

Supplementary Table DS1. Baseline characteristics of 67,306 individuals from the general population by telomere length

	Telomere length quartiles				p for trend
	1	2	3	4	
No. (%)	16,820 (25)	16,829 (25)	16,828 (25)	16,829 (25)	
Telomere length (bp), median (IQR)	4595 (3826-5072)	3619 (3198-4184)	3167 (2775-3664)	2591 (2269-3088)	
Age, years, median (IQR)	52 (42-61)	55 (45-65)	59 (49-68)	64 (54-72)	<1*10 ⁻³⁰⁰
Women, No. (%)	9877 (59)	9438 (56)	9198 (55)	8729 (52)	1*10 ⁻³⁷
Never smokers, No. (%)	7029 (42)	6557 (39)	6096 (36)	5700 (34)	1*10 ⁻⁵⁶
Drinks/week, median (IQR)	7 (3-14)	8 (3-15)	8 (4-15)	9 (4-16)	3*10 ⁻⁵³
Less than 3 years of education, No. (%)†	10,062 (60)	10,260 (61)	10,698 (64)	11,193 (67)	4*10 ⁻⁴²
Lowest income, No. (%)	2501 (15)	2809 (17)	3277 (19)	4230 (25)	8*10 ⁻¹³⁶
Low leisure time physical activity, inactive or less than 2-4h light/day, No. (%)	8658 (51)	8931 (53)	9100 (54)	9422 (56)	2*10 ⁻¹⁷
Body mass index, kg/m ² , median (IQR)	25 (23-28)	25 (23-28)	26 (23-29)	26 (24-29)	4*10 ⁻¹¹²
C-reactive protein, mg/L, median (IQR)	1.4 (1.1-2.4)	1.5 (1.1-2.6)	1.6 (1.2-2.7)	1.6 (1.2-3.0)	2*10 ⁻¹³³
Chronic disease, No. (%)	5647 (34)	6415 (38)	7320 (44)	8529 (51)	2*10 ⁻²⁵²

Baseline characteristics for participants in the Copenhagen General Population Study and the Copenhagen City Heart Study combined. IQR = interquartile range. † After primary and lower secondary school.

Supplementary Table DS2. Baseline characteristics of 67,306 individuals from the general population by endpoint

	Hospitalization/death with depression			Prescription antidepressant medication		
	Yes	No	p-value	Yes	No	p-value
No. (%)	1374 (2)	65,932 (98)		7748 (12)	59,558 (88)	
Age, years, median (IQR)	66 (56-74)	57 (47-67)	1*10 ⁻⁹¹	59 (49-69)	57 (47-67)	9*10 ⁻²⁹
Women, No. (%)	885 (64)	36,357 (55)	8*10 ⁻¹²	5194 (67)	32,048 (54)	1*10 ⁻¹⁰⁷
Never smokers, No. (%)	381 (28)	25,001 (38)	1*10 ⁻¹⁴	2228 (29)	23,154 (39)	6*10 ⁻⁶⁷
Drinks/week, median (IQR)	7 (2-14)	8 (4-15)	0.18	7 (3-14)	8 (4-15)	0.05
Less than 3 years of education, No. (%)†	1080 (79)	41,133 (62)	9*10 ⁻³⁵	5286 (68)	36,927 (62)	2*10 ⁻²⁶
Lowest income, No. (%)	572 (42)	12,245 (19)	6*10 ⁻¹⁰³	2212 (29)	10,605 (18)	1*10 ⁻¹¹³
Low leisure time physical activity, inactive or less than 2-4h light/day, No. (%)	951 (69)	35,160 (53)	1*10 ⁻³¹	4926 (64)	31,185 (52)	2*10 ⁻⁷⁷
Body mass index, kg/m ² , median (IQR)	25.7 (22.9-28.7)	25.5 (23.1-28.4)	0.73	25.6 (23.0-28.9.)	25.5 (23.1-28.4)	4*10 ⁻⁶
C-reactive protein, mg/L, median (IQR)	1.9 (1.3-3.7)	1.5 (1.1-2.7)	1*10 ⁻²⁰	1.7 (1.2-3.2)	1.5 (1.1-2.6)	3*10 ⁻²⁹
Chronic disease, No. (%)	998 (73)	26,967 (41)	2*10 ⁻¹²³	4138 (53)	23,827 (40)	3*10 ⁻¹¹²

Baseline characteristics for participants in the Copenhagen General Population Study and the Copenhagen City Heart Study combined. IQR = interquartile range † After primary and lower secondary school.

Supplementary Table DS3. Baseline characteristics of 65,096 individuals from the general population by allele score

Telomere shortening alleles	Allele score				p for trend
	5-6	4	3	0-2	
No. (%)	11,769 (18)	24,157 (18)	20,812 (32)	8358 (13)	
Telomere length (bp), median (IQR)	3311 (2769-3936)	3384 (2833-4033)	3446 (2893-4098)	3509 (2962-4189)	2*10 ⁻⁷⁵
Age, years, median (IQR)	57 (47-67)	57 (47-67)	58 (47-67)	57 (47-67)	0.46
Women, No. (%)	6497 (55)	13,207 (55)	11,598 (56)	4612 (55)	0.33
Never smokers, No. (%)	4476 (38)	9077 (38)	7845 (38)	3177 (38)	0.99
Drinks/week, median (IQR)	8 (3-15)	8 (4-15)	8 (4-15)	8 (4-15)	0.51
Less than 3 years of education, No. (%)†	7412 (63)	15,203 (63)	12,971 (62)	5187 (62)	0.08
Lowest income, No. (%)	2171 (18)	4440 (18)	3960 (19)	1509 (18)	0.77
Low leisure time physical activity, inactive or less than 2-4h light/day, No. (%)	6330 (54)	12,939 (54)	11,107 (53)	4486 (54)	0.70
Body mass index, kg/m ² , median (IQR)	26 (23-28)	26 (23-28)	26 (23-28)	26 (23-28)	0.19
C-reactive protein, mg/L, median (IQR)	1.6 (1.1-2.7)	1.6 (1.1-2.7)	1.5 (1.1-2.6)	1.6 (1.1-2.6)	0.21
Chronic disease, No. (%)	4879 (41)	14,164 (59)	12,175 (59)	4860 (58)	0.56

Baseline characteristics for participants in the Copenhagen General Population Study and the Copenhagen City Heart Study combined.

Only participants without missing values for any of the 3 genotypes are included.

† After primary and lower secondary school.

Supplementary Table DS4. Differences in telomere length after multifactorial adjustment

	Coefficient	SE	t	p	beta
Hospitalization/death with depression	-82.80	40.30	-2.04	0.041	-0.01
Age, days	-57.95	2.67	21.67	4*10 ⁻¹⁰⁴	-0.84
Men	-76.15	7.34	10.38	3*10 ⁻²⁵	-0.04
Smoke status (1. never smokers)					
2. former smokers	-20.87	7.74	-2.70	0.007	-0.01
3. current smokers	-79.21	9.25	-8.56	1*10 ⁻¹⁷	-0.03
Alcohol, drinks per week	-0.37	0.35	-1.05	0.292	-0.003
Education (1. no education)					
2. student	44.50	35.27	1.26	0.207	0.005
3. shorter education	-16.03	13.44	-1.19	0.233	-0.01
4. basic vocational training	8.25	11.83	0.70	0.486	0.004
5. higher education	17.93	13.00	1.38	0.168	0.01
6. university education	41.38	14.17	2.92	0.003	0.02
Income (1. low income)					
2. middle income	22.22	10.24	2.17	0.030	0.01
3. high income	11.38	11.96	0.95	0.342	0.01
Physical activity (1. 0-2 hours light/week)					
2. 2-4 hours light/week	21.90	13.92	1.57	0.116	0.01
3. >4 hours light or 2-4 hours vigorous/week	27.20	14.12	1.93	0.054	0.01
4. > 4 hours vigorous/week	52.64	19.00	2.77	0.006	0.01
Body mass index, kg/m ²	-6.17	0.82	-7.51	6*10 ⁻¹⁴	-0.03
Date of birth	-0.11	0.01	15.38	2*10 ⁻⁵³	-0.63
Batch					
2	821.66	11.26	72.96	<1*10 ⁻³⁰⁰	0.43
3	-219.07	14.41	15.21	3*10 ⁻⁵²	-0.11
Being in CGPS	303.71	33.00	9.20	4*10 ⁻²⁰	0.11

Based on 53,486 individuals from Copenhagen General Population Study and the Copenhagen City Heart Study combined. Individuals with antidepressant medication use but no hospitalization/death with depression as well as individuals with hospitalization/death with depression after study entry excluded. SE=standard error.

Supplementary Table DS5. Differences in telomere length after multifactorial adjustment

	Coefficient	SE	t	p	beta
Hospitalization/death with depression	-76.01	40.32	-1.88	0.06	-0.007
Age, days	-58.02	2.67	21.70	6*10 ⁻¹⁰⁴	-0.84
Men	-75.34	7.34	10.27	1*10 ⁻²⁴	-0.04
Smoke status (1. never smokers)					
2. former smokers	-19.65	7.74	-2.54	0.01	-0.01
3. current smokers	-76.91	9.27	-8.30	1*10 ⁻¹⁶	-0.03
Alcohol, drinks per week	-0.38	0.35	-1.10	0.27	-0.004
Education (1. no education)					
2. student	49.03	35.28	1.39	0.17	0.005
3. shorter education	-16.34	13.44	-1.22	0.22	-0.006
4. basic vocational training	7.74	11.83	0.65	0.51	0.004
5. higher education	17.17	12.99	1.32	0.19	0.01
6. university education	40.59	14.17	2.87	0.004	0.02
Income (1. low income)					
2. middle income	20.27	10.25	1.98	0.05	0.01
3. high income	8.46	11.98	0.71	0.48	0.004
Physical activity (1. 0-2 hours light/week)					
2. 2-4 hours light/week	20.21	13.92	1.45	0.15	0.01
3. >4 hours light or 2-4 hours vigorous/week	24.54	14.13	1.74	0.08	0.01
4. > 4 hours vigorous/week	50.41	19.00	2.65	0.01	0.01
Body mass index, kg/m ²	-5.87	0.83	-7.10	1*10 ⁻¹²	-0.03
Date of birth	-0.11	0.01	15.55	2*10 ⁻⁵⁴	-0.64
Batch					
2	821.40	11.26	72.95	<1*10 ⁻³⁰⁰	0.42
3	-219.13	14.40	15.21	4*10 ⁻⁵²	-0.11
Being in CGPS	303.76	32.99	9.21	3*10 ⁻²⁰	0.11
Chronic disease	-30.49	7.67	-3.98	7*10 ⁻⁵	-0.02
C-reactive protein	-1.11	0.65	-1.70	0.09	-0.01

Based on 53,486 individuals from Copenhagen General Population Study and the Copenhagen City Heart Study combined. Individuals with antidepressant medication use but no hospitalization/death with depression as well as individuals with hospitalization/death with depression after study entry excluded. SE=standard error.

Supplementary Table DS6. Differences in telomere length after multifactorial adjustment

	Coefficient	SE	t	p	beta
Prescription antidepressant medication use	-12.40	11.76	-1.05	0.29	-0.003
Age, days	-60.43	2.45	-24.63	6*10 ⁻¹³⁴	-0.88
Men	-74.06	6.72	-11.02	3*10 ⁻²⁸	-0.04
Smoke status (1. never smokers)					
2. former smokers	-21.56	7.11	-3.03	0.002	-0.01
3. current smokers	-88.04	8.32	-10.59	3*10 ⁻²⁶	-0.03
Alcohol, drinks per week	-0.59	0.31	-1.89	0.06	-0.006
Education (1. no education)					
2. student	65.78	35.15	2.05	0.04	0.01
3. shorter education	-8.58	11.98	-0.72	0.47	-0.003
4. basic vocational training	11.20	10.51	1.07	0.29	0.01
5. higher education	18.67	11.62	1.61	0.11	0.01
6. university education	42.08	12.84	3.28	0.001	0.02
Income (1. low income)					
2. middle income	30.274	9.02	3.41	0.001	0.02
3. high income	17.82	10.72	1.66	0.10	0.01
Physical activity (1. 0-2 hours light/week)					
2. 2-4 hours light/week	22.14	12.21	1.81	0.07	0.01
3. >4 hours light or 2-4 hours vigorous/week	31.00	12.46	2.49	0.01	0.02
4. > 4 hours vigorous/week	44.24	17.23	2.57	0.01	0.01
Body mass index, kg/m ²	-5.43	0.74	-7.38	2*10 ⁻¹³	-0.02
Date of birth	-0.12	0.01	-17.82	5*10 ⁻⁷¹	-0.67
Batch					
2	824.12	10.23	79.61	<1*10 ⁻³⁰⁰	0.43
3	-211.27	13.17	-16.05	6*10 ⁻⁵⁸	-0.11
Being in CGPS	327.22	30.20	10.83	2*10 ⁻²⁷	0.12

Based on 63,867 individuals from Copenhagen General Population Study and the Copenhagen City Heart Study combined. Individuals with hospitalization/death with depression but no prescription antidepressant medication use and individuals with prescription antidepressant medication use after study entry excluded. SE=standard error.

Supplementary Table DS7. Differences in telomere length after multifactorial adjustment

	Coefficient	SE	t	p	beta
Prescription antidepressant medication use	-9.83	11.77	-0.84	0.40	-0.003
Age, days	-60.49	2.45	-24.66	1*10 ⁻¹³³	-0.88
Men	-73.21	6.72	-10.89	1*10 ⁻²⁷	-0.04
Smoke status (1. never smokers)					
2. former smokers	-20.10	7.12	-2.82	0.005	-0.01
3. current smokers	-85.40	8.33	-10.25	1*10 ⁻²⁴	-0.04
Alcohol, drinks per week	-0.61	0.31	-1.95	0.05	-0.01
Education (1. no education)					
2. student	69.51	32.16	2.16	0.03	0.01
3. shorter education	-9.18	11.97	-0.77	0.44	-0.003
4. basic vocational training	10.50	10.51	1.00	0.32	0.01
5. higher education	17.50	11.62	1.53	0.13	0.01
6. university education	40.90	12.84	3.19	0.001	0.02
Income (1. low income)					
2. middle income	28.91	9.03	3.20	0.001	0.02
3. high income	14.87	10.73	1.38	0.17	0.01
Physical activity (1. 0-2 hours light/week)					
2. 2-4 hours light/week	20.29	12.22	1.66	0.10	0.01
3. >4 hours light or 2-4 hours vigorous/week	28.11	12.47	2.25	0.02	0.01
4. > 4 hours vigorous/week	41.83	17.24	2.43	0.02	0.01
Body mass index, kg/m ²	-5.15	0.74	-6.94	4*10 ⁻¹²	-0.02
Date of birth	-0.12	0.01	-18.01	2*10 ⁻⁷²	-0.67
Batch					
2	813.91	10.22	79.61	<1*10 ⁻³⁰⁰	0.43
3	-211.49	13.16	-16.07	5*10 ⁻⁵⁸	-0.11
Being in CGPS	327.32	30.19	10.84	2*10 ⁻²⁷	0.12
Chronic disease	-31.96	6.92	-4.62	3*10 ⁻⁶	-0.02
C-reactive protein	-0.92	0.58	-1.59	0.11	-0.01

Based on 63,867 individuals from Copenhagen General Population Study and the Copenhagen City Heart Study combined. Individuals with hospitalization/death with depression but no prescription antidepressant medication use and individuals with prescription antidepressant medication use after study entry excluded. SE=standard error.

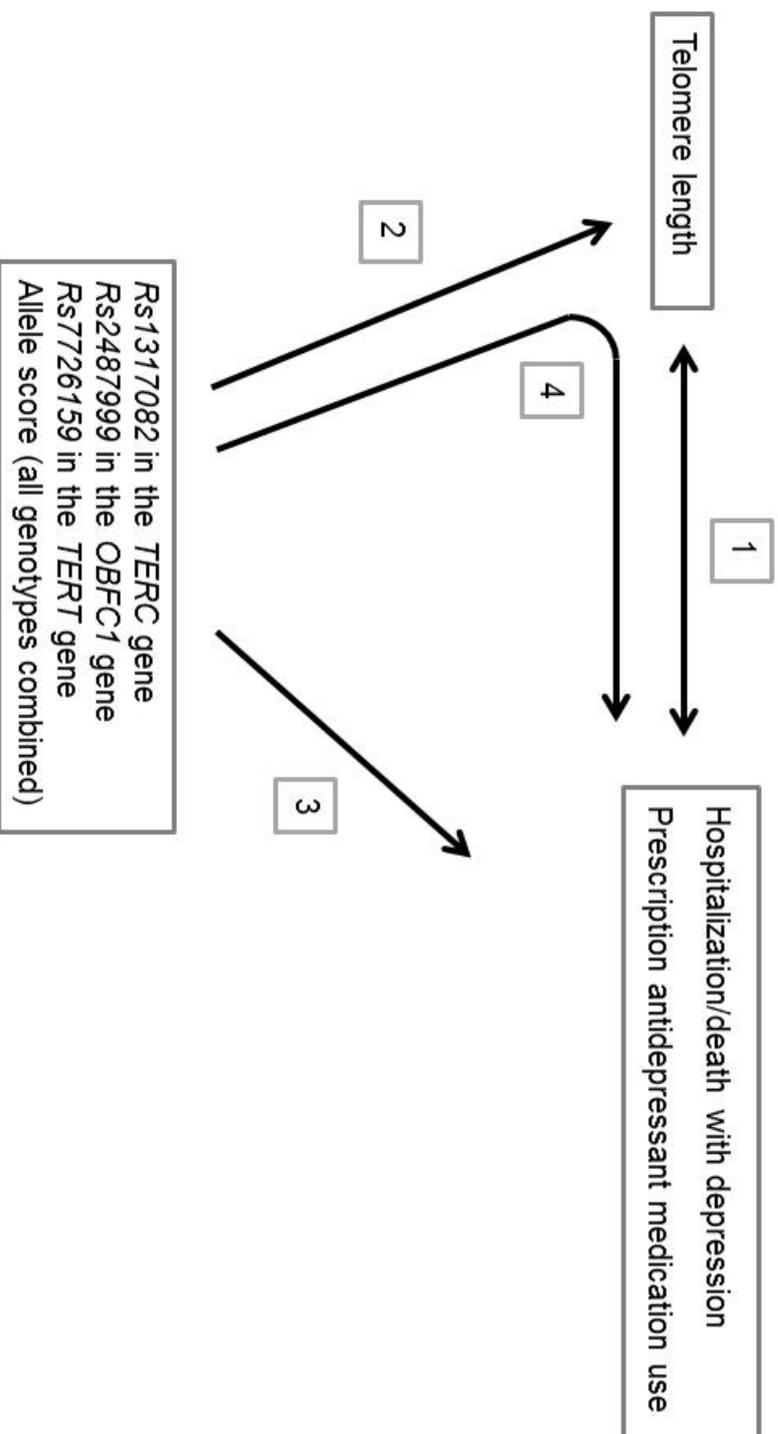
Supplementary Figure DS1.

Study design. Arrow 1 represents the observational analyses between telomere length and hospitalization/death with depression and prescription antidepressant medication examined cross-sectionally and prospectively (Figure 1 and 2). Arrow 2 represents the association between each of the genotypes and telomere length (Figure 3). Arrow 3 represents the association between each of the genotypes and hospitalization/death with depression and prescription antidepressant medication (Figure 3). Arrow 4 represents the instrumental variable analysis examining genetic risk estimates for hospitalization/death with depression and prescription antidepressant medication use for a 200 basepairs shorter telomere length (Figure 4).

Supplementary Figure DS2.

Prospective analyses of the association between a 200 basepair decrease in telomere length and hospitalization/death with depression or prescription antidepressant medication use. Overall based on 67,306 participants from the Copenhagen General Population Study and Copenhagen City Heart Study combined; however, as individuals either with hospitalization/death with depression or prescription antidepressant medication use at baseline were excluded, the number of individuals in the different analyses is smaller than 67,306. P values were corrected for multiple comparisons using the Bonferroni correction, that is, p-values were multiplied with 20 multiple tests. * not significant after correction for multiple comparison. Bp = basepairs. TL= telomere length. HR = Hazard ratio. CI = confidence interval. CRP = C-reactive protein.

Supplementary Figure 1



- 1: Observational analyses: Is short telomere length associated with depression? (Figure 1-2)
- 2: Genetic analyses: Are the genotypes associated with telomere length? (Figure 3)
- 3: Genetic analyses: Are the genotypes associated with depression? (Figure 3)
- 4: Instrumental variable analysis: Is genetically short telomere length associated with depression? (Figure 4)

Supplementary Figure 2

