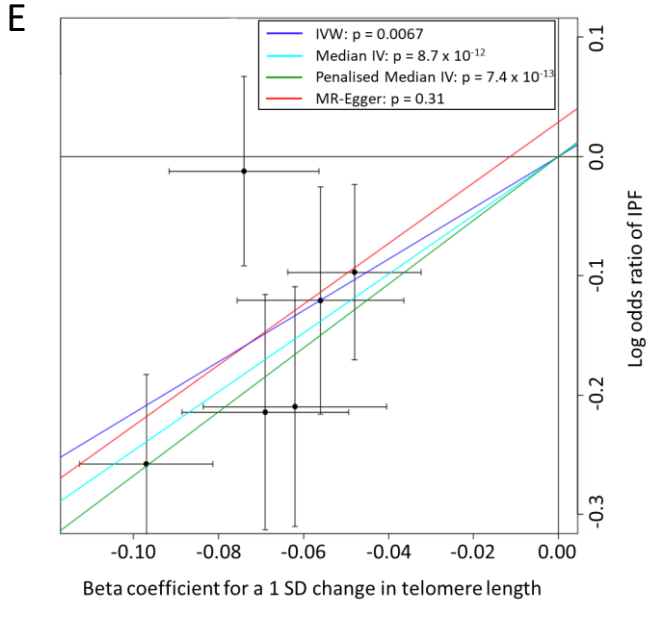
Supplementary Figure 1. Two-sample MR results for IPF and COPD showing evidence of telomere length causality in IPF but not in COPD Graphs show the strength of the relationship between disease incidence and telomere length SNP in cases vs controls on the y axis against the telomere length association from previous GWAS for each SNP on x axis. A non-zero gradient to the lines, with significant p values shown in the top left-hand box, is evidence of causality of telomere length for disease. (A) IPF ('narrow') with six variants (rs2736100 has been removed due to known association with IPF), (B) IPF 'broad' with all seven telomere length variants, (C) IPF 'broad' with six variants (rs2736100 removed), (D) COPD with six variants (rs2736100 removed), (E) IPF GWAS replication cohort with six variants (rs2736100 removed), (F) COPD GWAS replication cohort with six variants (rs2736100 removed)

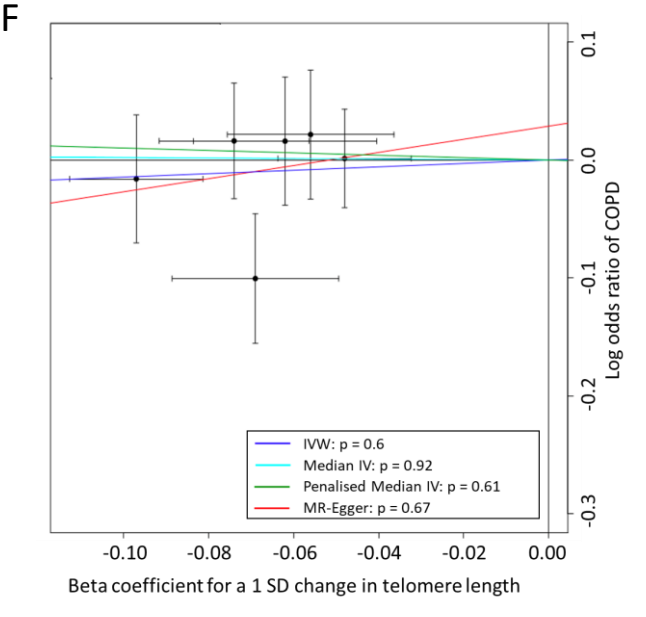

A
IVW: p = 0.01
Median IV: p = 0.014
Penalised Median IV: p = 0.018
MR-Egger: p = 0.18
Log odds ratio of IPF
Beta coefficient for a 1 SD change in telomere length


B
IVW: p = 0.0093
Median IV: p = 2.9 x 10-4
Penalised Median IV: p = 0.0023
MR-Egger: p = 0.18
Log odds ratio of IPF
Beta coefficient for a 1 SD change in telomere length


C
IVW: p = 0.023
Median IV: p = 0.043
Penalised Median IV: p = 0.042
MR-Egger: p = 0.21
Log odds ratio of IPF
Beta coefficient for a 1 SD change in telomere length

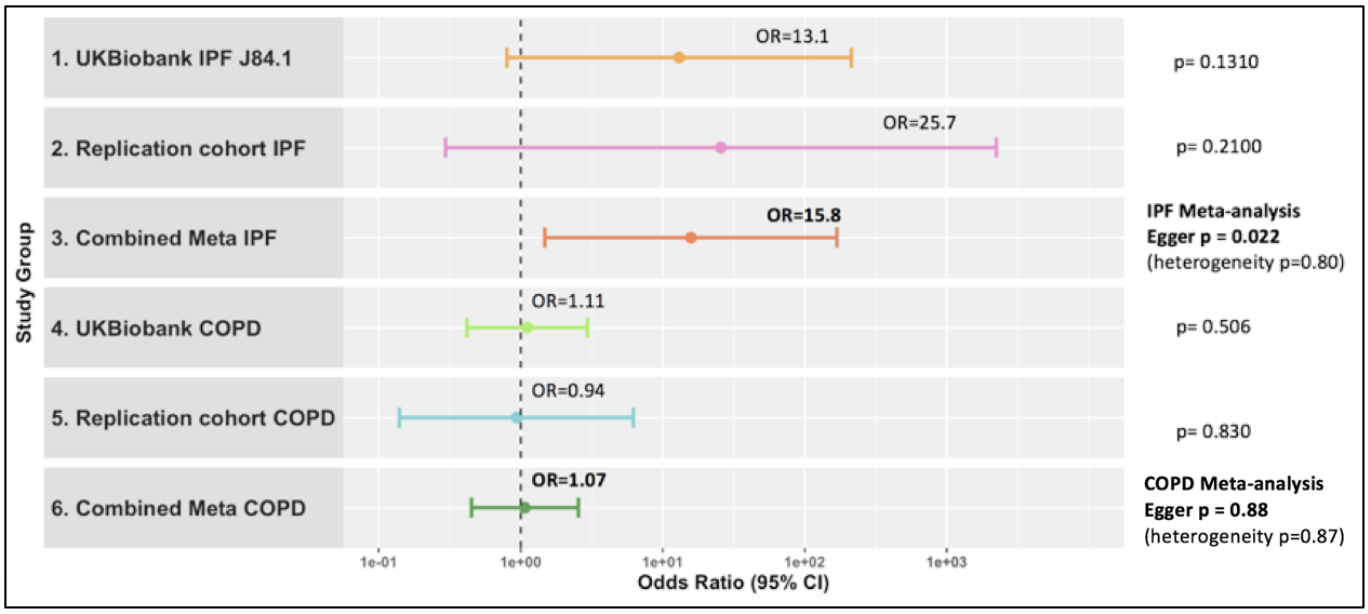

D
IVW: p = 0.58
Median IV: p = 0.87
Penalised Median IV: p = 0.95
MR-Egger: p = 0.85
Log odds ratio of COPD
Beta coefficient for a 1 SD change in telomere length


E
IVW: p = 0.0067
Median IV: p = 8.7 x 10-12
Penalised Median IV: p = 7.4 x 10-13
MR-Egger: p = 0.31
Log odds ratio of IPF
Beta coefficient for a 1 SD change in telomere length


F
IVW: p = 0.6
Median IV: p = 0.92
Penalised Median IV: p = 0.61
MR-Egger: p = 0.67
Log odds ratio of COPD
Beta coefficient for a 1 SD change in telomere length

Meta-analysis results using the Egger model

Supplementary Figure 2. Meta-analysis results for IPF and COPD in UK Biobank and replication cohorts showing significant evidence of telomere length causality in IPF and not COPD across cohorts using the Egger model. Odds ratios and 95% confidence intervals for IPF ('narrow') in UKB, IPF Replication Cohort, IPF meta-analysis, COPD in UK Biobank, COPD Replication Cohort and COPD meta-analysis using Egger Method.



Supplemental References

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2. The Telomeres Mendelian Randomization Collaboration. Association between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. JAMA oncology, 2017. 3(5): p. 636-651.
3. Coultas, D.B., et al., The epidemiology of interstitial lung diseases. American Journal of Respiratory and Critical Care Medicine, 1994. 150(4): p. 967-972.
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